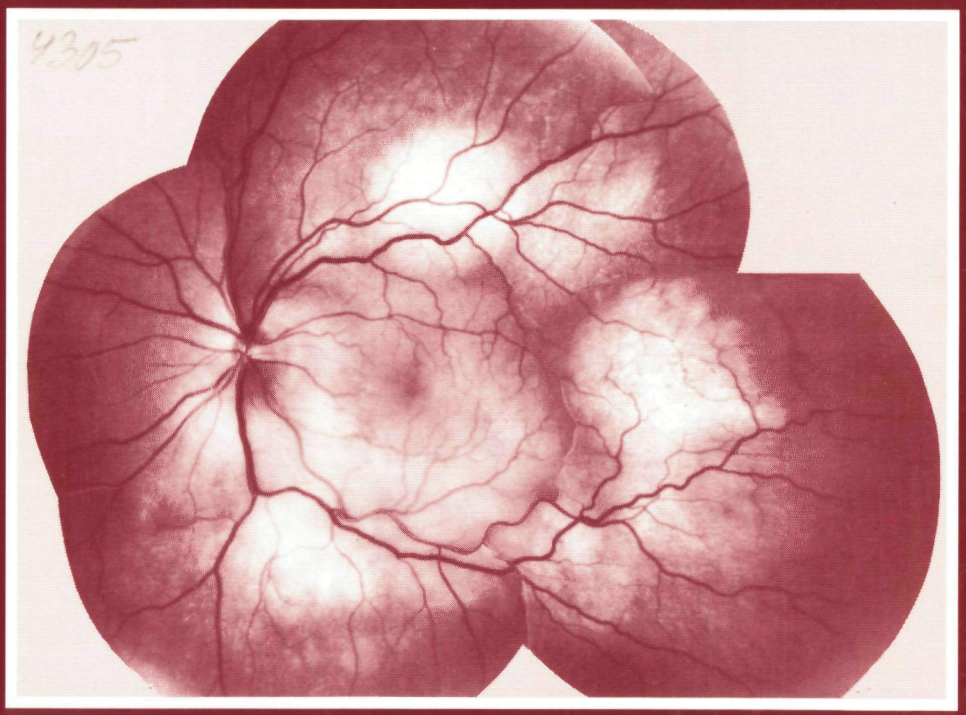
Uveal metastases

A clinical survey



H.M.A. Brink

Uveal metastases
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Een wetenschappelijke proeve op het gebied van de Medische Wetenschappen, in het bijzonder de Geneeskunde

Proefschrift

ter verkrijging van de graad van doctor aan
de Katholieke Universiteit Nijmegen,
volgens besluit van het College van Decanen in het
openbaar te verdedigen op
vrijdag 24 januari 1992
des namiddags te 3.30 uur

door

Hendrik Maria Alphons Brink

geboren op 15 maart 1961 te Valkenswaard

1992
Drukkerij Benda BV, Nijmegen

PROMOTORES:	Prof. Dr. A.F. Deutman
	Prof. Dr. F. Hendrikse
CO-PROMOTORES:	Dr. L.V.A.M. Beex
	Dr. J. Hoogenhout

Financial support was provided by the "Research Fonds Oogheelkunde" of the University of Nijmegen, the Stichting "De Drie Lichten" and Alcon Pharmaceuticals Ltd. (the Netherlands).

voor Annelies

Cover illustration: fundus photograph of the left eye showing three choroidal metastases from breast cancer

CIP-GEGEVENS KONINKLIJKE BIBLIOTHEEK, DEN HAAG

Brink, Hendrik Maria Alphons

Uveal metastases : a clinical survey / Hendrik Maria Alphons Brink ; [ill. H. Brink ... et al.]. - [S.l. : s.n.] (Nijmegen : Benda). - Ill.
Proefschrift Nijmegen. - Met lit. opg. - Met samenvatting in het Nederlands.
ISBN 90-9004777-8
Trefw.: oogheelkundige metastasen.

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Introduction

Metastases in the uvea may lead to partial or even complete blindness and so seriously deteriorate the quality of life of cancer patients.

If an underlying primary tumour elsewhere in the body is already known, the diagnosis of the intraocular metastases will be a sign of progression and dissemination. Uveal metastases may also, however, be the first sign of a hitherto unknown but meanwhile disseminated malignancy. In that case the patient, in addition to the direct eye problems, is for the first time to face the fact that he suffers from a serious disease.

A timely and correct diagnosis of uveal metastases is of great importance for an optimal and preferably not too taxing treatment that may contribute to preservation or major improvement of the quality of life of the patient in question.

This study was designed to investigate all aspects of the clinical picture of uveal metastases. Attention will be paid to the epidemiology of uveal metastases, to the various underlying primary tumours and the relationship with metastases elsewhere in the body, diagnostics and differential diagnostics by means of the various examination techniques available, the management and the treatment of this condition and its prognosis. The results of this study will be discussed in three parts:

1. The first part will deal with the literature on uveal metastases, with emphasis on the diagnosis and differential diagnosis.

2. The second part consists of a retrospective study of all patients with suspicion of an intraocular tumour who were seen in the Ophthalmological Clinic of Nijmegen University Hospital for diagnosis and treatment in the period from November 1970 to November 1990. Apart from patients with uveal metastases, data of patients with other intraocular tumours and lesions suspected of being tumours will be discussed to the extent of their relevance for the differential diagnosis. Special attention will also be given to the management to be conducted in patients in whom uveal metastases are established.

3. In the third part, a description will be given of a prospective study, over the period from February 1989 to July 1991, in patients with breast cancer. Its purpose is to determine the frequency of ocular symptoms and of uveal metastases in this patient population and to consider to what extent it is useful for patients with such a malignancy to be screened for ophthalmological abnormalities according to a fixed protocol.

The stereo photographs shown can be viewed with the aid of a prysmatic viewer (e.g. KMQ or Nesh prism stereo viewer). This viewer should be held in the right hand and used like spectacles. A prism bar held in the right hand, with the base of the prisms downward may also be used for this purpose. Instead of the two photographs three pictures will be seen. Vary the distance between the eyes and the photographs until the central picture is seen sharp without double contours. This picture will be three-dimensional.

Part 1
Review of the literature

1.1 Historical survey

In 1872 Perls published the findings at autopsy of a male aged 43 years who died of lungcancer. The eyes had been examined histologically.

> *'Beim Herausnehmen des hinteren Augenabschnittes links erscheint die Retina auf der inneren Seite und nach unten abgelöst, die Chorioidea hier fast in der ganzen Ausdehnung der hinteren Hälfte des Bulbus stark verdickt (bis zu 2 Mm), in der Tiefe theilweise sehr derb, fast knorpelhart, nach der Oberfläche zu rundliche, sechsergrosse, opak-weisse, wenig und leichtkörnig prominirende Geschwulstmassen bildend, von denen fast jede ein etwas vertieftes Centrum hat Am rechten Auge liegt die Retina der Chorioidea an, aber auch hier finden sich im hinteren Augenabschnitte in der Chorioidea mehrere flachprominirende bis linsengrosse Infiltrate von ähnlicher Beschaffenheit Die Infiltrate der Chorioidea gehören theilweise ihren tieferen Schichten an, eine dünne, gefässreiche, bräunliche Schicht zieht an vielen Stellen über sie weg, und ist namentlich in den Vertiefungen zwischen den körnigen Hervorragungen reichlich Nur die einzelnen Körner selbst sowie verschiedene vereinzelte ganz kleine Infiltrate von 1/2 - 1 Mm Durchmesser erschienen mit ganz weisser Oberfläche und liegen vollständig oberhalb der pigmentirten Gewebsschicht Die grösseren Infiltrate gehen bis an die Sklerotica, und sind derselben zum Theil angelöthet, ohne aber irgendwo in sie hineinzugreifen Auf dem Durchschnitte erscheinen die Infiltrate opak, gelblich-weiss, trocken, zum Theil etwas bröcklich, und namentlich in den grösseren zeigen sich dicht liegende gelbliche Pfröpfe zwischen denen hier und da ein bläulich weisses prominirendes und festeres Gewebe zu erkennen ist '*

Microscopically infiltrates of malignant cells were observed in the choroid as well as in the choriocapillaris The diagnosis of a choroidal metastasis was made The patient had not been known with visual complaints and had not been subjected to ocular examination

This article is generally considered as the earliest publication regarding a uveal metastasis (Duke-Elder and Perkins, 1966; Albert et al., 1967).

In 1870, Bromser described a patient with a malignant melanoma of the cheek who developed visual complaints in one eye. Five years later, orbital exenteration was performed because of an intraocular tumour. Leber (1885), who himself examined the patient in question and who directed the histological examination, was of the opinion that while the metastatic nature of the lesion had not been established with certainty, this diagnosis was highly probable Fuchs (1882) and Sattler (1926) did not regard the lesion as a metastasis, mainly because of the slow growth of the intraocular tumour and the absence of metastases elsewhere in the body (Fuchs, 1882; Sattler, 1926). However, in 1967 Font et al. in their article on malignant cutaneous melanomas metastatic to the uvea did mention Bromser's patient as the first case of uveal metastasis reported.

Hirschberg (1882) probably described the first patient in whom the diagnosis of a choroidal metastasis was made on clinical grounds. The patient was a female aged 52 known with breast cancer with visual complaints in the right eye since three months. Visual acuity on the right was 1/6, on the left vision was virtually normal Ophthalmoscopy revealed a few small pale-yellow, round, almost punctate foci near the optic disk in both eyes On the right there was in addition a vaguely delimited flat

elevation of the choroid which lifted the retina about 1.5 mm. The lesions were bilaterally progressive; vision deteriorated and the patient died. No autopsy was performed.

Ewing in 1890 described a patient with deterioration of vision due to a retinal detachment and an intraocular tumour in whom breast cancer was detected immediately after enucleation. This is the first patient known with a uveal metastasis in whom, apart from the choroid, the iris and ciliary body were involved also.

The first report in the Netherlands of a patient with a uveal metastasis was published by Nicolaï (1915).

In 1891, Elschnig in an article presented a survey of the 16 patients with uveal metastases known at the time. The survey was followed by numerous similar publications by, inter alia, Schultze (1893), Lagrange (1901), Usher (1923), Ask (1934), Lemoine and McLeod (1936), Greer (1950), Albert et al., (1967) and Schiffer et al. (1978). Up to 1991 some 1500 publications were directly or indirectly concerned with uveal metastases.

The earlier articles described almost exclusively the clinical picture and histological findings. Later publications refer to the treatment as well (Ucherman, 1917; Lemoine and McLeod, 1936).

Some important histopathological studies were reported by, inter alia, Hart (1962), Jensen (1970) and Hutchison and Smith (1979). Ferry and Font in three articles described patients with metastases to the eye and orbit of which histopathological material was available. The first part dealt with a clinicopathological study of 227 patients (Ferry and Font, 1974), in the second part, the 26 patients with metastases to the anterior segment were discussed in greater detail (Ferry and Font, 1975). The third part concerned 28 patients with orbital metastases (Font and Ferry, 1976).

Bloch and Gartner (1971) and Nelson et al. (1983) made post-mortem studies of patients with cancer at the time of death to determine the frequency of uveal metastases. In 1967, Albert et al. with the same objective published a series of articles on tumours metastatic to the eye. In the first part, the clinical incidence among 213 adult patients with a systemic malignancy was discussed (1967), the second part concerned a study in children in whom, however, no intraocular metastases could be demonstrated (1967a). The third part described a study of the fate of circulating tumour cells to the eye (1967b).

Mewis and Young (1982) performed clinical ophthalmological examinations of patients known with breast cancer in order to determine the incidence of choroidal metastases in this group of patients. Authors of other important publications on uveal metastases of breast cancer are Thatcher and Thomas (1975) and Freedman and Folk (1987). Mention should also be made of the article by Hemmes in the Nederlands Tijdschrift voor Geneeskunde of 1969 in which he described all 121 patients with uveal metastases in the Netherlands over the period 1909-1968.

Stephens and Shields in 1979 published their extensive clinical study on the diagnosis and treatment of uveal metastases. Finally, in 1990, Saßmannshausen et al. published an article reporting the largest number of patients (161) with uveal metastases from one clinic.

1.2 Anatomy and pathophysiology

Good insight into the pathogenesis and further development of uveal metastases requires knowledge of the anatomy of the vascular middle eye coat, the uvea.

1.2.1 Anatomy

Early practitioners of the anatomy of the eye were of the opinion that the uveal tract resembled the inside of a dark-coloured grape. Consequently, the word 'uvea' derives from the Latin for grape (Torczynski, 1982).

The uvea constitutes a thin continuous layer of blood vessels, melanocytes and connective tissues and has three distinct subdivisions: the choroid, the ciliary body and the iris.

The transition from iris to ciliary body is situated at the site of the recessus of the anterior chamber. Posteriorly the pars plana of the ciliary body merges with the choroid. Internally the boundary is marked by the ora serrata, a pigmented scalloped band situated anteriorly to the equator. Externally this juncture is situated at the level of the scleral insertion of the extraocular muscles of the eye. The optic nerve constitutes the posterior delineation of the choroid (Duke-Elder, 1946; Torczynski, 1982).

Internally the uvea is lined by derivatives of the neuroectoderm, viz. the retinal, ciliary and iridic epithelia, respectively. The boundary between the uvea and the epithelium is marked by a basement membrane. Externally the uvea is bordered by the sclera for the uveal part behind the scleral spur and by the aqueous humour of the anterior chamber at the site of the iris (Figure 1.2.1.1).

1.2.1.1 The choroid

The choroid, the posterior portion of the uvea, consists mainly of blood vessels in a loose connective tissue matrix with a profusion of nerve fibres and pigmented cells. The prime function of the choroid is the nourishing of the major part of the eye and especially of the retina (Jakobiec and Ozanics, 1982). The retina is supplied by the choroid to a depth of 130 μm. This comprises the layer of pigment epithelium, the rods and cones, the outer nuclear and plexiform layers and the entire thickness of the foveal retina. Sometimes, a cilioretinal artery is present which may supply a variable portion of the inner retinal layers (Hayreh, 1975).

The choroid is situated between the pigment epithelium and the sclera. Its attachment to the sclera is strongest at the scleral spur, round the optic nerve and at the entrance and exit points of the emissary vessels passing through the sclera. The choroid is thickest under the fovea (approximately 0.3 mm) and thinnest at the site of the ora serrata (0.1 to 0.15 mm) (Jakobiec and Ozanics, 1982). The thickness depends on the concentration of arteries and veins (Torczynski, 1982).

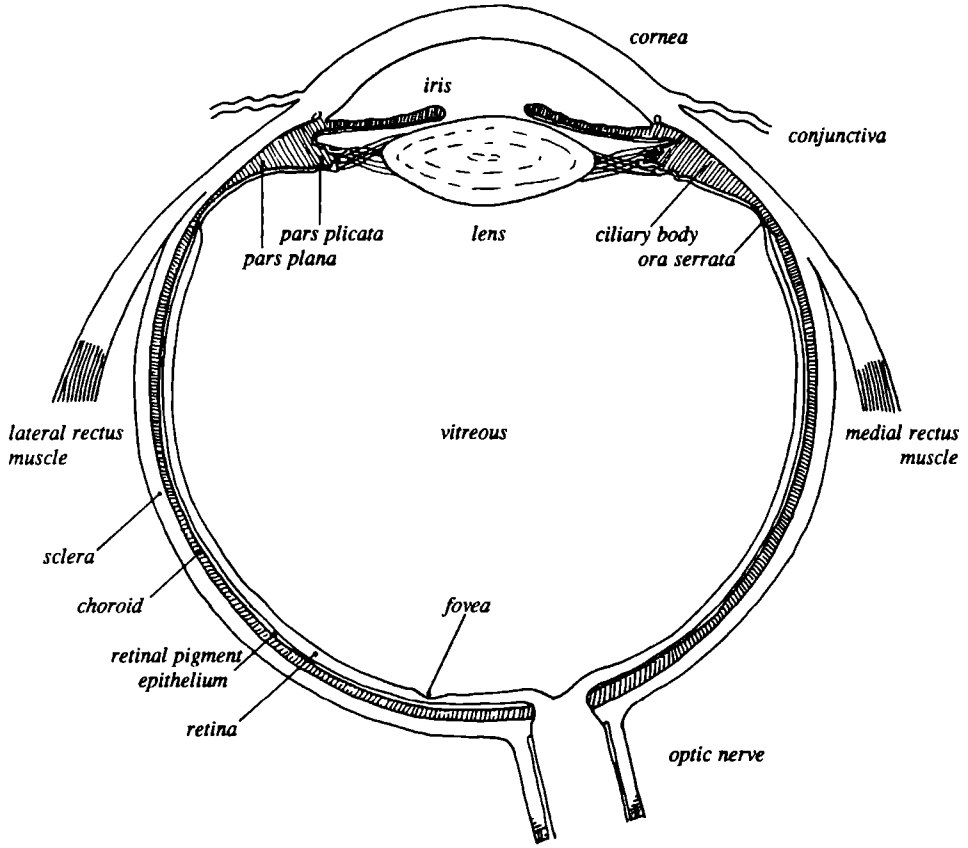


Figure 1.2.1.1 Horizontal section through the eye (after: Bloom and Fawcett, 1975; Ferner and Staubesand, 1975; Langman and Woerdeman, 1978).

From the outside inward the choroid is divided into four layers (Duke-Elder, 1946; Torczynski, 1982):

1. the suprachoroid;
2. the layer with the choroidal vessels;
3. the choriocapillaris;
4. Bruch's membrane.

On the outside the choroid is separated from the sclera by a loose connective tissue, the epi- or suprachoroid. This provides transit for the main branches of the ciliary arteries and nerves to the inside of the globe (Jakobiec and Ozanics, 1982).

The largest and outermost choroidal vessels constitute Haller's layer. Sattler's layer, which is situated below it, consists of intermediate-sized vessels.

The choriocapillary network is situated in close proximity to the retinal

photoreceptors (Jakobiec and Ozanics, 1982).

The distinction between these three layers can only be made at the posterior pole.

The boundary between the choriocapillaris and the retina is formed by Bruch's membrane which derives from both the choriocapillaris and the pigment epithelium. Bruch's membrane is an acellular membrane, approximately 2 μm thick, consisting of a network of collagenous and elastic fibres. It constitutes a filter or diffusion barrier to the passage of molecules from the choriocapillaris (Torczynski, 1982).

The outermost vessels round the papilla are choroidal branches of the short posterior ciliary arteries and radiate from the papilla. Most of the vessels of the outermost portion of the choroid, apart from the area surrounding the optic disk and below the macula, are veins. The arterioles have their closest concentration round the optic disk, especially nasally and temporally.

The choroidal arteries run a tortuous course and extend from the optic disk to the equator. Part of the branches curve posteriorly to supply the juxtaneural capillaries. Another part virtually immediately plunges deeply into the innermost layers of the choroid. In the submacular layer, individual branches are difficult to follow because of pronounced intertwining of arteries and veins (Torczynski, 1982.

The large choroidal arteries branch dichotomously, in rapid succession. Anastomoses between the larger choroidal arteries are infrequent. Frequent anastomoses are seen, on the other hand, in the smaller branches which form various plexuses. According to Hayreh (1975), however, choroidal arteries in vivo do not anastomose with each other at any level and constitute functional end arteries. He alleges that formation of anastomoses has only been demonstrated in post-mortem studies.

The terminal or precapillary arterioles that enter the choriocapillaris originate from the smaller arteries. Small branches of the short posterior ciliary arteries together with recurrent branches from the major arterial circle enter the choroid anteriorly (Torczynski, 1982).

The choriocapillaris consists of one single layer of large capillaries. The density of capillaries is practically the same in all portions of the choroid but the density of precapillary arterioles and postcapillary venules is higher in the submacular portion than equatorially. The capillaries consist of a continuous layer of fenestrated endolethial cells surrounded by a basement membrane. They are similar to the capillaries in the renal glomeruli and the small intestine. Among the endothelial cells zonulae occludentes exist.

Arterioles and venules form an alternating system segmenting the choriocapillaris. This lobular distribution in the posterior pole is supplied centrally by one or several precapillary terminal arteries and drains peripherally through venules (Torczynski, 1982). Each segment is a functional unit, in general with a polygonal shape without anastomoses with adjacent segments being demonstrable in vivo. Together they form a mosaic pattern bounded by the venous vessels (Hayreh, 1975).

At the site of the equator and anteriorly the arteries and veins join the choriocapillaris. Junctions of arterioles and capillaries as well as capillaries and venules have been described. There exists a transition zone between the posterior capillaries with a network-like configuration and the straighter peripheral capillaries where the pattern is more irregular. Anteriorly the capillaries end at the site of the ora serrata. Posteriorly, there is a sharp delineation at the site of entrance of the optic nerve.

The only capillaries in the choroid are located in the choriocapillaris. All vessels that supply and drain the choriocapillaris enter from the choroidal side (Torczynski, 1982).

1.2.1.2 The ciliary body

The ciliary body extends from the ora serrata, where the peripheral retina ends, to the root of the iris. In the meridian plane, the ciliary body is divided into the pars plana or orbicularis ciliaris and the pars plicata or corona ciliaris. The pars plana begins at the site of the ora serrata and ends distally in a thickened folded part, the pars plicata. The latter surrounds the main parts of the ciliary muscle. The connective tissue components anchor the ciliary body and the entire uvea behind it to the scleral spur (Figure 1.2.1.2.1).

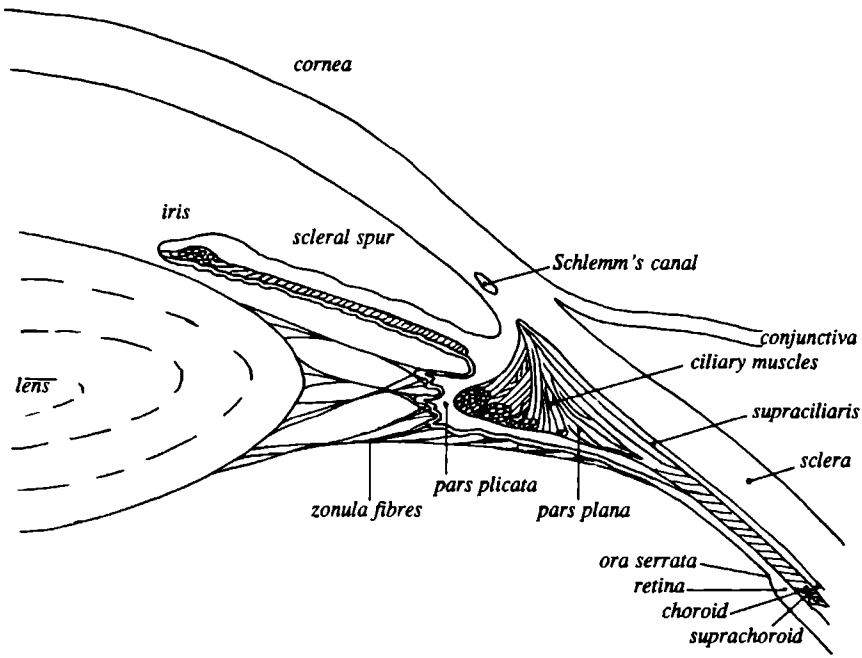


Figure 1.2.1.2.1 Anatomy of the ciliary body and the iris (after: Duke-Elder, 1946; Feneis, 1974; Bloom and Fawcett, 1975; Gardner et al., 1975; Langman and Woerdeman, 1975; Ferner and Staubesand, 1978).

From the inside (vitreal) to the outside (scleral) the ciliary body consists of (Duke-Elder, 1946; Jakobiec and Ozanics, 1982):

1. the internal limiting membrane, continuous with that of the retina;
2. the neuroectodermal unpigmented ciliary epithelium, a continuation of the neurosensory retinal tissue, which is responsible for the production of aqueous humour;
3. the neuroectodermal pigmented ciliary epithelium, a continuation of the retinal pigment epithelium;
4. the connective tissue stroma, which contains the ciliary muscles, nerves and

vessels; the stroma with the blood vessels constitutes the core of the ciliary processes;
5. the supraciliaris, a continuation of the lamina suprachoroidea, a loose fibroelastic tissue which connects the ciliary portion of the uvea with the sclera.

1.2.1.3 The iris

The anterior part of the uvea is formed by the iris. The thickness of the iris varies, with an average of 0.6 mm. In the horizontal plane a division may be made into the pupillary and the ciliary zone. The iridal stroma is continuous with the ciliary body.

Proceeding from the anterior chamber towards the lens, the uveal portions include (Jakobiec and Ozanics, 1982):

1. the anterior border layer, a discontinuous endothelium-like layer with fibroblasts, pigment and nerve cells; the colour of the iris depends primarily on the thickness of this layer and the amount of pigment it contains;
2. a thin fibrous layer, the anterior layer of the stroma;
3. the posterior layer or deep mesodermal layer which provides the supporting and supplying connective tissue together with nerves and blood vessels;
4. the sphincter muscle;
5. the dilator muscle;
6. the pigmented iris epithelium;
7. the pigmented posterior epithelium, a continuation of the unpigmented ciliary epithelium;
8. the lamina basalis, a forward extension of the retinal and ciliary basement membrane.

1.2.1.4 Uveal blood supply

The choroid receives its blood from three sources, all of them orbital branches of the ophthalmic artery which in its turn is a branch of the internal carotid artery. These three sources are the short posterior ciliary arteries, the long posterior ciliary arteries and the anterior ciliary arteries. Although the retinal vessels also arise from the ophthalmic artery, these two systems are entirely separate and distinct (Torczynski, 1982). The retina is supplied with blood by the central retinal artery, a branch of the ophthalmic artery which pierces the optic nerve to reach the retina (Figure 1.2.1.4.1).

The posterior ciliary arteries as a rule arise from the ophthalmic artery in two trunks, the nasal and the temporal (lateral) ciliary arteries, from which arise the long and short posterior ciliary arteries (Hayreh, 1975). Variations are frequent and six to eight branches, a combination of long and short posterior ciliary arteries, may arise directly from the ophthalmic artery. The pattern of scleral canals, through which the posterior ciliary arteries enter the sclera, is relatively constant, however. The lateral trunk of the ciliary arteries as a rule ultimately supplies a larger portion of the choroid than the medial trunk. The dividing line between the two areas of blood supply passes through the papilla

(Hayreh, 1975) The arterial and venous systems of the choroid do not parallel each other as is usual elsewhere in the body (Torczynski, 1982).

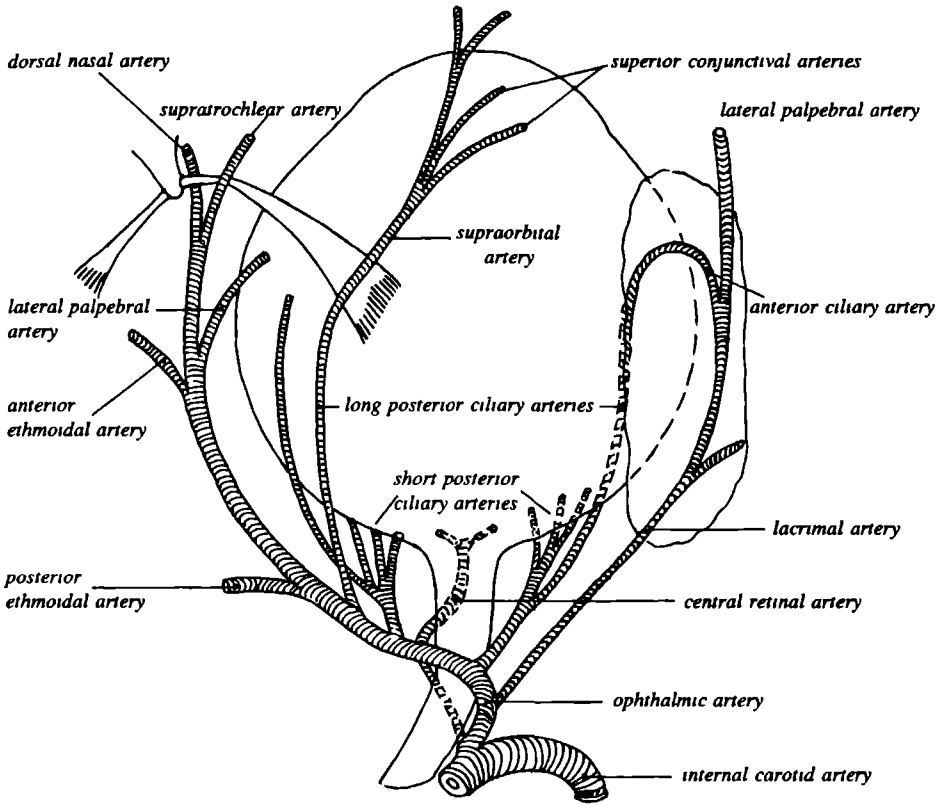


Figure 1 2 1 4 1 Arterial blood supply of the eye (after Duke-Elder, 1946, Fenels, 1974, Gardner et al , 1975, Langman and Woerdeman, 1978)

Fifteen to 20 ***short posterior ciliary arteries***, arising from the ophthalmic artery or the combined ciliary arteries, pierce the sclera near the optic nerve. The vessels are not distributed symmetrically round the disk but cluster in groups round the horizontal meridian, more vessels as a rule being situated temporally than nasally. The arteries are located between the optic nerve and the wreath of ciliary nerves, i e not farther than 2 to 2 5 mm from the dural sheath of the disk. Most vessels are found laterally and slightly inferior to the horizontal line at the site of the temporal border of the optic nerve, posterior to the site of entrance of the canal for the long temporal posterior ciliary artery and nerve (Torczynski, 1982). They pass the sclera at the level of the macula (Hayreh, 1975). A few short ciliary arteries enter above and below the optic nerve and a smaller cluster occurs nasally (Torczynski, 1982). The part of the fundus that is supplied by each individual artery varies markedly in size, shape and localization (Hayreh, 1975).

The short posterior ciliary arteries branch in the suprachoroid or in the outer layer of the choroid, and the choroidal branches radiate towards the equator in the outermost layer of the choroid. Some branches curve in a posterior direction to supply the choriocapillaris adjacent to the optic nerve. The short posterior ciliary arteries terminate principally in the choroid (Torczynski, 1982). Each terminal choroidal arteriole supplies a small segment of the choriocapillaris, bringing about a mosaic-like segmentation (Hayreh, 1975). In addition they supply the episcleral plexus, contribute to the pial plexus of the optic nerve and form the circle of Zinn-Haller, which is often incomplete. Occasionally, a branch enters the retina as a cilioretinal artery (Torczynski, 1982).

Two branches of the ophthalmic artery or of the two respective ciliary trunks constitute the nasal and temporal ***long posterior ciliary arteries***. In the orbit they run parallel to the optic nerve and pierce the sclera together with the long posterior ciliary nerve, 3 or 4 mm distant from the optic nerve and outside of the ring of the short ciliary nerves. These canals are 3 to 7 mm long and pass the sclera obliquely. The artery enters the suprachoroidal space posterior to the equator and slightly anterior to the macula. Generally, the long temporal posterior ciliary artery passes the sclera and the suprachoroid without ramifications, although these have been described in the scleral canal (Duke-Elder, 1946; Torczynski, 1982). The temporal long posterior ciliary artery supplies a part of the choroid directly behind the equator, virtually immediately from the moment when the artery pierces the sclera (Hayreh, 1975). The tributary of the temporal artery turns posteriorly and enters the submacular choroid. The main trunk of the artery branches anterior to the ora serrata, giving off a few recurrent branches to the anterior choroid, either directly to the choriocapillaris or as branches of the major anterior circle of the iris. The principal trunks of the long posterior ciliary arteries terminate in the major arterial circle of the iris (Figure 1.2.1.4.2).

The muscular arteries of the four rectus muscles of the eye follow the tendons to their scleral insertions where they pierce the sclera as the ***anterior ciliary arteries***. They are branches of the lacrimal artery which in its turn is a branch of the ophthalmic artery. The superior, medial and inferior rectus muscles each contain two arteries, while the lateral rectus muscle contains one. Other small branches of the muscular arteries supply the anterior conjunctiva, the episclera and the sclera near Schlemm's canal. The anterior ciliary arteries pass the sclera and the suprachoroidal space, enter the ciliary muscle and join the major circle of the iris. The latter does not constitute one single vessel but rather, an arterial plexus in the root of the iris which encircles the uvea anteriorly. Ten to 12 recurrent branches from the major arterial circle posteriorly enter the choroid for the blood supply of the choriocapillaris anterior. Recurrent branches anastomose with the choroidal branches of the short posterior ciliary arteries (Duke-Elder, 1946; Torczynski, 1982).

The ciliary blood supply is provided by the two long posterior ciliary arteries and by the anterior ciliary arteries. The posterior ciliary arteries run forward in the suprachoroidal space and close to the posterior margin of the ciliary body divide into two or more parts. These parts run forward to anastomose with branches of the anterior ciliary arteries and form the major arterial circle of the iris. This circle is situated just behind the root of the iris in front of the radial part of the ciliary muscle (Streeten, 1982).

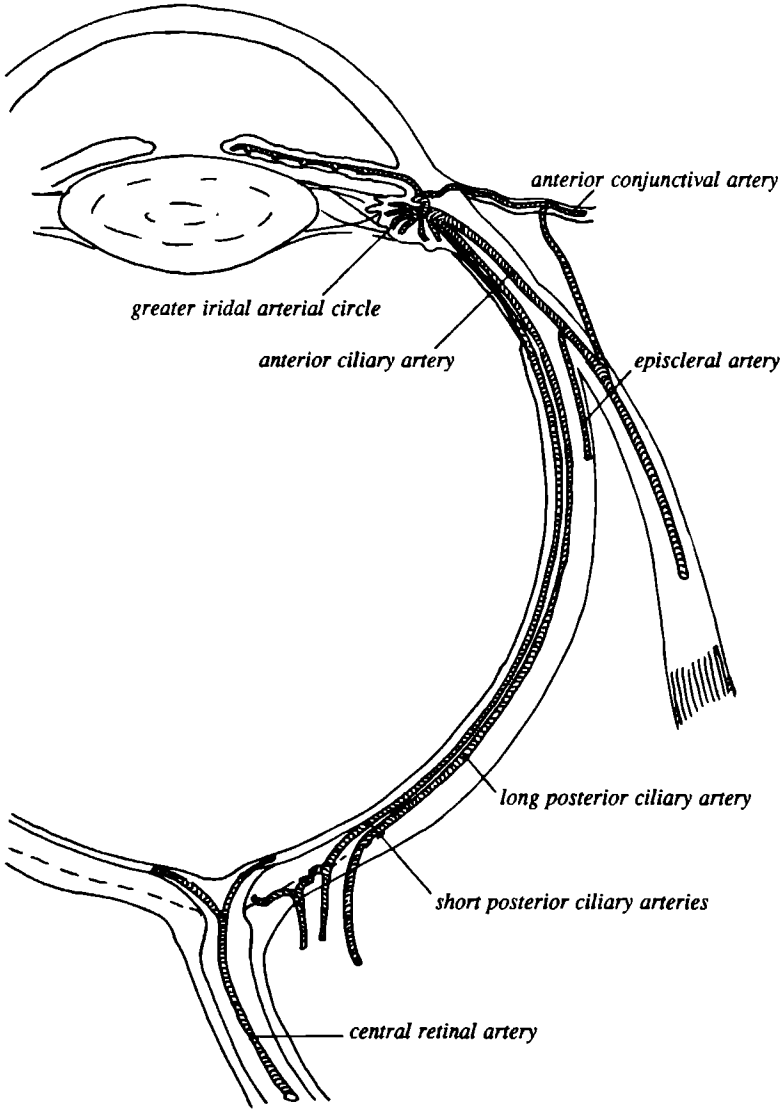


Figure 1.2.1.4.2 Arterial blood supply of the eye (after: Duke-Elder, 1946; Gardner, 1975; Ferner and Staubesand, 1978; Langman and Woerdeman, 1978; Schiebler and Schmidt, 1981).

The iris receives its arterial blood supply from the major arterial circle at the root of the iris in the stroma of the ciliary body. Branches of the minor circle also extend backward to supply the posterior part of the iris (Rodrigues et al., 1982).

The veins of the anterior uvea run a relatively straight, and those of the posterior pole a tortuous course. The entire choroid as well as a large part of the anterior uvea are

drained by the four vorticose veins (Duke-Elder, 1946; Torczynski, 1982) from a well-circumscribed segmental distribution of the veins in the choroid, ciliary body and iris (Hayreh, 1975). The four vorticose systems are formed by the confluence of choroidal veins and are situated in the oblique quadrants, two superior and two inferior, from where they curve to a central dilated ampulla Each ampulla narrows at the internal opening of the scleral canal and then becomes a vorticose vein. The ampullae and the veins draining into them are situated for the greater part in the outermost layer of the choroid and can easily be separated from the internal layers of the choroid. Venous anastomoses occur frequently

Part of the uveal blood of the iris and the ciliary body leaves the eye through a scleral plexus of anterior scleral (ciliary) veins near the limbus The vorticose veins drain into the superior and inferior orbital veins and leave the orbit through the superior and inferior orbital fissures (Duke-Elder, 1946, Rodrigues et al., 1982; Streeten, 1982; Torczynski, 1982). These veins debouch into the sinus cavernosus (Jakobiec and Ozanics, 1982).

1.2.2 Pathophysiology of uveal metastases

A metastasis is a secondary malignant lesion detached from the primary tumour. Virtually all malignant tumours have the capacity to metastasize which, however, varies greatly from one tumour to another. This variability is determined inter alia by factors such as histological characteristics, localization and size of the primary tumour Cells within one single tumour display a substantial variability This heterogeneity may result in distinct cytological differences between the primary tumour and the metastases (Spremulli et al., 1985)

Metastatic cells may be transported via lymphatic, venous or arterial canals or via pleural, peritoneal and cerebrospinal fluids If a tumour is to cause distant metastases, it has to have access to one of the above-named systems Malignant cells have to be detached and to survive in the transporting medium. Subsequently, they have to be arrested in a target organ, become implanted there and be provided with a new blood supply (del Regato, 1977, Spremulli et al., 1985).

Apart from, for instance, local invasion of epitheliomas or melanomas of the conjunctiva and of retinoblastomas, secondary tumours of the uvea always have a haematogenous pathogenesis. The eye is not included in the lymphatic drainage system (Bloom and Fawcett, 1975; Arné and Mathis, 1986) A few authors are of a different opinion, however Behr (1922) speaks of the 'Lymphbahnen der Chorioidea' and Pressburger (1927) of the lymph flow in the suprachoroidal space. Thomas and Sladden (1927) believed that there existed an invasion route along lymphatic canals to the posterior pole, which subsequently might extend forward via infiltration. Stuble (1922) described lymphatics in the iris, the ciliary body and the choroid. François et al (1967) described a canal-like network in the iris connected with the ciliary body and the choroid. Connections between the choroid and lymphatics were also postulated by Gruntzig (1982). Nemeth (1934) was of the opinion that the choroid is connected by lymphatics with the subclavian trunk and the jugular vein and that iridal metastases might be caused by a lymphogenous pathway. Shields (1983), on the other hand, declares that the intraocular structures possess

no lymphatic canals and that the uvea and retina can only be reached by metastases via a haematogenous route.

Two basic hypotheses to explain the pattern of haematogenous metastasization exist: the direct hypothesis and the cascade theory.

The direct hypothesis postulates that spread of neoplastic cells is a process in which distant metastases are the result of direct haematogenous dissemination from the primary tumour. The cascade theory, on the other hand, premises a process in several steps (Spremulli et al., 1985).

Bross et al. (1975) published a study on the pattern of metastasization in 4728 patients who had been subjected to autopsy. The findings demonstrated that in metastases a cascade process played a part in which in general one or several intermediary sites were involved, mostly the lung and the liver. These localizations in their turn might function as sources for further metastasization. Every step of the metastatic cascade appears to be a highly selective process. Only a small portion of the total number of cells become detached from the primary tumour and an even smaller portion of these survive the dissemination and are arrested elsewhere in the vascular system. Taking into account the interactions of the arrested cells with the local normal tissue, with regard to neovascularization and attacks by the defense mechanism of the host tissue, it is not surprising that only few of the remaining cancer cells survive and multiply to become metastases (Weiss, 1977; Spremulli et al., 1985). Although the localizations of metastases vary greatly, typical patterns of spread of various neoplasms can be described (Sugerbaker, 1981).

Different types of cancer cells vary greatly in their capacity of remaining viable at a distance from the primary tumour. In addition, certain inconstant immunological factors may play a part. Breast cancer cells, which are known to be very hardy, may survive and even multiply in circumstances unfavourable for other types of cancer cells (Reese, 1976).

It is therefore improbable that metastatic cells reach the eye in other ways than via the bloodstream (Ewing, 1890; Elschnig, 1891; Ask, 1934; Duke-Elder and Perkins, 1966; Ferry, 1967; Castro et al., 1982; Shields, 1983; Arné and Mathis, 1986).

Malignant cells may reach the vascular canals round the primary tumour following which they may pass through the pulmonary circulation. Subsequently they may be carried, whether or not as tumour emboli, through the heart to the aorta and the common carotid artery (Ferry, 1967). Owing to the right angle at which the ophthalmic artery arises from the internal carotid artery, it is difficult for metastatic cells in the bloodstream to reach the eye (Mullen et al., 1954; Ferry, 1967; Offret and Haye, 1971; Cieplinski et al., 1982). The brain and meninges could then be reached easier (Ellett, 1944; Duke-Elder and Perkins, 1966).

Unlike the tumour cells that reach the left common carotid artery, which arises directly from the aorta, the tumour cells have to follow a different route to the right common carotid artery, namely via the arteria innominata (the brachiocephalic trunk) (Ferry, 1967). This anatomical difference between the left and right common carotid arteries is regarded by certain authors as the cause of uveal metastases occurring more frequently in the left than in the right eye (Sattler, 1926; Ellett, 1944; Stevens and Reeh, 1958; Eross, 1959; Hart, 1962; Jensen, 1970; Meythaler and Herold, 1979).

Cieplinski et al. (1982) declare that for uveal metastases to develop tumour emboli rather than loose tumour cells are required. For this reason, pulmonary metastases ought

to be nearly always present. However, according to several investigators the lungs may be bypassed via Batson's plexus (Batson, 1940; Hogan and Zimmerman, 1962; Ferry, 1967; Castro et al., 1982). By this route, tumour cells are guided to the above-named vertebral system. Via the cranial venous sinuses the vorticose veins are ultimately reached. Batson's plexus contains no valves. Reversal of the flow is possible by changes in body posture and Valsalva manoeuvres. This might possibly explain the relatively high frequency of intraocular metastases of carcinomas of prostate and kidney but fails to account for the rarity of metastases of bladder cancer. Possibly, the uvea is not a good nutrient medium for bladder cancer (Cieplinski et al., 1982; Dieckert and Berger, 1982). Allegedly, many skeletal metastases may also come into being via the paravertebral canals (del Regato, 1977).

In haematogenous spread of tumour cells the distribution of the cellular agglomerates in the bloodstream may be of decisive importance. The smaller bacterial and viral tumour emboli are carried along in the centre of the bloodstream and reach the terminal circulation. Therefore, infectious emboli more readily proceed to the retina (Hart, 1962). Malignant tumour cell emboli, on the other hand, remain at the periphery of the bloodstream and tend more to follow the smaller arteries branching off, such as the choroidal vessels (Maxwell, 1954; Schiffer et al., 1978). The probability that malignant tumour cells reach the iris or the ciliary body is lower because of the flow conditions (Adda, 1937). Metastases in muscle tissue are rare, which is probably one of the reasons why few metastases are encountered in the ciliary body. Possibly, muscular movements in the iris and the ciliary body impede the implantation and growth of metastases (Ask, 1934). If the ciliary body is reached by tumour cells, the emboli usually are arrested there, which allegedly is why metastases occur less frequently in the iris (Sanders, 1938).

Most uveal metastases are localized in the choroid (Abramson, 1984). Because the short posterior ciliary arteries, which supply the posterior pole, are far more numerous than the long posterior ciliary arteries, which supply the anterior uvea, most tumour emboli pass through the short ciliary arteries and in particular reach the temporal choroid, which is supplied by the most numerous and largest blood vessels (Lemoine and McLeod, 1936; Kreibig, 1937; Duke-Elder and Perkins, 1966; Reese, 1976; Castro et al., 1982; Cieplinski et al., 1982; Shields, 1983). Terrien (1929) was of the opinion that the short ciliary arteries owing to their smaller calibre were less accessible to metastases and that the tumour emboli would already be stopped at the site of penetration of the vessels through the sclera.

Possibly, in many patients with a carcinoma, tumour emboli do reach the eye but they do not succeed in multiplying there and clinically no distinct lesions develop (Ferry, 1967). A tumour embolus which reaches the uvea may block the small blood vessels by proliferation of tumour cells. The malignant cells then infiltrate the intervascular space and spread in the direction of least resistance (Adda, 1937; Stallard, 1940; Leopoldsberger, 1943; Bonnet and Jambon-Genet, 1948; Castro et al., 1982).

Coman et al. (1951), as part of a study of the mechanism of metastases, carried out an experimental investigation in rabbits. They injected malignant tumour cells intracardially, following which metastases developed throughout the animal. They concluded that the rarity of metastases in certain organs is due not to chemical inhibition but to the fact that too few emboli reach these organs. The distribution of metastases could be explained by the mechanism of the circulation with the resulting distribution of tumour

emboli.

Basu et al. (1962) injected cell suspensions of a malignant tumour into the right common carotid artery in 256 rats. Forty per cent of the animals developed tumours in eye or orbit after three to five days. Metastases in the lungs were encountered in 95% and in the brain and meninges in 40%. In this connection an agglomeration of more than four cells was called a tumour. Unlike the situation in man, however, the rat eye receives its blood supply both via the external carotid artery (ocular muscles, orbit, long and short ciliary arteries) and via the internal carotid artery (retina, anastomoses with long ciliary arteries). Most metastases were encountered in the right orbit and eye. Of the intraocular tissues, the uvea was involved most frequently. Basu et al. in this study tested two hypotheses: first, the possibility that the implantation of tumour emboli at particular sites and their further development into metastases are determined by local biochemical factors (the soil theory); second, that the distribution of metastatic tumours depends predominantly on the circulation and consequently, on the number of tumour emboli that reach the organ in question and are arrested there (the mechanical theory). They preferred the latter, mechanical hypothesis: the intra- and extraocular tissues are fairly susceptible to metastases. For a metastasis to develop, a tumour embolus of two to four cells suffices. Most animals with ocular metastases also had metastases in the brain and meninges suggesting that anatomical factors play a part.

Frank et al. (1987) also injected tumour-cell suspensions into the internal carotid artery of 15 rabbits, following which 87% of the animals developed ocular and 93%, cerebral metastases. The blood-eye and blood-brain barriers were passed after five to seven days.

Albert et al. (1967b) in an animal experiment studied the fate of circulating tumour cells after injecting cells of transplantable tumours into the left ventricle of rabbits. In 20 of the 33 fully grown animals (61%) metastases developed in 34 eyes. No relationship with the age of the animals was found. It was interesting to note that the metastases were largely restricted to the iris, ciliary body and anterior part of the choroid (81%) while only a small proportion (12%) was localized in the posterior part of the choroid (7% other intraocular structures). The development of metastases proved independent of the concentration of the cells arrested in the area in question: in 14 grown animals, 173 arrested clusters of tumour cells and separate cells were encountered, viz. 77 in the anterior uvea and 91 in the medial and posterior uvea where, as mentioned, far fewer metastases developed (retina and optic nerve: 5). The authors concluded that in this experiment far more metastases developed than was known from clinical studies, possibly due to the direct injection of tumour cells into the arterial system.

It is noteworthy that in animals most metastases develop in the anterior uvea (Basu et al., 1962; Barron et al., 1963). In humans, on the other hand, metastases are mostly encountered in the posterior choroid. Although most tumour emboli get stuck in the medial and posterior parts of the choroid, the study of Albert et al. (1967b) revealed only few metastases there: the distribution of metastases, therefore, does not completely follow the distribution of the tumour emboli. This is in contrast to the studies mentioned earlier. Factors concerned with metastases in the eye may be different from those elsewhere in the body. Differences in structure and function between the various regions may play a part in this connection. For instance, the secretion of aqueous humour might promote the development of metastases (Albert et al., 1967b). Jampol et al. (1973) also made observations supporting this hypothesis.

In contrast to clinical studies, Albert et al. (1967b) observed as many metastases in

young animals as in fully grown rabbits: intraocular metastases, namely, developed in 12 of the 16 young rabbits (75%); these were all bilateral and the distribution was the same as that in the grown animals. Compared with control (grown) animals, the metastases in the young rabbits developed after a significantly shorter interval and the intraocular metastases were also larger after an identical interval.

In 33 animals (17 grown and 16 young ones) a complete autopsy was performed. This revealed intraocular metastases in 64% of the animals (21 animals), while 52% had metastases in the lungs, 52% in the kidneys, 48% in the liver, 42% in the adrenals, 30% in the brain, 12% in the skin, 9% in the mesentery and 3% in the digestive tract. In contrast to the other localizations, the eye was rarely found to hold more than three metastases. It was concluded that the incidence of metastases in the eye was similar to that of metastases in other organs (Albert et al., 1967b).

From these various experimental studies in animals we may conclude that there are indications that both the soil theory and the mechanical theory may play a part in the pathogenesis of uveal metastases. After direct injection of malignant tumour cells into the bloodstream, most of the test animals developed uveal metastases, which were predominantly localized in the anterior part of the uvea. Frequently, pulmonary and cerebral metastases were then encountered as well.

In humans of all ocular tissues the uvea is most frequently affected by metastases. However, metastases may also occur in other ocular structures (Table 1.2.2.1).

Table 1.2.2.1 Localization of intraocular metastases

	Bloch and Gartner, 1971		Ferry and Font, 1974		Hutchison and Smith, 1979		Castro et al., 1982	
Localization	N	%	N	%	N	%	N	%
Uvea	22	78	196	86	73	64	80	63
Orbit	4	14	48	21	32	28	38	30
Optic nerve	6	21	26	11	3	3	5	4
Retina	4	14	-	-	3	3	4	3
Sclera	3	11	-	-	-	-	1	1
Extraocular muscle	1	4	-	-	-	-	-	-
Eyelid	-	-	-	-	3	3	3	2

total % exceeds 100 because of multiplicity of sites in individual eyes and patients

In ophthalmological practice metastases in the orbit are the second most frequent, after uveal metastases. It is difficult in these cases to determine precisely which tissues in the orbit have been infiltrated by malignant cells. In general the bone, the muscles and the orbital fat are involved. The ratio of these is approximately 2:2:1. However, the various primary tumours show different localizations of predilection. For instance, metastases of carcinoma of the prostate are usually localized in the bony orbit, metastases of breast cancer in the orbital fat and the muscles and metastases of cutaneous melanoma in the muscles (Goldberg et al., 1990). Metastases localized in the extraocular muscles of the

eye are rare (Ashton and Morgan, 1974; Capone and Slamovits, 1990). The survival of patients with orbital metastases is usually better than that of patients with uveal metastases (Font and Ferry, 1976; Freedman and Folk, 1987).

The oculomotor nerve, the trochlear nerve and the abducens nerve may be involved in a systemic malignancy in the form of meningeal carcinomatosis or a metastasis in the apex of the orbit (Bullock and Yanes, 1980). If a metastasis is localized in the optic nerve, it usually affects the parenchyma rather than the sheath of the optic nerve (Ginsberg et al., 1970; Arnold et al., 1981).

Metastases in the retina occur only rarely and are described virtually exclusively as case histories (Klein et al., 1977; Young et al., 1979; Letson and Davidorf, 1982; Leys et al., 1990). Metastases in the conjunctiva and sclera are also exceptional (Thiel, 1928; Eichholtz, 1971; Radnot, 1977; Daicker et al., 1988). Regarding metastases in the eyelid, there have been only sporadic publications (Seddik et al., 1968; Kindermann et al., 1981; Shields et al., 1988a). A few times, patients have been described with metastatic cells in the vitreous or the anterior chamber without presence of a distinct intraocular tumour (Char et al., 1980; Piro et al., 1982).

1.3 Epidemiology

1.3.1 Frequency

In the first half of this century, uveal metastases were regarded as extremely rare (Lagrange, 1901; Sattler, 1926; Casanovas, 1936; Asbury and Vail, 1940; Greear, 1950; Mayer and Nassar, 1958). There were, however, a number of investigators according to whom these intraocular metastases occurred more often than reported up to then (Devereux Marshall, 1902; Van der Hoeve, 1927; DeLong, 1933; Ask, 1934; Adda, 1937; Lopes d'Andrade, 1949).

By the time several hundreds of case reports of patients with intraocular metastases had been published, as well as a number of review articles on this subject, it became clear that the frequency of uveal metastases was higher than had so far been assumed in the literature (Dickson, 1958; Gerhard et al., 1975; François et al., 1976).

Table 1.3.1.1 presents a survey of a number of publications in which the total number of uveal metastases with the preceding primary tumour is stated up to the moment of publication of the article in question.

This table first of all shows that the data in the various articles are incomplete and that the authors disagree regarding the condition or the primary tumour. For instance, according to Bietti (1938) reports of 28 uveal metastases of pulmonary tumours had been published, while Streiff (1949) 11 years later referred to only 18 cases. In addition, it is noticeable that the proportion of breast cancer decreased from about 80% in the last century to 64% according to the study of Schiffer et al. in 1978. The more patients with uveal metastases were described, the more cases were published of patients with metastases of primary tumours reported only sporadically or not at all.

The increased frequency of uveal metastases diagnosed is probably partly due to the improvement of the prognosis of patients with a malignancy resulting from, for instance, chemotherapy (Alberti and Halama, 1987). The improved recognition of the ocular lesion over the years is also of great importance (Brink et al., 1988). Dickson (1958) named improved follow-up of oncological patients and closer cooperation between the various specialists as additional causes of the more frequent diagnosis of uveal metastases.

It is assumed that 2 to 9% of all intraocular tumours are metastases (Wilder, 1946; Spaeth, 1951; Bellone and Cagigrigoriu, 1969; Farnarier et al., 1972). Primary melanomas of the uvea are encountered more frequently (Hart, 1962; Offret and Haye, 1971; Aasved and Seim, 1973; Ferry, 1973; Ferry and Font, 1974). In Table 1.3.1.2 the numbers of uveal metastases are compared with the numbers of primary malignant melanomas of the uvea as reported by several authors.

The table shows that uveal melanomas occur more often than uveal metastases. In clinical studies the proportion of metastases in relation to melanomas is far larger than that found at histopathological examination. It should be noted in this connection that the histopathological patient material had been largely obtained by enucleation of eyes suspected of a malignant uveal melanoma. This obviously influenced the ratio of metastases versus melanomas. Although, therefore, melanomas are diagnosed more often than metastases of the uvea, various investigators point out that actually, metastases are

Tabel 1.3.1.1 Survey of publications on uveal metastases according to the total numbers of patients and the primary tumour

	Total	Breast		Lung		Genital		Skin		Gastro-intestinal		Miscel-laneous		Unknown	
Author	N	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Perls, 1872	1	-	-	1	100	-	-	-	-	-	-	-	-	-	-
Schultze, 1890	5	4	80	1	20	-	-	-	-	-	-	-	-	-	-
Elschnig, 1891	8	6	75	1	13	-	-	-	-	1	13	-	-	-	-
Schultze, 1893	16	13	81	2	13	-	-	-	-	1	6	-	-	-	-
Lagrange, 1901	25	19	76	3	12	-	-	1	4	1	4	1	4	-	-
Krukenberg, 1903	37	27	75	4	11	-	-	-	-	3	8	2	6	1	/
Usher, 1923	90	65	72	10	11	2	2	-	-	6	7	7	8	-	-
Ask, 1934	211	123	67	20	11	9	5	4	2	15	8	12	7	28	/
Lemoine and McLeod, 1936	231	135	67	24	12	10	5	4	2	16	8	14	7	28	/
Bietti, 1938	267	157	66	28	12	14	6	4	2	19	8	17	7	28	-
Streiff, 1949	300	218	73	18	6	16	5	4	1	24	8	20	7	-	-
Hollwich and Lemke, 1965	530	336	63	87	16	36	7	10	2	30	6	31	6	-	-
Seddik et al., 1968	752	494	67	109	15	42	6	4	1	41	6	43	6	19	/
Schiffer et al., 1978	745	477	64	117	16	46	6	* 22	* 3	44	6	39	5	-	-

* *skin and bone*

the most frequent intraocular tumours (Bloch and Gartner, 1971; Ferry, 1973; Ferry and Font, 1974; Daicker, 1981; Abramson, 1984).

Table 1.3.1.2 Frequencies of occurrence of uveal metastases and uveal melanomas

	Uveal metastases		Uveal melanomas	
Author	N	%	N	%
Clinically:				
Albert et al., 1967	*# 24	28	61	72
Godtfredsen, 1944	* 6	25-33	-	67-75
Brink et al., 1988	* 47	14	-	86
Histopathologically:				
Wilder, 1946	2	6	30	94
Heath, 1964	** 6	5	113	95
Ferry en Font, 1974	196	4.2	4500	95.8
Hart, 1962	133	3.2	4000	96.8
Jensen, 1970	18	1.9	942	98.1
Lommatzsch et al., 1985	*** 3	0.1	2678	99.9

** choroid; ** iris; ** intraocular, probably all uveal;*
 # according to Ferry (1967) 24 of the 45 metastases localized in the uvea

Jensen (1970) reported 18 uveal metastases among 4.3 million inhabitants of Denmark over the period 1944-1968: an incidence of 1.7 per 100.000 inhabitants per year. François et al. (1976) mentioned a similar incidence, of 2 per 100.000.

However, according to Nelson et al. (1983) in the United States at least 16.000 patients who die from a malignancy per year develop intraocular metastases. Breast cancer by itself would already account for 10.000 intraocular metastases annually (Abramson, 1984). Bence (1985) calculated that theoretically ocular and orbital metastases might occur in 21.000 to 45.000 patients per year, as against the far smaller number of 1500 to 2000 uveal melanomas. This would put the incidence figures for uveal metastases between 5 and 15 per 100.000 inhabitants per year.

The incidence of malignant uveal melanomas is in the range of 0.4 to 0.9 per 100.000 inhabitants (Lommatzsch et al., 1985; Egan et al., 1988; Mahoney et al., 1990).

Establishing the frequency of uveal metastases and comparing it with the frequency of other intraocular tumours is very difficult for a number of reasons:

- The various publications refer to patients from either clinical or histopathological populations. The histopathological patient group is characterized by a relatively large number of patients with suspicion of a malignant melanoma. Consequently, these different patient populations should not be compared with one another just like that.
- The data originate from far-apart years with altered interest in particular diseases and with new diagnostic possibilities.

- A major problem in establishing the frequency of uveal metastases is due to the fact that these tumours do not necessarily cause symptoms, especially when they are localized outside the macular area. In that case they might frequently remain unnoticed (Aasved and Seim, 1973; François et al., 1976).
- If the patient's visual acuity is poor due to amblyopia or opaque media, this may cause the metastases to escape notice (Thompson et al., 1961).
- Intraocular metastases occur particularly often in oncological patients in a terminal phase (Gillet, 1971). The patient's bad general condition may then render him unable to mention any symptoms, or systematical ophthalmological examination may no longer be considered feasible (Greear, 1950; Hart, 1962; Gillet, 1971; Aasved and Seim, 1973; François et al., 1976; Daicker, 1981; Castro et al., 1982; Letson et al., 1982; Bence, 1985; Arné and Mathis, 1986). Another possibility is that the physician in charge underestimates the severity of the possible visual symptoms or blames them on the many drugs administered (Thompson et al., 1961; Viegas Mendonça and Ferraz de Oliveira, 1968; Daicker, 1981; Letson et al., 1982). In addition, the physician in charge frequently is not an ophthalmologist but a surgeon or internist (Thompson, 1961; François et al., 1976; Reese, 1976).
- There may be a long interval between the detection of the primary tumour and the onset of the intraocular lesion. The uveal metastases may then not be recognized as such and the tumour in the eye may not be connected with an earlier malignancy (Viegas Mendonça and Ferraz de Oliveira, 1968).
- Post-mortem examination of a patient with a neoplasm as a rule does not include histopathological examination of the eye (Hogan and Zimmerman, 1962; Viegas Mendonça and Ferraz de Oliveira, 1968; Aasved and Seim, 1973; François et al., 1976; Castro et al., 1982). If performed at all, the examination as a rule is restricted to the posterior segment of the eye (Reese, 1976). Also, unlike eyes with uveal melanomas, eyes with metastases are rarely enucleated, so that no pathological examination is performed. As mentioned before, this fact naturally is extremely relevant to the patient populations of pathological institutes (Bence, 1985).

Table 1.3.1.3 summarizes the data from the literature on the frequency of uveal metastases in a patient population with known malignancies. Clinically uveal metastases were observed in 0.07 to 2.3% of the patients, and at pathological examination in 0.5 to 11%.

Table 1.3.1.4 lists the frequencies of intraocular metastases according to the nature of the primary tumours. The data of Godtfredsen (1944) originate from a radiotherapeutic institute and represent proportions of all patients known with malignancies. However, these patients were not examined systematically, in contrast to the study of Albert et al. (1967), in which patients with a malignancy were examined with the specific purpose of finding choroidal metastases.

If the eyes of patients with known malignancies were examined histopathologically, metastases were found much more frequently than at clinical examination. According to Nelson et al. (1983), 90% of the metastases demonstrated histopathologically are not noticed clinically.

The data in Table 1.3.1.4 show that breast cancer relatively frequently causes intraocular metastases. Table 1.3.1.5 presents a survey of the frequency of intraocular metastases in patients with breast cancer.

Table 1.3.1.3 Frequency of uveal metastases in a patient population with known malignancies

Author	Number of patients with malignancy		Uveal metastases N	%
Clinically:				
Gailloud, 1975	1500	**	1	0.07
Godtfredsen, 1944	8712	*	6	0.07
Thompson et al., 1961	11000	*	11	0.1
Albert et al., 1967	# 213	*	5	2.3
Histopathologically:				
Guthert et al., 1965	1000	*	5	0.5
	# 594	*	5	0.8
Kunze and Wurgatsch, 1972 ∞	569		8	1.4
	# 336		8	2.4
Nelson et al., 1983	## 530	*	15	2.8
	### 376	*	15	4.0
Bloch and Gartner, 1971	230		22	9.6
Timm, 1967	80		9	11

** choroid; ** probably choroid; # patients with disseminated malignancies; ## malignancy at moment of death; ### died of malignancy; ∞ all malignancies except bone marrow, lymph nodes and thymus*

Table 1.3.1.5 Frequency of intraocular metastases in patients with breast cancer

Author	Total number of patients with breast cancer N		Intraocular metastases N	%
Clinically:				
Godtfredsen, 1944	1287	choroid	2	0.2
Thompson et al., 1961	3300	choroid	11	0.3
Thatcher and Thomas, 1975	10592	choroid	42	0.4
Hemmes, 1969	*/**	uvea	92	0.5
Schinz, 1939	536	choroid	3	0.6
Röttinger et al., 1976	*	choroid	26	2
Vanni and Barilla, 1960	219	choroid	5	2.3
Albert et al., 1967	52	choroid	4	8
Mewis en Young, 1982	250	choroid	67	27
Histopathologically:				
Kunze and Wurgatsch, 1972	35	uvea	2	6
Nelson et al., 1983	31	choroid	3	10
Bloch and Gartner, 1971	52	eye/orbit	19	37

** total number of patients not mentioned; ** number of deceased patients with breast cancer*

Tabel 1.3.1.4 Frequencies of intraocular metastases according to the nature of the primary tumours

Author	Localization	Number of intraocular metastases / number of primary tumours													
		Total		Breast		Lung		Genital		Skin		Gastro-intestinal		Miscel-laneous	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%
Clinically:															
Godtfredsen, 1944	choroid	6/8712	0,1	2/1287	0,2	2/156	1,3	1/71	1,4	-/-	-	-/-	-	0/7198	0
Albert et al., 1967 *	choroid	5/213	2,3	4/52	8	1/50	2	0/8	0	-/-	-	0/30	0	0/73	0
Histopathologically:															
Kunze en Wurgatsch, 1972 **	uvea	8/569	1,4	2/35	6	5/131	4	0/98	0	0/10	0	1/179	1	0/116	0
Nelson et al., 1983 ***	choroid	15/376	4,0	3/31	10	6/89	7	0/19	0	2/25	8	3/38	8	1/174	1
Timm, 1967	uvea	9/80	11	3/8	38	2/29	7	1/14	7	-/-	-	1/17	6	2/12	17
Bloch and Gartner, 1971	eye/orbit	28/230	12	19/51	37	3/53	6	3/19	16	-/-	-	1/47	2	2/59	3

* *with widespread dissemination;* ** *excluding localizations in bone marrow, lymph nodes and thymus;* *** *patients died of malignacy*

Godtfredsen (1944), Thompson et al. (1961), Thatcher and Thomas (1975) and Röttinger et al. (1976) compared the numbers of known choroidal metastases with all patients with breast cancer diagnosed in the same period in the clinics in question. Most of these patients with breast cancer had not been subjected to ocular examination. According to Thatcher and Thomas (1975) probably not all patients with choroidal metastases were recorded so that the actual proportions of patients with metastases will have been larger.

Albert et al. (1967) and Mewis and Young (1982) in patients with known breast cancer searched specifically for choroidal metastases, and their percentages consequently are substantially larger than those of the other investigators. Albert et al. (1967) examined patients with an already metastasized carcinoma.

Of the 250 patients examined by Mewis and Young (1982), 98 had no visual complaints. Nevertheless, choroidal metastases were diagnosed in nine patients (9%). Of the 152 patients with visual complaints, 58 were found to have choroidal metastases, a proportion of 38%!

1.3.2 Primary tumours

Table 1.3.2.1 surveys, as completely as possible, the various ***primary tumours*** reported to have caused uveal metastases. For the references, a selection has been made from the various case reports and survey articles published on uveal metastases. Mostly, articles from authoritative periodicals and publications of recent data were used.

In establishing the frequency of uveal metastases (see Chapter 1.3.1), it proved difficult to compare data from different studies, and the same is true of the literature on the nature and localization of the primary tumours. The data relate to periods at long intervals, during which changes took place in frequencies of various malignancies and in diagnostic techniques, and they concern clinical studies as well as records of pathological institutes. Moreover, many publications refer to 'intraocular' metastases, without clearly stating the exact localization, or to 'choroidal' metastases, thereby excluding metastases in the iris and the ciliary body.

Tables 1.3.2.2 and 1.3.2.3 survey the primary tumours mentioned in a number of original articles from various institutes. Table 1.3.2.2 lists the absolute numbers of patients, Table 1.3.2.3 the percentages. A distinction is made between clinical and histopathological patient material.

A number of authors have further subdivided gastrointestinal and genital tumours. In such cases, the metastases originating from, for instance, the various genital tumours are added up and mentioned in parentheses in the column 'genital'. If in such a column numbers of patients are listed without parentheses, the author(s) made no subdivision of the various localizations.

Table 1.3.2.3 shows that the percentages of choroidal and uveal metastases in clinical studies match very well. The data from histopathological institutes are divergent. They refer to a smaller number of patients from only three institutes.

Table 1.3.2.1 *Survey of malignant tumours reported to have caused uveal metastases*

Breast cancer	
female	Thatcher and Thomas, 1975; Letson et al., 1982; Mewis and Young, 1982
male	Lakhanpal et al., 1982; Reynard and Font, 1983; Schlaen and Naves, 1986
Bronchial cancer	
epithelial carcinoma	Wright and Meger, 1962; Witschel et al., 1975
small cell carcinoma (oat cell)	Ferry and Font, 1975; Shields, 1983
adenocarcinoma	Walker, 1974
large cell carcinoma	Buys et al., 1982
carcinoid	Bell et al., 1975; Riddle et al., 1982; Balestrazzi et al., 1989
Gastrointestinal tract	
oesophagus	Mullaney, 1970; Mooy et al., 1990
stomach	Rootman and Butler, 1982; Takahashi et al., 1984; Karnad et al., 1986
pancreas	Stephens and Shields, 1979; Char and Christensen, 1980
liver	Taake et al., 1963; Yeatts et al., 1982
ileum carcinoid	Riddle et al., 1982
caecum	Shields, 1983
colon	Schneider and Bosshard, 1978; Nelson et al., 1983
sigmoid	Carr et al., 1986
rectum	Ferry, 1973; Cole and Farah, 1985
Urinary tract	
kidney	Voight and Pulhorn, 1977; Kindermann et al., 1981; Pau, 1981
ureter	Pe'er and Zimmerman, 1984
bladder	Gordon and Munro, 1974; Resnick et al., 1975; Cieplinski et al., 1982
Genital tract	
female	
ovary	Seddik et al., 1968; Frank et al., 1979
uterus	Keates and Billig, 1970; Haye and Calle, 1972; Pau, 1979; Planten, 1981
cervix uteri	Kurosawa and Sawaguchi, 1987; Saßmannshausen et al., 1990
vagina	Streiff, 1949
male	
testis	
seminoma	Hemmes, 1969; Freyler and Egerer, 1977
embryonal cell carcinoma	Ferry, 1973; Lodato et al., 1983
teratoma/ choriocarcinoma	Chitwood, 1953; Graether, 1963; Meythaler and Herold, 1979
epididymis	Sautter, 1948
prostate	Dieckert and Berger, 1982; Freedman and Folk, 1987; Dobrowsky, 1988

to be continued on next page

Table 1.3.2.1 (continued)

Nervous system	
neuroblastoma	Hutchison and Smith, 1979; Arné et al., 1983
adrenal gland	Guthert et al., 1965; Alio et al., 1982; Bowns et al., 1983
olfactory nerve	Davis and Robertson, 1973; Daicker, 1981
Bone	
osteosarcoma	Spaulding and Woodfin, 1968; Jampol et al., 1973; Rossano, 1973
Ewing sarcoma	Jampol et al., 1973
Skin	
eyelid	
malignant melanoma	Adamuk, 1909
basocellular carcinoma	Oksala, 1962
lip	Goodsitt, 1945; Cury, 1958; Hart, 1962
cheek (buccal)	Godtfredsen, 1944
malignant melanoma	Fishman et al., 1976; Lommatzsch and Tost, 1979; de Bustros et al., 1985; Oosterhuis et al., 1987; Eide and Syrdalen, 1990
Merkel cell carcinoma	Alexander et al., 1989; Small et al., 1990
Eye	
malignant uveal melanoma	Shields et al., 1988
malignant conjunctival melanoma	Andersen, 1947
retinoblastoma	Howard, 1962
Miscellaneous	
atrial myxoma	Stowe et al., 1979
larynx carcinoma	Bessieres et al., 1956
vocal chord	Timm, 1967
soft tissue sarcoma	Rootman et al., 1979; Pak et al., 1987
thyroid	Gysin and Gloor, 1979; Offret et al., 1979; Daicker, 1981
mediastinum	Lahav et al., 1978; Tarkkanen et al., 1979
thymoma	Tsuboi, 1934
adrenal gland	François et al., 1952
salivary gland	
parotid gland	Lommatzsch, 1989; Saßmannshausen et al., 1990
submaxillary gland	Gutman et al., 1986
submandibular gland	Jenrette and Fitzgerald, 1982

Author	Total	Breast	Lung	Parotid gland	Thyroid	Pancreas	Gastrointestinal	Stomach	Colon	Rectum	Genital tract	Prostate	Testis	Ovary	Uterus	Kidney	Skin	Neuroblastoma	Carcinoid	Miscellaneous	Unknown
Clinically:																					
Van der Hoeve, 1927	20	18	-	1	-	-	(1)	1	-	-	-	-	-	-	-	-	-	-	-	-	-
Haye and Calle, 1972	31	26	3	-	-	1	-	-	-	-	(1)	-	-	-	1	-	-	-	-	-	-
Meythaler and Herold, 1979	21	16	-	-	-	-	(1)	1	-	-	(1)	-	1	-	-	-	1	-	-	-	2
Freedman and Folk, 1987	61	29	13	-	-	-	(2)	-	2	-	(4)	1	3	-	-	-	1	-	-	7	5
Brink et al., 1988	47	36	5	-	1	1	-	-	-	-	(1)	-	1	-	-	-	-	-	-	-	3
Saßmannshausen et al., 1990	159	119	19	1	2	-	6	-	-	-	(4)	-	1	-	3	2	3	-	-	-	3
Total choroid	**339**	**244**	**40**	**2**	**3**	**2**	**(10)**	**2**	**2**	**-**	**(11)**	**1**	**6**	**-**	**4**	**2**	**5**	**-**	**-**	**7**	**13**
Hemmes, 1969	121	92	13	3	-	-	-	-	-	-	(5)	-	2	*1.5	*1 5	-	2	-	-	-	6
Stephens and Shields, 1979	70	45	10	-	-	1	3	-	-	-	-	-	-	-	-	1	3	-	1	-	6
Total uvea	**191**	**137**	**23**	**3**	**-**	**1**	**3**	**-**	**-**	**-**	**(5)**	**-**	**2**	**1.5**	**1.5**	**1**	**5**	**-**	**1**	**-**	**12**
Total choroid / uvea	**530**	**381**	**63**	**5**	**3**	**3**	**(13)**	**2**	**2**	**-**	**(16)**	**1**	**8**	**1.5**	**5.5**	**3**	**10**	**-**	**1**	**7**	**25**
Histopathologically:																					
Castro et al., 1982	51	30	19	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2	-	-	-
Total choroid	**51**	**30**	**19**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**2**	**-**	**-**	**-**
Jensen, 1970	18	6	6	-	-	-	-	-	-	-	2	-	-	-	-	1	3	-	-	-	-
Ferry and Font, 1974	196	81	62	-	1	1	(5)	1	2	2	(8)	2	6	-	-	7	-	-	-	-	31
Total uvea	**214**	**87**	**68**	**-**	**1**	**1**	**(5)**	**1**	**2**	**2**	**(10)**	**2**	**6**	**-**	**-**	**8**	**3**	**-**	**-**	**-**	**31**
Total choroid / uvea	**265**	**117**	**87**	**-**	**1**	**1**	**(5)**	**1**	**2**	**2**	**(10)**	**2**	**6**	**-**	**-**	**8**	**3**	**2**	**-**	**-**	**31**

Author	Total	Breast	Lung	Parotid gland	Thyroid	Pancreas	Gastrointestinal	Stomach	Colon	Rectum	Genital tract	Prostate	Testis	Ovary	Uterus	Kidney	Skin	Neuroblastoma	Carcinoid	Miscellaneous	Unknown
Clinically:																					
Van der Hoeve, 1927	20	90	-	5	-	-	(5)	5	-	-	-	-	-	-	-	-	-	-	-	-	-
Haye and Calle, 1972	31	84	10	-	-	3	-	-	-	-	(3)	-	-	-	3	-	-	-	-	-	-
Meythaler and Herold, 1979	21	76	-	-	-	-	(5)	5	-	-	(5)	-	5	-	-	-	5	-	-	-	10
Freedman and Folk, 1987	61	48	21	-	-	-	(3)	-	3	-	(7)	2	5	-	-	-	2	-	-	11	8
Brink et al., 1988	47	77	11	-	2	2	-	-	-	-	(2)	-	2	-	-	-	-	-	-	-	6
Saßmannshausen et al., 1990	159	75	12	1	1	-	4	-	-	-	(3)	-	1	-	2	1	2	-	-	-	2
Total choroid	**339**	**72.0**	**11.8**	**0.6**	**0.9**	**0.6**	**(2.9)**	**0.6**	**0.6**	**-**	**(3.2)**	**0.3**	**1.8**	**-**	**1.2**	**0.6**	**1.5**	**-**	**-**	**2.1**	**3.8**
Hemmes, 1969	121	76	11	2	-	-	-	-	-	-	(4)	-	2	1	1	-	2	-	-	-	5
Stephens and Shields, 1979	70	64	14	-	-	1	4	-	-	-	-	-	-	-	-	1	4	-	1	-	9
Total uvea	**191**	**71.7**	**12.0**	**1.6**	**-**	**0.5**	**1.6**	**-**	**-**	**-**	**(2.6)**	**-**	**1.0**	**0.8**	**0.8**	**0.5**	**2.6**	**-**	**0.5**	**-**	**6.3**
Total choroid / uvea	**530**	**71.9**	**11.9**	**0.9**	**0.6**	**0.6**	**(2.5)**	**0.4**	**0.4**	**-**	**(3.0)**	**0.2**	**1.5**	**0.3**	**1.0**	**0.6**	**1.9**	**-**	**0.2**	**1.3**	**4.7**
Histopathologically:																					
Castro et al., 1982	51	59	37	-	-	-	-	-	-	-	-	-	-	-	-	-	-	4	-	-	-
Total choroid	**51**	**59**	**37**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**4**	**-**	**-**	**-**
Jensen, 1970	18	33	33	-	-	-	-	-	-	-	11	-	-	-	-	6	17	-	-	-	-
Ferry and Font, 1974	196	41.3	31.6	-	0.5	0.5	(2.6)	0.5	1.0	1.0	(4.1)	1.0	3.1	-	-	3.6	-	-	-	-	15.8
Total uvea	**214**	**40.7**	**31.8**	**-**	**0.5**	**0.5**	**(2.3)**	**0.5**	**0.9**	**0.9**	**(4.7)**	**0.9**	**2.8**	**-**	**-**	**3.7**	**1.4**	**-**	**-**	**-**	**14.5**
Total choroid / uvea	**265**	**44.2**	**32.8**	**-**	**0.4**	**0.4**	**(1.9)**	**0.4**	**0.8**	**0.8**	**(3.8)**	**0.8**	**2.3**	**-**	**-**	**3.0**	**1.1**	**0.8**	**-**	**-**	**11.7**

Table 1.3.2 4 presents a survey of the various groups of primary tumours that had led to uveal metastases. Here, again, a distinction is made between clinical and histopathological studies.

Table 1.3.2.4 Frequency of uveal metastases # according to primary tumours

Localization primary tumour	Clinically * N = 530 %	Histopathologically ** N = 265 %
Breast	72	44
Lung	12	33
Genital tract	3	4
Skin	2	1
Gastrointestinal tract	2	2
Miscellaneous	4	4
Unknown origin	5	12

** Van der Hoeve, 1927, Hemmes, 1969, Haye and Calle, 1972, Meythaler and Herold, 1979, Stephens and Shields, 1979, Freedman and Folk, 1987, Brink et al , 1988, Saßmannshausen et al , 1990,*
*** Jensen, 1970, Ferry and Font, 1974, Castro et al , 1982*
 # including publications concerning choroidal metastases only

It appears that both clinically and histopathologically, breast cancer is the primary tumour most frequently diagnosed, followed by lung cancer. There is, however, a striking difference between the percentages of frequency. clinically, 72% of the primary tumours are breast cancer as against 44% in the histopathological study group. Lung tumours are regarded as primary tumours on clinical grounds in 12% of the patients with uveal metastases, as against 33% of the patients from institutes of pathology.

In the histopathological patient group a higher proportion of unknown primary tumours occurs than in the clinical patient group. However, in the patient population of histopathological studies many patients are included in whom the eye was enucleated on the diagnosis of 'malignant melanoma' and mostly no malignancy elsewhere in the body was known.

In Table 1.3.2.5 the primary tumours are classified according to sex In females, 88% of the uveal metastases originated from breast cancer clinically and 77% histopathologically, while 5% and 13%, respectively, originated from lung cancer. In males, lung tumours were clinically regarded as the cause of uveal metastases in 42% and histopathologically in 52%, while metastases from other localizations also occurred more frequently.

It is hard to give an unambiguous and satisfactory explanation of the major differences between the frequencies of different malignant tumours and the frequencies of metastasization of these malignancies to the eye. The very high percentage of intraocular metastases of breast cancer is striking in this respect

First of all the frequencies of the various primary tumours themselves should be compared (Jensen, 1970). In adults, cancer of breast and lung occur frequently, which greatly influences their share in choroidal metastases (Jampol et al., 1973).

Table 1.3.2.5 *Frequency of uveal metastases according to the localization of the primary tumour and to sex*

Localization primary tumour	Clinically * %		Histopathologically ** %	
	Male N = 36	Female N = 155	Male N = 101	Female N = 113
Breast	3	88	0	77
Lung	42	5	52	13
Genital tract	6	2	10	0
Skin	11	1	2	1
Gastrointestinal tract	3	1	3	2
Miscellaneous	17	0	10	0
Unknown origin	19	3	23	7

** Hemmes, 1969; Stephens and Shields, 1979; ** Jensen, 1970; Ferry and Font, 1974*

Table 1.3.2.6 compares the percentages of incidence of different groups of malignancies in the United States with the percentual distribution of uveal metastases over the various primary tumours. It should be noted that the frequencies of the different malignancies have fluctuated over the years. For instance, in the period 1930-1985, the mortality of males due to lung cancer has risen by approximately a factor 15, while that of gastric cancer decreased by a factor 5. In women, mortality due to uterine and gastric cancer decreased and that due to lung cancer increased (Silverberg et al., 1990).

Table 1.3.2.6 *Incidence of various groups of malignancies in the United States and the distribution of uveal metastases over these various primary tumours in terms of percentage*

Localization primary tumour	Primary tumour *			Uveal metastases		
	total	male	female	total **	male ***	female ***
Breast	16 %	0 %	31 %	76 %	4 %	91 %
Lung	16	21	11	13	51	5
Genital tract	19	24	15	3	7	2
Skin	3	3	3	2	13	1
Gastrointestinal tract	25	26	24	2	4	1
Miscellaneous	21	26	16	4	21	0

** Silverberg et al., 1990; ** frequency of occurrence of clinical uveal metastases (after Table 1.3.2.4); *** frequency of occurrence of uveal metastases in the sexes (after Table 1.3.2.5)*

As table 1.3.2.6 shows, breast cancer accounts for 16% of all newly detected malignant tumours but is responsible for 76% of the uveal metastases. Other authors also state that only 10 to 16% of all cancers in the human body are breast cancer, while 45 to 80% of all intraocular metastases originate from this tumour (Hollwich and Lemke, 1965; Ferry, 1967; Hemmes, 1969; Schiffer et al., 1978).

Lung cancer accounts for 16% of all primary tumours and for 13% of the uveal metastases. Hemmes (1969) gives these proportions as 20% and 11%, respectively. In males, 21% of cancers are lung cancer, but this tumour generates 51% of the uveal metastases (Table 1.3.2.6). Schiffer et al. (1978) described 22 and 47%, respectively.

Noticeable is the low proportion (4%) of uveal metastases of tumours of the digestive tract, which account for 20% of all primary malignancies (Ferry, 1967). According to Schiffer et al. (1978), as many as 15% of the uveal metastases in males derive from gastrointestinal tumours while of all malignancies in males, 48% are localized in the digestive tract.

From incidence figures of malignant tumours the distribution of the nature of the primary tumours in patients with uveal metastases can only partially be explained. Most noticeably, the frequently occurring gastrointestinal and genital tumours rarely metastasize to the uvea.

Ask (1934) believed that the high frequency of breast cancer was caused by the already high frequency of this tumour, and its strong tendency to metastasize. Apart from the incidence, metastatic characteristics of a tumour are also important (Jensen, 1970). Breast cancer tends to haematogenous metastasization and issues a large number of malignant cells into the circulation (Lemoine and McLeod, 1936). Although in most carcinoma patients some tumour cells will enter the bloodstream, they are only rarely viable and, if implantation occurs at all, growth follows only sporadically (Stanford and Reese, 1971). Various types of cancer cells differ greatly in their possibilities to remain viable distant from the primary tumour. It is known in this connection that the cells of breast cancer are very hardy and may survive and even multiply in circumstances unfavourable to other types of cancer cells. The large proportion of breast cancer among uveal metastases may be attributable to this property (Mullen et al., 1954; Reese, 1976). Lemoine and McLeod (1936) postulated that breast cancer cells may have a specific affinity for uveal tissue, and particularly for the choroid.

Furthermore, metastatic cells from breast cancer have only to pass the lung filter to cause disseminations in the eye, whereas other tumours, such as gastrointestinal tumours, in general first have to pass the liver as well. This might be another reason why breast cancer relatively often causes uveal metastases (Schinz, 1939; Gillet, 1971; Schiffer et al., 1978). Another factor is the anatomically relatively short way from the breast to the eye (Schiffer et al., 1978).

The ***survival*** of patients with particular malignant tumours also plays a part (Schinz, 1949). The relatively long survival of patients with breast cancer renders distant metastases possible (Streiff, 1959; Hollwich and Lemke, 1965; Schiffer et al., 1978). Table 1.3.2.7 presents a survey of the survival of patients with various primary malignancies.

Table 1.3.2.7 *Five-year survival of white patients with various primary malignancies in the United States in terms of percentage* *

Malignancy	Period				
	1960-1963	1970-1973	1974-1976	1977-1979	1980-1985
All malignancies **	39	43	50	50	51
Breast cancer ***	63	68	75	75	76
Lung cancer	8	10	12	13	13
Stomach cancer	11	13	14	16	16
Colonic cancer	43	49	50	52	55
Rectum cancer	38	45	48	50	53
Prostatic cancer	50	63	67	71	73
Cutaneous melanoma	60	68	79	81	81

** Silverberg et al., 1990; ** leukaemia and lymphoma included; *** females*

Patients with breast cancer have a distinctly longer survival than patients with pulmonary and gastric malignancies. However, carcinomas of the colon, rectum and prostate and malignant cutaneous melanomas also have a relatively long 5-year survival rate, while of these tumours, only few intraocular metastases have been reported.

Therefore, no adequate explanation exists of the differences in frequency of the various primary tumours in uveal metastases.

The ***interval*** between the onset of the primary tumour and the intraocular metastases varies between detection of the metastasis at the same time as the primary lesion and a diagnosis of the metastases only many years later. On average the interval is 41 to 43 months (Table 1.3.2.8). The interval between breast cancer and the intraocular metastases (average 24 to 72 months) is much longer than that in lung tumour cases (average interval 1 to 11 months).

Intraocular metastases from breast cancer are rarely detected within one year after the diagnosis of the primary tumour, whereas metastases of lung tumours mostly occur within that same period (Jensen, 1970; Aasved and Seim, 1973). The first four years after the diagnosis of breast cancer some 80% of the uveal metastases are diagnosed, distributed evenly over these years. Thereafter they are rare (Hemmes, 1969).

Reportedly it is only metastases of breast cancer that may be discovered longer than 10 years after the primary tumour (Ferry, 1973).

Uveal metastases may also develop before a malignancy elsewhere in the body is known. This is allegedly the case in 10 to 46% of the uveal metastases (Table 1.3.2.9). On average, the primary tumour is then detected after 4 months (0.5 to 30 months) (Ferry, 1973). In the literature up to 10% of patients with breast cancer are described in whom uveal metastases were detected before occurrence of the primary tumour.

In patients with lung cancer the primary tumours are mostly diagnosed only after uveal metastases have been encountered. In 65 to 90% of the cases the metastases are the first sign of a malignancy.

Gastrointestinal tumours (Stephens and Shields, 1979; Abramson, 1984; Arné and Mathis, 1986) and renal carcinomas (Ferry and Font, 1974) also very frequently cause metastases before the primary tumour is known.

Table 1.3.2.8 *Interval between onset of the primary tumour and detection of the uveal metastasis*

Author	Interval between onset of the primary malignancy and uveal metastasis (months) Mean	Range
All malignancies:		
Brink et al., 1988	41	0-156
Schiffer et al., 1978	42	-
Stephens and Shields, 1979	43	-
Breast cancer:		
Röttinger et al., 1976	24	0-192
Stolzenbach and von Domarus, 1978	24	6-72
Thatcher and Thomas	26	0-114
Meythaler and Herold, 1979	* 30	-
Hemmes, 1969	33	0-109
Thompson et al., 1961	36	6-89
Mewis and Young, 1982	36	6-171
Ferry and Font, 1974	39	0-300
Merriam, 1961	42	1-120
Hart, 1962	42	-
Hollwich and Lemke, 1965	42	-
Stephens and Shields, 1979	46	8-240
Brink et al., 1988	46	-
Chu et al., 1977	48	3-240
Saßmannshausen et al., 1990	* 53	-
Hutchison and Smith / Castro et al., 1982	61	0-192
Letson et al., 1982	72	12-192
Lung cancer:		
Brink et al., 1988	1	-
Saßmannshausen et al., 1990	* 2	-
Stephens and Shields, 1979	6	2-15
Ferry and Font, 1974	11	0-72

* *median*

Table 1.3.2.9 *Uveal metastases diagnosed before or after the primary tumour in terms of percentage*

Author	Diagnosis uveal metastasis before primary tumour %	Diagnosis uveal metastasis after primary tumour %
All malignancies:		
Wilder, 1946	10	90
Meythaler and Herold, 1979	10	90
Saßmannshausen et al., 1990	11	89
Stephens and Shields, 1979	31	69
Ferry and Font, 1974	46	*# 54
Breast cancer:		
Meythaler and Herold, 1979	0	100
Ferry and Font, 1974	9	* 91
Stephens and Shields, 1979	9	91
Abramson, 1984	10	90
Lung cancer:		
Ferry and Font, 1974	65	*## 24
Stephens and Shields, 1979	70	30
Abramson, 1984	90	10

** metastases in eye and/or orbit, # 3.1% at the same moment as the primary tumour, 0.4% unknown; ## 11% at the same moment as the primary tumour*

1.3.3 Connection with metastases elsewhere in the body

A number of authors state that uveal metastases occur more often and possibly exclusively in patients with a tumour that has already spread extensively (Adda, 1937; Papolczy, 1936; Guthert et al., 1965; Kunze and Wurgatsch, 1972; Meur et al., 1974; Nelson et al., 1983). These patients mostly have reached a terminal stage of their disease (Hart, 1962; Gillet, 1971; Daicker, 1981).

According to Saßmannshausen et al. (1990), 60% of the patients with choroidal metastases already have metastases elsewhere in the body; according to Timm (1967), this proportion is 82%. Hart (1962) stated that in 12 of the 55 patients with ocular metastases no metastases elsewhere in the body were known at the time of the enucleation of the affected eye. However, this refers to a histopathological examination of eyes mostly enucleated under the false diagnosis of a malignant uveal melanoma. Probably no distant metastases were known.

According to Bullock and Yanes (1980), the interval between the primary tumour and metastases not localized in the eye is 49 months on average (varying from 0 to 16 years), while the interval between the primary tumour and choroidal metastases on

average is 72 months (12 months to 16 years)

Mewis and Young (1982) described nine choroidal metastases in 98 patients with breast cancer who had no visual complaints. These nine patients were already known with extensive spread of the tumour. In 152 patients who did have visual complaints, 58 choroidal metastases were established; the ocular metastases occurred at all stages of the primary tumour. According to Letson and Davidorf (1982), in 20% of the patients with a choroidal metastasis from breast cancer the ocular metastasis was the first sign of systemic metastasization, while in 27% of the patients choroidal metastases were discovered at the same time as metastases elsewhere in the body Chu et al. (1977) also reported that 20% of the choroidal metastases preceded systemic metastases.

Reportedly, in nearly all cases ***lung metastases*** had preceded intraocular metastases, thus enabling subsequent spread of tumour cells to the eye (Ask, 1934; Ferry, 1967; Gillet, 1971, François et al., 1976). Nevertheless, in 15 to 17% of the patients with ocular metastases no lung metastases were observed (Lemoine and McLeod, 1936; Ferry, 1967) Small intraocular metastases can be seen clinically before lung metastases are large enough to be visualized radiologically (Mewis and Young, 1982) At autopsy, it is possible for small metastases in the lungs to be overlooked (Lemoine and McLeod, 1936; Ferry, 1967; Gillet, 1971; Castro et al., 1982).

Lemoine and McLeod (1936) suggest that tumour cells might pass through the lungs without being arrested there. Another possibility is that tumour cells bypass the pulmonary circulation and reach the eye via Batson's plexus and the vertebral system (see Chapter 1 2) (Ferry, 1967, Gillet, 1971; Castro et al , 1982).

Mewis and Young (1982) believed that local tissue factors may inhibit the growth of metastatic foci. They describe 67 patients with choroidal metastases of breast cancer. In 40 patients (60%), metastases were observed in the pulmonary parenchyma or the pleura. These metastases were diagnosed before choroidal metastases in 27 cases, at the same time as the ocular metastases in seven cases and later on, in six cases. If the lung metastases were detected before the metastases in the choroid, the interval ranged from 1 to 39 months (median 13 months). In patients with breast cancer, lung metastases in general occur in a proportion of 69% (Haagensen, 1971)

Since the eye and the brain have the same blood supply, it is assumed that if intraocular metastases are encountered, there will be haematogenous ***cerebral metastases*** as well (Allen, 1968, Jensen, 1970; Abramson, 1984). However uveal metastases are to be considered extracerebral metastases.

Cerebral metastases occur more frequently than ocular metastases (Cieplinski et al,, 1982). According to Guthert et al. (1965), in patients with a malignant tumour cerebral metastases are found 12 times as often as intraocular metastases. This is due to the extensive ramifications of the vascular system, the size of the brain and the resulting greater risk of haematogenous spread.

Frequently, nevertheless, no cerebral metastases can be demonstrated in patients with intraocular metastases; this is due to the fact that very small metastases can be diagnosed in the eye while this is not possible in the brain. Still, it is important for patients with intraocular metastases to be examined for metastases in the central nervous system as well (Abramson, 1984).

Haagensen (1971) stated that in general, 22% of the patients with breast cancer have cerebral metastases. Di Stefano et al. (1979) reported 101 patients with cerebral

metastases of breast cancer. In only four patients were choroidal metastases established as well. These authors deny a correlation between cerebral metastases and localizations of metastases elsewhere in the body.

Thatcher and Thomas (1975) established cerebral metastases in five out of 42 patients with choroidal metastases of breast cancer (12%). Mewis and Young (1982) in 30 out of 67 patients with choroidal metastases of breast cancer found metastases in the central nervous system. In two cases, metastases in the nervous system were detected earlier than choroidal metastases, in 15 cases they were detected at the same time and 13 times, choroidal metastases preceded metastases in the nervous system. Accordingly, in patients with breast cancer, metastases in the central nervous system appear to manifest themselves at the same time as or áfter the diagnosis of ocular metastases. Choroidal metastases may represent the smallest detectable metastatic lesions in systemic dissemination of a malignancy (Mewis and Young, 1982).

1.3.4 Demography

The age and sex distributions of patients with uveal metastases are influenced greatly by the nature of the primary tumour causing the ocular lesion.

Table 1.3.4.1 presents a survey of the ***sex distributions*** in intraocular metastases according to various authors.

Table 1.3.4.1 Sex distribution in patients with intraocular metastases

Author	Number of metastases	Male		Female	
		N	%	N	%
Clinically:					
Brink et al., 1988	* 47	7	15	40	85
Hemmes, 1969	** 121	19	16	102	84
Saßmannshausen et al., 1990	*# 161	30	19	131	81
Stephens and Shields, 1979	** 70	17	24	53	76
Freedman and Folk, 1987	*** 112	34	30	78	70
Histopathologically:					
Wilder, 1946	** 40	12	30	28	70
Castro et al., 1982	***## 126	42	36	75	64
Hutchison and Smith, 1979	**### 73	28	42	39	58
Hart, 1962	** 118	51	43	67	57
Jensen, 1970	** 18	8	44	10	56
Ferry and Font, 1974	** 196	93	47	103	53

** choroid; ** uvea; *** eye and/or orbit*

 # including two lymphomas; ## in nine patients sex unknown; ### in six patients sex unknown

In the literature the male:female ratios are variable. Clinically, the proportions of males vary from 15 to 30% and those in females from 70 to 85%. Histopathologically, this proportion is 30 to 47% in males and 53 to 70% in females. This is due to the fact that most primary tumours causing intraocular metastases are breast cancers and occur in females (Bonnet and Jambon-Genet, 1948; Daicker, 1981). Since histopathological examinations in particular also reveal uveal metastases in other malignancies, and these patients may equally well be males, the emphasis in this group lies less on the female sex.

The proportion of females among all patients with uveal metastases reported in the literature varies between 69 and 79% (Usher, 1923; Ask, 1934; Hollwich and Lemke, 1965; Schiffer et al., 1978).

The mean *age* of patients with intraocular metastases is between 50 and 60 years (Table 1.3.4.2).

Table 1.3.4.2 Age of patients with intraocular metastases

Author		Localization	Number of metastases	Age (yr) mean	Age (yr) range
All malignancies:					
Meythaler and Herold, 1979	*	choroid	21	50	-
Jensen, 1970	**	uvea	18	51	-
Ferry and Font, 1974	**	eye/orbit	227	53	4-79
Brink et al., 1988	*	choroid	# 49	54	16-79
Saßmannshausen et al., 1990	*	choroid	## 161	54	-
Hutchison and Smith, 1979	**	eye/orbit	94	57	21-88
Castro et al., 1982	**	eye/orbit	103	57	8-88
Breast cancer:					
Hart, 1962	**	eye/orbit	60	49	33-68
Stolzenbach and von Domarus, 1978	*	choroid	8	49	34-69
Chu et al., 1977	*	choroid	57	50	-
Mewis and Young, 1982	*	choroid	67	51	28-71
Thatcher and Thomas, 1975	*	choroid	42	∞ 51	37-74
Meythaler and Herold, 1979	*	choroid	16	53	-
Röttinger et al., 1976	*	choroid	26	54	35-67
Hutchison and Smith, 1979	**	eye/orbit	38	61	39-88
Lung cancer:					
Hart, 1962	**	eye/orbit	28	51	24-72
Hutchison and Smith, 1979	**	eye/orbit	17	55	28-68

** clinical; ** histopathological*

 # including one leukaemia and one lymphoma; ## including two lymphomas; ∞ median

Of the patients with metastases, over three-quarters are between the ages of 40 and 69 years. Fewer than 4% of the patients are younger than 30 years (Table 1.3.4.3).

Although in children tumour cells have been demonstrated in the peripheral blood and even in the choroidal vessels (Bothman and Blankstein, 1942), they hardly if ever have ocular metastases (Albert et al., 1967a). It is possible that in children local environmental factors render the eye unsusceptible to malignant tumours (Albert et al., 1967a; François et al., 1967). Such metastases as do occur are mostly disseminations of sympathoblastomas (Toppel, 1968).

In animal experiments, on the other hand, intraocular metastases occur as often in young as in fully grown specimens (Albert et al., 1967b).

The youngest patient with uveal metastases described in the literature was a three-day-old girl with bilateral iridal metastases of a neuroblastoma detected a few days after the iridal tumour (Bowns et al., 1983). Other uveal metastases of neuroblastomas in children were described by Bothman and Blankstein (1942), Guthert et al. (1965), Hutchison and Smith (1979), Alio et al. (1982), Arné et al. (1983) and Castro et al. (1982). Rootman et al. (1979) described a choroidal metastasis of a congenital fibrosarcoma in a two-year-old boy. Other primary tumours in children under the age of 10 to be mentioned are retinoblastoma of the same (Middleton, 1952) or of the other eye (Howard, 1962), tumours originating from the testicles (Goldstein and Wexler, 1935; Ferry, 1973) and thyroid carcinoma (Stangl, 1977). Between the ages of 10 and 20, uveal metastases were described of a bronchial carcinoid (Rosenbluth et al., 1960; Ferry, 1973; Fu et al., 1974 and Riddle et al., 1982), a colonic carcinoma (Ferry, 1973), a cutaneous melanoma (Font et al., 1967; Spencer, 1986), a choriocarcinoma of the testicle (Godtfredsen, 1944a) and a choriocarcinoma of the uterus in a pregnant woman aged 19 years (Keates and Billig, 1970).

There are only few known cases of patients over 80 with uveal metastases: the oldest patient was a male aged 88 with in his right eye a choroidal metastasis of an adenocystic carcinoma of the salivary gland (Gutmann et al., 1986). Kerman and Fishman (1987), also, described a male aged 81 with an uveal metastasis of a tumour originating from a salivary gland. Other reported cases involved a male aged 82 with an iridal metastasis of a thyroid carcinoma (Weisenthal et al., 1989) and a male aged 85 with an uveal metastasis of lung cancer (Eichholtz, 1976).

Geographical position and ***race*** possibly play a part in the occurrence of uveal metastases.

Only little is known about the race of patients with intraocular metastases. Virtually all publications on uveal metastases originate from European countries or from the United States.

Only a few American authors state the race of their patients (Table 1.3.4.4). They fail to state, however, the racial distribution of the population from which these patients came.

It is known that malignant tumours occur in different races in different proportions. For instance, in the United States tumours originating from the lung and bronchus are encountered far more often among whites, Negroes and inhabitants of Hawai than among American Indians and people of Hispano-American extraction (deVita et al., 1989).

The mortality from malignancies als varies accorcing to geography (Tabel 1.3.4.5).

Table 1.3.4.3 Age distribution in patients with intraocular metastases

Author			Localization	Total numbers of patients	Age 0- 9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	unknown
All malignancies:													
Hemmes, 1969		*	uvea	121	-	-	3	15	32	41	22	7	1
Jensen, 1970		**	uvea	18	-	1	1	1	5	3	7	-	-
Ferry and Font, 1974		**	eye/orbit	227	1	2	5	26	55	51	63	18	6
Stephens and Shields, 1979		*	uvea	70	-	-	3	2	12	30	16	7	-
Total	**(N)**			**436**	**1**	**3**	**12**	**44**	**104**	**125**	**108**	**32**	**7**
	(%)				**0.2**	**0.7**	**2.8**	**10.3**	**24.2**	**29.1**	**25.2**	**7.5**	/
Breast cancer:													
Meyer and Herold, 1979		*	uvea	21	-	-	1	3	6	7	2	2	-
Mewis and Young, 1982		*	choroid	67	-	-	1	8	24	18	13	3	-
Total	**(N)**			**88**	**-**	**-**	**2**	**11**	**30**	**25**	**15**	**5**	**-**
	(%)				**-**	**-**	**2.3**	**12.5**	**34.1**	**28.4**	**17.0**	**5.7**	**-**

** clinically; ** histopathologically*

Table 1.3.4.4 Racial distribution of patients with intraocular metastases

Author	Total number of patients and localization		Race white	black	yellow	unknown
Wilder, 1946	N	40 choroid	40	-	-	-
	%		100	0	0	-
Ferry and Font, 1974	N	227 eye and/or orbit	196	17	2	12
	% *		91	8	1	-
Stephens and Shields, 1979	N	70 uvea	65	5	-	-
	%		93	7	-	-

* *percentage of patients with known race*

Table 1.3.4.5 Age-adjusted death rates per 100.000 population according to localization of the primary tumour: 1984-1986 *

Localization	Country Netherlands male	Netherlands female	United States male	United States female	Japan male	Japan female
All malignancies	271 2	142.8	216.6	140.3	198.4	104.1
Breast	-	32.4	-	27.4	-	6 7
Lung	103.8	10.4	73.5	26.2	38.2	10.5
Colon and rectum	25.7	19.6	24.2	17.5	18.2	12.2
Stomach	20.7	8.8	7.4	3.4	54.6	25.0

* *Silverberg et al , 1990*

Kurimoto and Ito (1970) collected data concerning 21 patients with a choroidal metastasis reported in Japan during the period 1957-1970. Fifty-two percent of these metastases were caused by lung cancer and only 24% by breast cancer. Ueno et al. (1986) described 165 Japanese patients with uveal metastases, of which 38.8% originated from lung cancer, 32.7% from breast cancer and 4.8% from gastric cancer.

1.4 Diagnostics

In this chapter the signs and symptoms that cause a patient with uveal metastases to visit the ophthalmologist are described as well as the various diagnostic techniques used for making the differential diagnosis of intraocular tumours.

Conditions that have to be differentiated from uveal metastases are described in Chapter 1.5.

1.4.1 Signs and symptoms

Choroidal metastases may remain asymptomatic for a long time (François et al., 1976; Shields, 1983; Abramson, 1984). As a rule, symptoms manifest themselves if the macula is affected or secondary retinal detachment occurs (Lommatzsch, 1989).

Mewis and Young (1982) carried out ocular examinations in 250 patients with breast cancer. Of these patients, 152 had been referred because of symptoms. Choroidal metastases were found in 58 patients (38%). Of the 98 patients without ocular symptoms, nine women (9%) were found to have metastases in the choroid.

In most patients with choroidal metastases symptoms have only recently developed at the time of diagnosis. Most symptoms have been present for less than 3 months (Hart, 1962; Jensen, 1970). Jensen (1970) in none of his patients found symptoms that had been present for longer than one year.

In lesions in the macular area, ***visual acuity*** deteriorates rapidly (Stevens and Reeh, 1958) and this also occurs during development of a retinal detachment (Bonnet and Jambon-Genet, 1948). If metastases are localized in the peripheral choroid, it takes longer for symptoms to appear (Stevens and Reeh, 1958).

At the first ocular examination, 12 to 13% of the patients have no complaints. These asymptomatic choroidal metastases are only detected fortuitously at routine ophthalmoscopy (Mewis and Young, 1982; Brink et al., 1988). However, most metastases cause signs or symptoms for which the patient seeks medical aid (Tables 1.4.1.1).

The main complaints at the first ocular examination are decrease of the visual acuity and blurred vision (Ferry, 1973; Ferry and Font, 1974; Abramson, 1984; Gartner, 1985; Brink et al., 1988). They are reported in 66 to 98% of the patients (Table 1.4.1.2). Vision may even decrease to no light perception (Reddy et al., 1981). Hart (1962) in 16 of the 60 patients with choroidal metastases (27%) found only light perception or total blindness. Freedman and Folk (1987) in 72 eyes with choroidal metastases found a mean visual acuity of 20/70. The cause of this high percentage is the frequent localization in the posterior pole of the eye (Goldsmith, 1958; Simpson, 1961; Ferry, 1967).

Table 1.4.1.1 Presenting signs and symptoms in uveal metastases *

Sign/symptom	Stephens and Shields, 1979 Uveal metastases (N=70)		Freedman and Folk, 1987 Intraocular metastases (N=58)	
	N	%	N	%
Decreased visual acuity	56	80	57	98
Pain/headache	10	14	9	16
Photopsia	9	13	-	-
Red eye	5	7	4	7
Floaters	5	7	12	21
Field defect	2	3	18	31
Photophobia	1	1	-	-
Iris lesion	1	1	-	-
Metamorphopsia	-	-	3	5
Diplopia	-	-	3	5
Proptosis	-	-	1	2
Ptosis	-	-	1	2
Anisocoria	-	-	1	2
Asymptomatic	4	6	1	2

* *total % exceeds 100 because some patients had more than one complaint*

Table 1.4.1.2 Frequency of decreased visual acuity and blurred vision in patients with uveal metastases at the first ophthalmological examination

Author	Total number of patients and localization		Decreased visual acuity and blurred vision	
			N	%
Mewis and Young, 1982	67	choroid	44	66
Stephens and Shields, 1979	70	uvea	56	80
Hemmes, 1969	73	uvea	61	84
Ferry, 1978	164	choroid	139	85
Gillet, 1971	37	choroid	32	86
Letson, 1982	15	choroid	14	93
Röttinger et al., 1979	26	choroid	25	96
Freedman and Folk, 1987	58	choroid	57	98

Hypermetropia may develop due to an elevation of the retina by the underlying tumour. It may become manifest by the patient's having to wear increasingly strong positive glasses. The hypermetropia as a rule amounts to 1 to 3 diopters, but may increase to 7 diopters (Mérigot de Treigny, 1921; Bonnet and Jambon-Genet, 1948; Goldsmith, 1958; Offret and Haye, 1971). It may be the earliest sign of a tumour in the eye (Stewart, 1960). In such cases, the visual acuity after correction may remain adequate for a long time (Duke-Elder and Perkins, 1966).

Involvement of the central portion of the choroid may lead to ***metamorphopsia*** and ***micropsia*** (Mérigot de Treigny, 1921; Bonnet and Jambon-Genet, 1948; Goldsmith, 1958; Hemmes, 1969; Cole and Farah, 1985; Freedman and Folk, 1987; Brink et al., 1988).

Visual field defects are usually secondary to a non-rhegmatogenous retinal detachment (Allen, 1968; Abramson, 1984; Gartner, 1985; Brink et al., 1988). These defects are encountered in variable proportions of the patients, viz. in 3% (Stephens and Shields, 1979) to 31% (Freedman and Folk, 1987).

Patients regularly complain of ***floaters*** (Stephens and Shields, 1979; Freedman and Folk, 1987; Wharam and Schachat, 1989).

Sometimes the patient observes ***flashes of light*** (Hemmes, 1969; Stephens and Shields, 1979; Wharam and Schachat, 1989). However, according to Stevens and Reeh (1958), these occur more frequently in retinal detachments with a rhegmatogenous cause.

Other infrequent signs and symptoms are ***diplopia*** (Hemmes, 1969; Mewis and Young, 1982; Cole and Farah, 1985; Freedman and Folk, 1987), ***photophobia*** (Stephens and Shields, 1979; Mewis and Young, 1982), ***ptosis*** (Mewis and Young, 1982; Freedman and Folk, 1982) and abnormalities of ***colour vision*** (Hemmes, 1969).

Prominent ***episcleral vessels*** are seen in 6% of the patients (Stephens and Shields, 1979).

Redness of the eye is described repeatedly (Hemmes, 1969; Stephens and Shields, 1979; Freedman and Folk, 1987). ***Pain*** in the eye or periorbital pain may also constitute a first symptom (Ferry, 1978; Spencer, 1986; Castro et al., 1982; Letson et al., 1982). In 10 to 20% of the cases this pain is mentioned as the first symptom (Table 1.4.1.3). During the subsequent course this proportion may increase even further (Stephens and Shields, 1979; Brasseur et al., 1983).

Table 1.4.1.3 *Frequency of painful eye or periorbital pain in patients with uveal metastases at the first ophthalmological examination*

	Total number of patients and localization		Ocular and periorbital pain	
Author			N	%
Hemmes, 1969	73	uvea	7	10
Stephens and Shields, 1979	70	uvea	10	14
Freeman and Folk, 1987	58	choroid	9	16
Hart, 1962	60	choroid	11	18
Ferry, 1978	164	choroid	33	20

Pain may be due to uveitis which may or may not be associated with a secondary glaucoma (Bonnet and Jambon-Genet, 1984; Ferry, 1967/1978; Shields and Young, 1980; Shields, 1983).

Intratumoral necrosis in choroidal metastases may lead to these inflammatory alterations that may conceal the clinical picture (Ferry, 1967). Ferry and Font (1974) in

16 of 219 patients (7.3%) with metastases in the eye or the orbit described a uveitis, associated in most cases with glaucoma. In 15 of these patients (94%) the metastasis was localized in the anterior segment of the uvea.

A choroidal metastasis may present not only as uveitis but also as posterior scleritis (Yeo et al., 1983).

Another cause of pain in the eye may be pressure exerted by the tumour on a ciliary nerve (Jaensch, 1950).

Glaucoma occurs in 5.5% of the patients with a metastasis in eye or orbit (Ferry, 1973). Possible mechanisms of this glaucoma are increasing pressure due to the size of the tumour in a limited space; anterior displacement of the lens causing blockage of the anterior chamber; blocking of the angle of the anterior chamber by exfoliated tumour cells; pressure of the tumour on the choroidal vessels (De Ocampo, 1961).

In a group of 227 patients with ocular metastases, the diagnosis of 'glaucoma' was made 17 times. It was described as absolute in eight and as secondary in nine cases; in three of the latter it was due to iridocyclitis. In none of the 17 cases had the possibility of an intraocular tumour been considered. In most patients the uveal metastasis had an anterior localization and no primary tumour was known at the time (Ferry and Font, 1974).

Shields et al. (1987) reported a secondary increase of the intraocular pressure (over 23 mm Hg by applanation tonometry) in 12 of 256 eyes with a uveal metastasis (5%). An increased pressure was found in only three of the 242 choroidal metastases, in contrast to seven out of 11 iridal metastases and two out of three metastases in the ciliary body. Of the patients with choroidal metastases, two had metastases of a bronchial carcinoma and one, a cutaneous melanoma metastatic to the choroid. In all three cases the angle of the anterior chamber was blocked secondary to anterior displacement of the iris-lens diaphragm from either choroidal detachment or total retinal detachment (Shields et al., 1987).

Stephens and Shields (1979) and De Bustros et al. (1985) reported a patient with angle closure glaucoma due to a haemorrhagic detachment of the choroid.

Stephens and Shields (1979) in one out of 79 eyes with a choroidal metastasis described glaucoma as the first symptom. Freedman and Folk (1987) reported increased intraocular pressure in two of the 58 patients with a metastasis in the choroid.

Alterations in the retina, which may or may not be due to a total retinal detachment, cause retinal hypoxia and frequently lead to neovascularization of the iris, peripheral anterior synechiae and intractible glaucoma (Ferry, 1967/1978). Pain caused by this glaucoma is one of the commonest reasons to enucleate an eye with a choroidal metastasis (Ferry, 1967; Haye, 1972; Ferry, 1978). As a rule, however, the patient's life expectation is too short for development of this final glaucoma (Mérigot de Treigny, 1921; Ferry, 1967).

The reason why few choroidal metastases are accompanied by glaucoma is the fact that these tumours are frequently localized in the macular area. The consequent loss of visual acuity will usually call attention to the tumour before a rise of the intraocular pressure takes place (Shields et al., 1987). Because the rise of pressure occurs only late, tonometry is of little value for the diagnosis of choroidal metastases (Cohen, 1937). This rise of intraocular pressure allegedly appears later in choroidal metastases than in other intraocular tumours (Stevens and Reeh, 1958).

Metastases in the iris are generally asymptomatic. Sometimes, the iris colour may change, especially in blue eyes (Abramson, 1984).

Ferry (1978) and Ferry and Font (1975) in 60% of the patients with a ***metastasis in the anterior segment*** reported decreased visual acuity as the first symptom. In the longer term, reduced vision was even observed in 80% (Table 1.4.1.4). According to other authors, however, visual disorders occur far less often and are usually mild (Shields and Young, 1980; Shields, 1983). Tilting of the lens is sometimes observed (Wharam and Schachat, 1989).

Table 1.4.1.4 Presenting signs and symptoms in metastases to the anterior segment *

	Ferry and Font, 1975	
Sign/symptom	N	%
Decreased visual acuity	15	58
Mass	15	58
Red eye	12	46
Pain	11	42
Iridocyclitis	10	38
Glaucoma	7	27
Hyphaema	1	4
Asymptomatic	1	4

* *total % exceeds 100 because some patients had more than one sign or symptom*

Metastases in the anterior segment may remain unnoticed until anterior uveitis or secondary glaucoma occurs causing pain in the eye (Ferry, 1978; Shields, 1983; Spencer, 1986; Lommatzsch, 1989; Wharam and Schachat, 1989). Necrosis is the cause of this uveitis and secondary glaucoma. Even the cornea and sclera may be involved, rendering the diagnosis still more difficult (Ferry, 1967; Reese, 1976). This iridocyclitis may be accompanied by a hypopyon (Takahashi et al., 1984), by prominent episcleral vessels (Stephens and Shields, 1979; Shields, 1983) and by synechiae (Duke and Kennedy, 1958; Denslow and Kielar, 1978; Frank et al., 1979).

Ferry and Font (1975) in ten of the 26 patients with metastases in the iris and the ciliary body (40%) described iridocyclitis at the first ophthalmological examination. During the subsequent course, iridocyclitis was diagnosed in one other patient. In five cases, the eye was enucleated on this diagnosis and presence of a metastasis in the anterior uvea was only established at histopathological examination (Ferry, 1973; Ferry and Font, 1975).

In uveitis due to metastases in the anterior uvea, breast cancer is only rarely found to be the primary tumour, although this is the tumour that most frequently gives rise to uveal metastases (inter alia Baudet et al., 1983; Scholz et al., 1983; Woog et al., 1984).

Iritis is observed particularly often in iridal metastases of malignant skin melanomas (Char, 1980; De Bustros et al., 1985). Uveitis may also occur in choroidal metastases of skin melanomas (De Bustros et al., 1985). Wormald and Harper (1983) in

this connection described a 'black hypopyon' which consists of tumour cells and pigment-containing macrophages and may give rise to a secondary glaucoma.

Uveitis is observed with striking frequency in metastases of lung cancer in the iris and ciliary body (inter alia Duke and Kennedy, 1958; Talegaonkar, 1969; Reese, 1976) and in metastases of clear-cell tumours of the kidney (hypernephroma, Grawitz's tumour) (inter alia Chance, 1906; Hird, 1921; Laszczyk, 1975).

In the presence of uveitis that fails to respond to standard treatments, and of symptoms indicative of systemic diseases, such as weight loss and cough, the physician should consider the possibility of a pathological condition metastatic to the eye (Scholz et al., 1983).

Rubeosis iridis is regularly described in patients with a metastasis in the anterior segment (Duke and Kennedy, 1958; Schulze, 1967). Ferry (1973) described rubeosis in ten out of 26 patients with a metastasis in the iris or ciliary body (40%). This rubeosis is due to ischaemia of the anterior segment or secondary to a tumour angiogenic factor (Gimbrone et al., 1973; Freeman and Friedman, 1975). New blood vessels which form on the anterior surface of the iris impair the outflow of the aqueous humour, causing glaucoma (Schulze, 1967). However, Shields et al. (1987) never described neovascularization in uveal metastases.

The early necrosis in iridal metastases as mentioned before frequently leads to uveitis and secondary glaucoma (Ferry, 1967; Reese, 1976; Meythaler and Barthelmess, 1980) Other possible causes of glaucoma are tumorous infiltration of the trabecular meshwork and closure of the angle of the anterior chamber by the tumour mass (Daicker, 1981).

In the study of Ferry and Font (1975), a glaucoma was the first sign of an intraocular tumour in seven out of 25 patients with metastases in the anterior segment (28%). In the longer term, they described a rise of the intraocular pressure in 14 patients (56%). Glaucoma, therefore, is one of the symptoms with which an iridal metastasis may present (Castro et al., 1982; Abramson, 1984; Takahashi et al., 1984; Lommatzsch, 1989).

Duke-Elder and Perkins (1966) report increased intraocular pressure in 20% of the iridal metastases while Char (1989) did so in one-half of the cases.

Shields et al. (1987) established a secondary rise of the intraocular pressure to over 23 mm Hg in seven out of 11 patients with an iridal metastasis (64%) and in two out of three patients with metastases in the ciliary body. In eight of these nine patients either tumour invasion or angle closure was the cause of the glaucoma.

Open as well as closed angle mechanisms may occur in glaucoma. In some patients with an open angle, the trabecular meshwork is covered by a sheet of tumour cells, causing the socalled malignant epithelialization of the angle (Ferry and Font, 1975). In other patients with an open angle, the trabecular meshwork and the emissary veins may be infiltrated by neoplastic cells. The angle may also be closed by tumour lobules that have broken through the boundaries of the uvea or by peripheral anterior synechiae (Ferry, 1967; Ferry and Font, 1975).

Chapter 1.4.2 deals with intraocular haemorrhages and retinal detachments which may occur as complications in uveal metastases.

1.4.2 Ophthalmoscopy and slit lamp examination

Metastases have a characteristic ophthalmoscopic image. Gass (1974) describes choroidal metastases in his book 'Differential diagnosis of intraocular tumours' as *'... typically amelanotic, white or cream-colored, slightly elevated lesions with ill-defined margins'.* Arné and Mathis (1986): *'Certain caractères sont en faveur du diagnostic de métastases choroïdiennes: tumeurs volontiers bilatérale ou multiples, siègeant avec prédilection au pôle postérieur, peu saillantes, non-pigmentées, à bords irréguliers'.* In 'Tumors of the eye' (1976), Reese describes choroidal metastases as follows: *'... examination reveals a more or less solid-appearing detachment of the retina, invariably in the posterior pole. The elevated area is pinkish white, fading off into the normal-appearing surrounding retina. The tumor surface is frequently mottled. An occasional hemorrhage and some slight pigmentary changes may be seen over the involved area. Such lesions are often pale gray, pale yellow or yellowish gray. Multiple tumor foci are in some instances noted throughout the fundus.'* Shields in 'Diagnosis and management of intraocular tumors' (1983): *'Ophthalmoscopic examination of a choroidal metastasis characteristically reveals a creamy yellow placoid lesion in the posterior choroid. Tumors that are slightly more elevated frequently produce a serous detachment of the fovea and alterations in the retinal pigment epithelium. The retinal pigment epithelium changes can be rather marked, appearing as well-delineated clumps of golden brown pigment on the surface of the tumor.'* To conclude, Lommatzsch's description of choroidal metastases in 'Intraokulare Tumoren' (1989): *'Ophthalmoskopisch sieht man gelbliche fleckige, oft nur gering prominente Bezirke. Typisch ist die begleitende seröse Ablatio retinae, die manchmal den gesamten Tumor verdeckt und Anlaß zur Fehldiagnose geben kann. Die Veränderungen im Pigmentepithel über einer solchen Metastase sind charakteristisch und führen zu einer leopardenfellartigen goldbraunen Pigmentierung der Tumoroberfläche. Manche Metastasen wachsen aber auch kugelförmig und sind ophthalmoskopisch dann nicht von einem amenalotischen Melanom zu unterscheiden. Finden sich jedoch mehrere Tumorknoten am Fundus, so spricht dies mit großer Wahrscheinlichkeit für eine Metastase.'*

The principal ophthalmoscopic features of ***choroidal metastases***, therefore, are the shape, delineation, colour and localization of the lesion, together with their bilateral or multiple occurrence and any secondary alterations. These, accordingly, will be discussed in succession.

Shape: the first ophthalmoscopic sign of a choroidal metastasis is a colour change of a small, well-delimited zone of the retina as a more or less pale yellow diffuse area of retinal oedema (Gilbert, 1939). These round or oval foci are typically very flat or only slightly elevated without much displacement of the overlying retinal vessels (Sattler, 1926; Stevens and Reeh, 1958; Gass, 1972; Gartner, 1985). A latent choroidal metastasis is also described as nodular miliary (Bonnet and Jambon-Genet, 1948). In the initial phase the tumour is not more than a few disk diameters wide (Stevens and Reeh, 1958; Ferry, 1967). The elevation as a rule amounts to less than 6 diopters (Stevens and Reeh, 1958).

At successive examinations a number of changes are seen and the lesion in only a few weeks' time assumes a different aspect (Bonnet and Jambon-Genet, 1948; Albert et al., 1967b). The tumour in general grows diffusely laterally of the choroid with only a minimal increase in thickness, because it chooses the line of least resistance (Ferry, 1967;

Gass, 1974). Separate foci may fuse into a large placoid tumour (Sattler, 1926). Homogeneous solitary tumours also occur (Pau, 1979). In case of a nodular miliary lesion, increase of volume occurs and the lesion runs into a dome-shaped elevated mass.

The tumour extends to the vitreous, bringing about an oval little-elevated tumour which grows more convex (Bonnet and Jambon-Genet, 1948). Sometimes, the tumour is irregular and multinodular (Stephens and Shields, 1979; Shields, 1983).

In a number of patients, the tumour is markedly elevated and dome-shaped as in a primary melanoma (Shields, 1983). Such an elevated, localized growth reportedly occurs in tumours at the periphery, in contrast to the flatter lesions with a broad base in the posterior pole (Simpson, 1961). Metastases of breast cancer are said to grow without much elevation (Simpson, 1961), but exceptionally may be very large (Char, 1989). This in contrast to metastases of lung cancer (Norton, 1969). Other authors state that metastases of breast cancer on the contrary are mostly more elevated than metastases of lung cancer (Freedman and Folk, 1987).

It is rare for metastases to break through Bruch's membrane (Gass, 1974). The mushroom shape, typical of large melanomas, therefore almost never occurs and is described only sporadically (Friedenwald et al., 1957; Howard, 1965; Regan, 1966; Ferry, 1967; Shields, 1983; Gartner, 1985; Spencer, 1986; Kerman and Fishman, 1987; Char, 1989). Mostly, these metastases are mistaken for primary malignant melanomas of the choroid. If the eye is enucleated, histopathological examination reveals a lesion of metastatic nature, often a metastasis of a bronchial carcinoma (Jarrett, 1976) or sometimes, of a clear cell tumour of the kidney (hypernephroma, Grawitz tumour) (Hart, 1962).

The ***delineation*** of the lesion is described by a number of investigators as ill-defined without sharp or discrete margins (Stevens and Reeh, 1958; Gillet, 1971; Gass, 1974). Other authors describe the edges of the tumour as well-delineated and abrupt (Sattler, 1926; Gilbert, 1939; Shields, 1983).

The ***colour*** of the tumour is described as amelanotic, yellowish, pinkish, greyish-white to white or yellowish-grey (Table 1.4.2.1).

Table 1.4.2.1 Colours of choroidal metastases

Colour	Author
Amelanotic	Gass, 1974; Stephens and Shields, 1979; Shields, 1983
Yellow (pale-yellow, yellowish-white, yellowish-brown, yellowish-pink, creamy)	Sattler, 1926; Gilbert, 1939; Bonnet and Jambon-Genet, 1948; Simpson, 1961; Gass, 1974; Hayreh, 1974; Maor et al., 1977; Shields, 1977b; Schiffer et al., 1978; Shields, 1983; Gartner, 1985
Pinkish	Norton, 1969; Haye, 1972; Reese, 1976
Greyish-white or white	Bonnet and Jambon-Genet, 1948; Norton, 1969; Gass, 1974
Grey or yellowish-grey	Stevens and Reeh, 1958; Simpson, 1961; Schiffer et al., 1978; Pau, 1979

In spite of this range of colouring, a choroidal metastasis as a rule is described as light in colour. Metastases have no intrinsic tumour pigment. Exceptions to this rule are metastases of malignant skin melanomas, which are often pigmented (Shields, 1976/1983; Char, 1989). However, owing to the mostly rapid growth, secondary alterations occur in the retinal pigment epithelium. These consist in general of depigmentation, degeneration, mobilization and destruction of the pigment epithelium. Sometimes, spotty lumps of dark grey or orange pigment are seen on the tumour surface. These pigmentary changes may be interpreted as proof of production of pigment by the tumour. Biomicroscopy is of great value for the differentiation of this surface pigment from the intrinsic pigment of melanomas (Gass, 1972).

The pigment changes lead to the mottled aspect, so characteristic of metastases, with depigmentation on the tumour surface (Gilbert, 1939; Stevens and Reeh, 1958; Norton, 1969; Hayreh, 1974; Reese, 1976; Maor et al., 1977). Shields (1983) and Lommatzsch (1989) described this as golden-brown leopardskin-like. The cause of this mottled aspect is proliferation of the retinal pigment epithelium; it is independent of whether the tumour is or is not pigmented (Wallow and Ts'o, 1972).

The ill-defined margin of the lesion may be slightly pigmented (Gillet, 1971) and fades into the surrounding normal-appearing retinal colour (Reese, 1976).

Shields et al. (1976) in all patients with a choroidal metastasis of an adenocarcinoma described lumps of lipofuscin on the tumour surface as reddish-brown or dull brown pigment. According to Smith and Irvine (1973) this never occurs in metastases.

Damage to the pigment epithelium leads to a ***cystoid oedema*** of the overlying retina which turns more or less cloudy. This cloudiness therefore is not due to invasion of the tumour into the retina. The area of retinal oedema as a rule is much larger than the area of the underlying choroidal lesion (Simpson, 1961; Ferry, 1967). Restriction of the lesion to the choroid without involvement of the overlying retinal pigment epithelium is also possible, however (Gass, 1972).

A serous exudation occurs in the subretinal space and less often in the subpigment epithelial space (Simpson, 1961; Ferry, 1967; Gass, 1972; Schatz et al., 1978). In the process, the subretinal humour increases and the cloudy exudates may mask the underlying tumour picture and give it a white appearance (Stevens and Reeh, 1958; Simpson, 1961; Ferry, 1967; Norton, 1969; Gass, 1974). The cloudy-turbid, flatly detached retina fairly often bulges markedly (Ferry, 1967; Pau, 1979). This serous ***retinal detachment*** occurs frequently in the macula (Gass, 1972; Shields, 1983).

A retinal detachment occurs often in choroidal metastases and is a typical feature. It may be observed even in the earliest phases of the tumour (Witmer, 1967). In general, the retinal detachment is flat; it reportedly occurs in 90% of all choroidal metastases (Norton, 1969; Reese, 1976; Shields, 1976/1977b; Pau, 1979; Stephens and Shields, 1979; Freedman and Folk, 1987). No retinal breaks are seen in the process (Albert et al., 1967), although Howard (1968) reports a retinal break in 5 to 10% of retinal detachments secondary to tumours.

A choroidal metastasis may also be accompanied by a choroidal detachment, just as may occur in malignant melanomas. This is rare, however (Sneed et al., 1991).

Table 1.4.2.2 Localization of uveal metastases

Author	Total number of patients/eyes	Choroid				Ciliary body				Iris			
		Choroid *		Choroid only		Ciliary body **		Ciliary body only		Iris ***		Iris only	
		N	%	N	%	N	%	N	%	N	%	N	%
Hemmes, 1969	∞ 121 patients	111	92	109	90	7	6	2	2	7	6	4	3
Ferry and Font, 1974	196 patients	170	87	140	71	# 56	# 29	0	0	# 56	# 29	6	3
Stephens and Shields, 1979	∞∞ 83 eyes	78	94	77	93	3	4	3	1	4	5	3	4
Castro et al., 1982	94 eyes	80	85	80	85	9	10	9	10	5	5	5	5

** also a localization in the ciliary body and/or the iris; ** also a localization in the choroid and/or the iris; *** also a localization in the choroid and/or the ciliary body; # 56 patients (29%) metastases in the 'anterior segment' and also in the choroid, 23 patients (12%) metastases in the 'anterior segment' only; ∞ six patients uveal localization unknown; ∞∞ two patients uveal localization unknown*

Localization: metastases are localized in the uvea more often than in any other ocular structure (Simpson, 1961; Jensen, 1970; Shields, 1976; Hutchison and Smith, 1976; Castro et al., 1982; Shields, 1983). Ferry (1973) and Ferry and Font (1974) reported a proportion of 86.3%.

The frequent involvement of the uvea in metastatic processes is due to its relatively extensive vascularization and to the fact that it constitutes a nutritional condition suitable for metastases (see Chapter 1.2) (Lemoine and McLeod, 1936).

Within the uvea, the choroid is involved most frequently (Sanders, 1938; Ferry and Font, 1975) (Table 1.4.2.2). The proportions mentioned vary between 85 and 94%. Only few uveal metastases are localized in the anterior segment: 4 to 10% in the ciliary body and 5 to 6% in the iris (Hemmes, 1969; Ferry, 1973; Ferry and Font, 1974/1975; Stephens and Shields, 1979; Castro et al., 1982). Ferry and Font (1975) reported a larger proportion of disseminations in the anterior segment, viz. 29% of all patients with uveal metastases. In 13% of the patients, only the anterior segment is affected, without involvement of the choroid.

Most metastases in the posterior pole have a temporal localization (Duke-Elder and Perkins, 1966; Ferry, 1967; Ferry and Font, 1973; Meythaler and Herold, 1979; Castro et al., 1982; Gartner, 1985; Arné and Mathis, 1986; Freedman and Folk, 1987; Brink et al., 1988; Hoogenhout et al., 1989). This predilection for the temporal choroid is also mentioned in older literature on uveal metastases (Lagrange, 1901, Maggiore, 1922). The macula is said to be involved in about 15% (Brink et al., 1988; Hoogenhout et al., 1989) or in 40% of the cases of choroidal metastases (Freedman and Folk, 1987; Wharam and Schachat, 1989). However, choroidal metastases may also occur outside the posterior pole (Bonnet and Jambon-Genet, 1948). Proportions vary from 8% (Freedman and Folk, 1987) to 19% (Hoogenhout et al., 1989), 55% (Pau, 1979) and even 67% (Saßmannshausen et al., 1990).

The predilection of uveal metastases for the posterior pole is related to the distribution of the supplying vessels. The ciliary arteries arise from the ophthalmic artery less sharply than its central branch (DeLong, 1933). The posterior segment of the uvea receives its blood supply from 20 short posterior ciliary arteries, the anterior segment from 2 long posterior and 7 short anterior ciliary arteries. Most thrombi of tumour cells land in the posterior short ciliary arteries and are carried to the choroid, especially to the area temporal of the optic disk where the supply vessels have the largest number and diameter (Lagrange, 1901; Duke-Elder and Perkins, 1966; Gillet, 1971; Reese, 1976; Meythaler and Herold, 1979; Castro et al., 1982; Gartner, 1985).

A lower frequency of metastases in the iris and the ciliary body might also be connected with the muscles in this region, the movements of which might impair the implantation of metastases (Ask, 1934; Schlagenhauff, 1950). Moreover, inflammatory reactions in metastases in the anterior segment might mask the tumour, causing it to be diagnosed less readily (Duke-Elder and Perkins, 1966) (see Chapter 1.2.2).

In older literature on uveal metastases it is generally assumed that metastases occur more often in the left than in the right eye. This was supposed to be due to the fact that the left carotid artery branches off from the aorta more at right angles than the right one, and is larger as well. As a consequence, tumour emboli would be carried sooner to the left eye (Lagrange, 1901; Sattler, 1926). Usher (1923), on the other hand, was of the opinion that metastases are distributed equally over both eyes.

Recent literature shows that there is no clear predilection for the right or the left eye (Table 1.4.2.3).

Table 1.4.2.3 Laterality of uveal metastases in terms of percentage

Author	Total number of eyes *	Localization	Right eye %	Left eye %
Pau, 1979	25	choroid	36	64
Stephens and Shields, 1979	78	uvea	42	58
Hutchison and Smith, 1979	94	eye/orbit	44	56
Castro et al., 1982	118	intraocular	46	54
Merriam, 1961	27	choroid	48	52
Mewis and young, 1982	82	choroid	48	52
Ferry and Font, 1974	196	uvea	50	50
Saßmannshausen et al., 1990	214	choroid	51	49
Hoogenhout et al., 1989	39	choroid	55	45
François et al., 1976	50	choroid	56	44

* *eyes with known localization*

Table 1.4.2.4 Bilateral ocular metastases

Author	Total number of patients	Localization	Bilateral metastases N	%
Ferry and Font, 1974	186	uvea	10	5
Jensen, 1976	18	eye	1	5
Maggiore, 1922 *	70	choroid	12	17
Castro et al., 1982	101	eye/orbit	17	17
Hutchison and Smith, 1979	78	eye/orbit	14	18
Stephens and Shields, 1979	70	uvea	13	19
Lemoine and McLeod, 1936 *	229	uvea	48	21
Hemmes, 1969	121	choroid	32	25
Usher, 1923 *	98	choroid	30	30
Freedman and Folk, 1987	58	choroid	17	30
Saßmannshausen et al., 1990	160	choroid	54	34
François et al., 1976	37	choroid	13	35
Brink et al., 1988	49	choroid	17	35
Mewis and Young, 1982	67	choroid	27	40
Merriam, 1961	35	choroid	20	57
Meythaler and Herold, 1979	21	choroid	12	57

* *review of literature*

Ocular metastases occur ***bilaterally*** in 20 to 40% of the cases (Table 1.4.2.4). A lower proportion, of 5%, is reported by Ferry (1973), Ferry and Font (1974) and Jensen, 1976). Meythaler and Herold (1979) indicate a larger proportion, of 57%, while according to Bonnet and Jambon-Genet (1948) bilateral metastases are even found in as many as 75% of the patients.

Thorough examination will in the long run reveal metastases in both eyes in the majority of the patients (Gillet, 1971).

Multiple lesions in one or both eyes occur often in choroidal metastases and are characteristic of the metastatic origin of the tumours (François and De Vos, 1958; Norton, 1969; Theodossiadis, 1978; Shields and Young, 1980; Shields, 1983; Arné and Mathis, 1986). If multiple lesions are observed, a metastatic process is practically certainly involved (Gartner, 1985). Ferry (1969), however, is of the opinion that multiple metastases in one eye occur only occasionally.

As Table 1.4.2.5 shows, the proportions of multiple choroidal metastases in one eye vary from 15 to 36%. The study of Mewis and Young (1982) was exclusively concerned with patients with breast cancer. Their proportion of multiple lesions is distinctly higher than in the other three study groups, with a more mixed population of malignancies.

Table 1.4.2.5 Frequency of occurrence of multiple choroidal metastases in one eye

Author	Total number of eyes	Multiple metastases N	%	Number of lesions
Brink et al., 1988	66	10	15	2 - 4
Stephens and Shields, 1979	83	14	17	2 - 6
Freedman and Folk, 1987	77	17	22	*
Mewis and Young, 1982	67	24	36	3 - 16 **

** number of lesions not mentioned; ** total number of lesions in both eyes*

In uveal metastases, ***haemorrhages*** may sometimes occur as the first sign of an intraocular malignancy. This may render the diagnosis more difficult (Maxwell, 1954; Evans et al., 1971; Castro et al., 1982; Gartner, 1985). The localizations of these haemorrhages may be on the tumour surface and retinal (Vanni and Barilla, 1960; Thompson et al., 1961; Reese, 1976), beneath the pigment epithelium (Gass, 1974), or subhyaloidal (Evans et al., 1971) and they may also occur as a haemorrhagic retinal detachment masking the tumour (Gass, 1967; De Bustros et al., 1985). Vitreous haemorrhages are also possible in choroidal metastases (Koenig et al., 1963; Font et al., 1966; Ginsberg et al., 1970). However, occurrence of haemorrhages in intraocular metastases is rare. Freedman and Folk (1987) at the first ocular examination of 58 patients with an intraocular metastasis found a retinal haemorrhage in only one patient and vitreous haemorrhages in only two.

Uhthoff (1891), on the other hand, was of the opinion that choroidal carcinomas have a distinct tendency to bleed. The alleged cause of this was erosion of the vessel walls. Together with developing necrosis, these haemorrhages would explain inflammation-like abnormalities and attacks of serious pain.

Castro et al. (1982) attributed the presence of haemorrhages to small choroidal

vessels being blocked by tumour cells. This may lead to a rupture and subsequently, to a haemorrhage in the choroid. These haemorrhages may cause the characteristic mottled aspect of the tumour surface.

At histological examination, fresh or older haemorrhages are often encountered in the cell nests, often associated with necrosis (Sattler, 1926; Ginsberg, 1928; DeLong, 1933)

Ferry (1967) described ***iridal metastases*** as follows: *'In a typical case metastatic carcinoma of the iris appears clinically as a nodular lesion at the anterior surface of the iris with fairly well-defined borders. More than one nodule may be present, and any part of the iris may be involved. Most often the color of the tumor is gray or light brown, and the tumor often contains very prominent blood vessels.'*

The shape of the lesion is also described as diffuse or diffuse nodular (Gartner, 1985, Char, 1989). Several lesions of different sizes may be present. Sometimes, iridal metastases are very subtle and only to be observed with the slit lamp (Shields, 1983). The pupils may be irregular (Gartner, 1985).

Just as in choroidal metastases the colour is highly variable. Iridal metastases are nearly always amelanotic (Stephens and Shields, 1979, Shields, 1983; Char, 1989) Occasionally, a grey, red or reddish brown colour is described (Gartner, 1985).

According to certain investigators, iridal metastases show no predilection for any particular quadrant (Usher, 1923; Shields, 1983). However, Ferry and Font (1975) in 26 patients with metastases only in the anterior segment found a predilection for the horizontal over the vertical meridian.

The consistency of the tumour is gelatinous (Shields, 1983; Lommatzsch, 1989) or fleshy (Stephens and Shields, 1979).

On the tumour surface vessels are often seen (Shields, 1983; Gartner, 1985). A hyphaema may be present (Duke and Kennedy, 1958; Shields and Young, 1980). Ferry and Font (1975) in six out of 26 patients (29%) with a metastasis in the iris and sometimes in the ciliary body as well, encountered a hyphaema In case of a recurrent hyphaema the possibility of iridal metastases should be considered (Smith, 1976). The hyphaema often causes an iridal metastasis to go unnoticed (Dhermy, 1979, Castro et al., 1982; Abramson, 1984)

In addition, there may be signs of inflammation, with or without a hypopyon (Kanski, 1984).

Metastases in the ciliary body are rare (Ferry, 1973; Ferry and Font, 1975). They are hardly distinguishable from amelanotic melanomas (Shields, 1983; Lommatzsch, 1989) In general they start in the anterior part of the ciliary body, in the area of the angle of the anterior chamber, and invade both the angle and the base of the iris. They occur more rarely in the pars plana and the posterior part of the ciliary body (Hogan, 1964). Sometimes, prominent episcleral vessels indicate the presence of a tumour (Shields, 1983). Regarding multiple lesions in the ciliary body no literature is available. A hyphaema may be present (Kreibig, 1936; Schlagenhauff, 1950; Font et al., 1967).

1.4.3 Fluorescein angiography

Fluorescein angiography is a technique of sequentially visualizing the fluid dynamics within the vascular system of the retina and uvea and the perfusion of the tissue which it supplies (Federman and McGuire, 1989). The first ophthalmological description of this technique dates from 1961 (Novotny and Alvis, 1961).

Sodium fluorescein is highly water soluble and in blood is partly bound to albumin. It is excreted rapidly, mostly by the liver and the kidney. In the bloodstream, fluorescein is excited by light with a wavelength of 465 nm; it has an emission spectrum of 525 nm. Following injection into an arm vein, the area to be examined is illuminated and after filtration, photographed (Federman and McGuire, 1989; Richard, 1989).

In particular, angiography with use of indocyanin green under infrared illumination renders the deeper vascularization (choroid) clearly visible (Bacin et al., 1981; Bisschoff, 1985)

The commonest side effect of fluorescein angiography is transient nausea, 15 to 20 seconds after injection. Some patients complain of itching. Anaphylactic shock has been described but is a highly exceptional complication (Bresnick, 1969; Stein and Parker, 1971; Federman and McGuire, 1989)

Technique at angiographic examination of the fundus, two separate vascular systems are to be distinguished. the superficial retinal circulation and the choroidal vasculature situated beneath the retinal pigment epithelium (RPE) (Bresnick, 1969). In lightly pigmented fundi the fluorescein staining of the large choroidal vessels can be observed, following which the choriocapillaris fills in irregular patches, just before the retinal arteries (Federman and McGuire, 1989).

After injection fluorescein reaches the retinal vessels in 8 to 10 seconds. The fluorescein study can be divided into an arterial, arteriovenous and venous phase (Bresnick, 1969). The capillaries of the retina are not fenestrated and in normal circumstances show no leakage, in contrast to the fenestration of the endothelium of choroidal vessels through which fluorescein rapidly escapes into the extracellular space (Federman and McGuire, 1989). Owing to this leakage and because of staining of the collagen tissue of the sclera, the fluorescence persists for a long time even after the fluorescein has left the retinal vessels (Bresnick, 1969)

The degree of pigmentation and pathological alterations of the RPE have great influence on the angiographic features of the choroid. In normal circumstances the RPE constitutes a barrier to leakage or transportation of fluorescein.

Compared with the normal fluorescence of the fundus, hyper- and hypofluorescence are distinguished. Hyperfluorescence occurs owing to the abnormal presence of fluorescein in a location, a higher-than-normal concentration of dye in any location where it is also observed under normal circumstances or increased transmission of fluorescence from an area of normal dye concentration and distribution due to a pathological overlying condition. Hypofluorescence occurs because of decrease of fluorescence in a region where it is normally found and by block of the transmission of fluorescence caused by overlying pathological alterations.

Tumour cell masses are in general associated with increased vascularization, resulting in more fluorescein in the area. This fluorescein probably leaks rapidly into the stroma, which results in hyperfluorescence. Hyperfluorescence may also be caused by transmission through defects in the RPE and by presence of the substance in cystic retinal

spaces (Federman and McGuire, 1989).

The earliest descriptions of fluorescein angiography in uveal metastases date from 1964 (Norton et al.). In metastases no pathognomonic image is seen. The fluorescence varies greatly in dependence on changes of the RPE, tumour pigment and tumour vessels, vascular permeability, secondary degeneration and necrosis and haemorrhages in the lesion (Wessing, 1968, Farnarier et al., 1973; Fishman, 1977, Schiffer et al., 1978; Danis, 1979). The image is independent of the histology of the primary tumour (Kolin, 1969; Hayreh, 1974; Amalric, 1979).

In the early vascular phase, ***choroidal metastases*** are described as invisible or hypofluorescent (Norton et al , 1964, Gass, 1972). If fluorescence is seen at all, it occurs only in the arteriovenous phase (Offret and Haye, 1971) or in the venous and late phases (Orsoni, 1968, Tanev and Ilieva, 1980; Bonnin, 1986, Lommatzsch, 1989). Sometimes, early fluorescence is observed, as in haemangiomas (Schiffer, 1978)

The fluorescence in metastases is usually spotty and not very pronounced; it is distributed fairly evenly and renders the tumour homogeneously fluorescent, with a poorly delineated margin (Wessing, 1977; Bonnin, 1986). A secondary detachment of pigment epithelium or retina is of great importance. In case of destruction of the RPE, hyperfluorescence occurs (Gass, 1972; Kelley, 1977, Wharam and Schachat, 1989). An extensive detachment frequently causes a mottled aspect in the arteriovenous phase (Norton, 1969) As a rule any subretinal fluid becomes fluorescent at the same time as or after the tumour, due to accumulation of fluorescein (Norton, 1969; Gass, 1974; Bonnin, 1986) Owing to the subretinal fluid, the retinal capillaries in the early phase are clearly visible but not abnormal (Bonnin, 1986) or only dilated without microaneurysms or leakage (Wessing, 1977), although Karel and Peleska (1972) described a patient with microaneurysms Sometimes, cystoid retinal oedema is present owing to damage to the RPE (Schatz et al , 1978), while according to other authors this argues against a metastasis (Davis and Robertson, 1973, Fishman, 1977, Schiffer et al., 1978).

In metastases, hyperfluorescent spots are described which are particularly clear in the venous phase (Farnarier et al , 1973, Scheffer, 1973, Shields, 1983; Turut et al., 1987) These spots are brought about by drusen in Bruch's membrane and by multiple defects of the RPE (Voigt and Pulhorn, 1977).

Regarding the presence of large vessels in the tumour there is no consensus in the literature. According to certain authors, these are not present in metastases (Davis and Robertson, 1973; Hayreh, 1974, Fishman, 1974, Schiffer et al., 1978, Danis, 1979; Lommatzsch, 1989), but other investigators do describe them, especially in spherical tumours (Gass, 1974, Voigt and Pulhorn, 1977, Wessing, 1977; Shields, 1983).

Orange or brown pigment on the tumour surface remains hypofluorescent (Schatz et al., 1978; Shields, 1983). Socalled 'multilake' areas argue against a metastasis (Hayreh, 1974; Schiffer et al., 1978, Shields, 1983)

A number of authors have attempted to distinguish patterns in the fluorescein angiography of choroidal metastases. Davis and Robertson (1973) described three types: the most frequent was a generally early, arterial or arteriovenous, increasing fluorescence; less often, a blockage of the background fluorescence was observed against which the entire tumour stood out as a dark or irregular spotty area with only arteriovenous and late but progressive and diffuse staining. In one patient an early arteriovenous fluorescence was seen which decreased in the course of the examination with only punctate

fluorescence in the late phase. The authors emphasize that no single pattern is characteristic of metastases.

Hayreh (1974) distinguished four groups. In flat mottled, yellowish-brown tumours progressive fluorescence in the arterial or arteriovenous phases is described with late staining. In moderately elevated localized uniformly yellowish-brown tumours, masking of the choroidal fluorescence in the early phase was seen, with a slowly diffusing staining in the arteriovenous and late phases. In large yellowish-white lesions, no fluorescence was seen. This is rare. Finally, the least common, lesions which fluoresce in the arterial and the arteriovenous phases and which fluorescence fades as the choroidal fluorescence decreases, which indicates an unmasking of the choroidal staining. The late fluorescence is restricted to spots. Hayreh found no typical pattern of metastases, either. Consequently, the diagnosis of a choroidal metastasis cannot be made solely on the basis of the fluorescein angiogram (Schiffer et al., 1978).

Owing to the anterior location the vascular structure of the ***iris*** is in part immediately visible. Iridal capillaries normally do not leak. An iridal tumour standing out as a dark spot is regarded as benign. Mottled or diffuse leakage and weak fluorescence at the central margin of the tumour indicate malignancy (Demeler, 1981).

Iridal metastases are more vascularized than can be established clinically and cause leakage of fluorescein (Freeman and Friedman, 1975). A network of vessels is seen, which fill in early phases and leak profusely. This leakage is not restricted to the margin of the mass, as in melanomas, but also occurs at the pupillary margin or other not tumour-related iridal structures (Kottow, 1978). According to Demeler (1981), marginal fluorescence occurs only in melanomas. In metastases he also did not observe the fluorescence at the tumour base, as seen in peripherally localized, highly prominent melanomas of the root of the iris.

In connection with technical problems, fluorescein angiography in tumours of the ***ciliary body*** has been described only sporadically (Federman and McGuire, 1989; Fries and Cher, 1990). Obtaining data is possible if the iris also is involved in the process (Brovkina and Chichua, 1979).

1.4.4 Echography

Echography (ultrasonography, USG) plays an important part in the diagnostics of intraocular tumours, particularly in case of opaque media (cataract, vitreous haemorrhages) and in bullous retinal detachments with cloudy subretinal fluid (Lommatzsch, 1989).

In 1956, echographic ocular examination was applied for the first time to patients with an intraocular tumour (Mundt and Hughes, 1956; Oksala and Lehtinen, 1957). Initially, only solid processes could be detected and no conclusion could be drawn regarding the histological nature (Buschmann, 1966; Bellone and Cagigrigoriu, 1969). Coleman in 1973 was the first to succeed in differentiating between benign and malignant lesions. Subsequently, more sophisticated echographic diagnostic criteria for the various intraocular tumours were laid down (Coleman et al., 1974; Ossoinig and Blodi, 1974).

Technique: the patient is preferably examined in the supine position. The cornea and conjunctiva are anaesthetized locally and after application of a contact fluid (methylcellulose 2%), the transducer is placed in direct contact with the globe. The eye is then examined systematically in all quadrants. Any abnormalities found may be photographed or stored in a computer. Echographic examination gives the patient no discomfort (Jakobiec, 1978; Verbeek, 1985).

At echographic examination tissue is scanned with a piezoelectric resonator crystal: the transducer. It emits pulses of ultrasound and is alternatingly transmitter and receiver. After the sound emitted has engaged in interaction with the tissue (reflection, absorption, scattering) it is received back by the transducer. In ophthalmology, use is made of sound waves with frequencies from 8 to 12 MHz. The reflected sound energy is converted into an electronic signal and visualized by means of an oscilloscope or TV monitor.

These echoes are reproduced unidimensionally by means of the A- (Amplitude) scan and bidimensionally by means of the B- (Brightness) scan. The amplitude of the echoes provides quantitative information on the acoustic properties of the tissues. The grey tone of the B-scan is a more qualitative measure of these properties. The anatomical morphological information in the A-scan is limited to distances and dimensions of reflecting structures. The B-scan gives a bidimensional image the topography of which is a faithful representation of the anatomy.

Membranes present in the vitreous humour can be differentiated with quantitative (***A-scan***) and kinetic criteria. Solid lesions with a prominence of at least 0.5 mm can be detected by means of echography. However, for further differentiation of the pathology by means of the echogram several echo spikes, and consequently a longer tract, are required because it is necessary to evaluate degree of reflection, homogeneity, vascularity and attenuation. To be considered for echographic differential diagnostics, therefore, tumours must have a prominence of 2 to 2.5 mm or more. For this purpose the A- and B-scans supplement one another. This implies that a series of criteria are used in which both imaging techniques play a part.

The height or amplitude of the echo spikes from the infrastructure of the tumour which are brought about by tissue inhomogeneities, vacuoles, necrotic zones, etcetera, is compared with the retinal reflectivity. With marked variations in the socalled acoustic impedance (product of sound velocity and mass density) these tumour echoes are relatively high, while they have a low amplitude in tissues composed of relatively small structures. In homogeneous tissues, with tightly packed cells, a relatively low degree of absorption will occur, which results in a gradual decrease of the amplitude of the echo spikes. It should be noted that the representation of this decrease in the A-scan depends on the type of amplifier in the echo apparatus and on its adjustment. Numerous and irregular tissue interfaces in the tumour render the echographic image inhomogeneous (Coleman et al., 1974; Ossoinig and Blodi, 1974).

The attenuation of the ultrasound can be measured by means of an absorption coefficient, called the kappa angle, which is determined by the decrease of the amplitude of the echoes by the tumour mass (Ossoinig and Blodi, 1974; Verbeek, 1985).

With the aid of the bidimensional ***B-scan*** it is possible to determine the shape of the lesion and the size of the tumour base. In choroidal melanoma, the choroid is infiltrated completely by homogeneous tumour tissue. In the echogram this leads to an

acoustic gap in the reflectivity pattern of the choroid. This is called the choroidal excavation, a term comparable to the papillary abnormality in glaucoma: the glaucomatous excavation. In melanomas this choroidal excavation is observed with a variable frequency (Coleman et al., 1974; Poujol, 1986). Incompletely known influences of the apparatus are undoubtedly involved here.

From the infrastructure of the tumour fast, spontaneous movements can be recorded (vascularity) which are caused by the bloodstream in the tumour vessels.

In large, prominent tumours attenuation of the ultrasound by the tumour mass is established; this is depicted as a shadowing in the orbital fat behind the tumour. Between the tumour mass and the orbital shadow the orbital fat pattern is intact (Coleman, 1975). Any penetration of the tumour through the sclera into extraocular structures can be established if the reflectivity of the tumour tissue is different from that of the surrounding orbital fat. In the low-reflective choroidal melanoma, a clear spot in the high-reflective orbital fat contiguous to the tumour is detected then.

Apart from contact echography, ***immersion B-scan*** echography may be used. This method permits good examination of the anterior segment. When the transducer is applied directly to the globe, the region immediately behind the transducer lies in a dead zone (5 mm large). This zone is followed by an area in which structures can only poorly be assessed. As a consequence, the first 5 to 8 mm of the eye cannot be inspected accurately. With the aid of a perspex cylinder (diameter 18 to 22 mm, height 20 mm) filled with methylcellulose 2% placed on the anaesthetized cornea, the cornea, anterior chamber, iris, ciliary body and lens can be imaged adequately (Verbeek, 1990; Verbeek and Mitropoulos, 1991). An older immersion method uses a waterbath applied to the eye (Ossoinig, 1972).

Uveal metastases at echographic examination as a rule show up as flat solid lesions with a relatively broad base (Coleman, 1973; Brink et al., 1988; Guthoff, 1988). More convex or lobular tumours are also observed (Coleman et al., 1974; Shields and Tasman, 1977). The mushroom shape, typical of melanomas, is described only sporadically (Kerman and Fishman, 1987). The prominence of metastases is usually less than 7 mm (Poujol, 1986).

A high initial echo, originating from the tumour surface and caused by the interface between the vitreous humour and the retina is followed subretinally by spikes of high reflectivity bunched closely together (Coleman, 1973; Chang et al., 1978; Poujol and Chaintron, 1988). The tumour is delimited posteriorly by a high scleral spike. The relatively high tumour echoes are caused by the numerous interfaces between groups of tumour cells and tissue partitions, intercellular substances and areas with necrosis (Ossoinig and Blodi, 1974). Owing to this non-homogeneous tissue structure, the internal tumour echoes of metastases form an irregular picture (Goes, 1981; Verbeek, 1985; Poujol, 1986; Bigar, 1988). When the intensity of the transmitted energy is reduced, the image of a metastasis remains solid, in contrast to melanoma (Coleman et al., 1974).

A choroidal excavation is observed either not at all (Coleman et al., 1974; Gonvers et al., 1979; Kerlen, 1980) or only rarely (Neetens et al., 1984). Only Poujol (1986) described such an excavation in 42% of the patients. Vascularity is observed only sporadically (Ossoinig and Blodi, 1974; Neetens et al., 1984; Freedman and Folk, 1987). Neetens et al. (1984) and Coleman and Abramson (1989) described an orbital shadow in

large metastases.

A few investigators point out that metastases may sometimes show a low reflectivity. These are tumours with closely packed, evenly distributed cells such as metastases of an oatcell carcinoma, seminoma, thyroid carcinoma and malignant skin melanoma, which as a rule have a regular infrastructure (Freyler and Egerer, 1977; Ossoinig and Harrie, 1983; Doro et al., 1984; Kerman and Findl, 1984; Verbeek, 1985; Brink et al., 1988; Guthoff, 1988). In these tumours, vascularity is often observed (Verbeek, 1985; Freedman and Folk, 1987).

In metastases different malignancies are described as the primary tumours. This is the cause of the histological diversity of tumours that may metastasize to the choroid and of the fact that their echograms are less clear-cut than those of the malignant choroidal melanoma. For this reason, in the clinical and echographic diagnostics of tumours, the metastasis should always be differentiated from the homogeneous melanoma (Coleman, 1973; Verbeek, 1985; Brink et al., 1988).

Computer analysis of the spectral data of a solid process is a recent development in echography. It allows a quantitative analysis of echograms as obtained with the B-scan. This might allow a differential diagnosis between spindle B melanomas and mixed-epithelioid melanomas and metastases (Thijssen and Verbeek, 1981; Reibaldi et al., 1988). According to Coleman and Lizzi (1983), this can even be done with 98% reliability.

1.4.5 Computed tomography (CT scan)

With the aid of computed tomography (CT scan), the eye can be examined in its relation to other structures in the orbit. The retina, choroid and sclera are depicted as one layer. Excentric thickening of this layer without inflammatory changes, associated masses, nerve thickening or muscle enlargement may be a sign of a neoplasm of the choroid (Bernardino et al., 1978). In tumours with a prominence less than 3 mm, echography is superior to CT scanning (Desjardins, 1986a; Peyman and Mafee, 1987). For examination of lesions of the ciliary body the CT scan is reported to be more suitable (Damato and Foulds, 1986).

Computed tomography is said to be the examination of first choice for the detection of extrascleral growth (Peyster et al., 1985; De Keizer et al., 1986; Desjardins, 1986a) and to be a good method for in-vivo determination of the size of the tumour (Peyster et al., 1985).

In metastases, variable images of elevated or flat and diffuse masses are described (Mafee et al., 1985; Desjardins, 1986a; Peyman and Mafee, 1987). The tumours can be visualized better after contrast enhancement (Desjardins, 1986a; Yeo et al., 1983). An associated retinal detachment is observed frequently (Bellamy and Husband, 1985).

Differentiation between metastases and melanomas of the choroid by means of the CT scan may be difficult (Mafee et al., 1985; Peyman and Mafee, 1987).

1.4.6 Magnetic resonance imaging (MRI)

Magnetic resonance imaging (MRI) is based on manipulation of protons in tissues which may be regarded as elementary magnets. They may be aligned in parallel to the permanent magnetic field of the examination apparatus. Under the influence of high-frequency impulses the elementary magnets take up energy, which causes the net magnetization to turn to a direction perpendicular to the main magnetic field. After cessation of the impulses an alternating current is induced in the receptor coil: the MR signal (Guthoff and Seiler, 1989). The intensity of the signal depends on the proton density of the tissue, on the T_1 relaxation time (the return of the protons to their original state), the T_2 relaxation time (the description of the phase cohesion loss) and on the movements of the hydrogen nuclei (Chambers et al., 1987; Guthoff and Seiler, 1989; Kolodny et al., 1989). Higher resonance frequencies give MR images with a better signal-noise ratio (Kolodny et al., 1989).

MRI shows a clear distinction of an intraocular tumour from the vitreous humour, the sclera and the ciliary body. For this reason, MRI appears to be a more sensitive method for demonstration of extraocular growth than echography (De Keizer et al., 1989). Like the CT scan, however, MRI requires a minimal prominence of 3 mm for good visualization (Chambers et al., 1987; Mafee et al., 1987).

Metastases display variable intensities at both T_1 and T_2 weighted images. The causes of this may be an accompanying haemorrhage, exudation, necrosis and the quantity of melanin (Haik et al., 1987b). In general, a hyperintensity is described in T_1 and T_2 weighted images of metastases (Chambers et al., 1987; Mafee et al., 1987; Peyman and Mafee, 1987; Guthoff and Seiler, 1989). For further contrast enhancement Gadolinium DTPA (Brab et al., 1991) or ^{31}P (De Potter et al., 1991) may be used.

1.4.7 Perimetry

The visual field is that portion of space in which to the steadily fixating eye several objects are visible simultaneously. Small objects are perceived only if they are localized close to the visual axis of the eye. Larger and brighter stimuli are required to be perceived in the peripheral visual field. The purpose of perimetry is to perform a quantitative examination of the visual acuity in all parts of the visual field. Defects in the normal visual fields may be detected, quantified and plotted as contour lines, isopters, within which an identical object is observed (Harrington, 1956).

A scotoma is an area of decreased visual acuity within an area of (relatively) normal visual acuity. It is called absolute if at the site of the scotoma no stimuli at all, regardless of size or brightness, are perceived. The site of the optic nerve constitutes such an absolute scotoma in the visual field. If a larger or brighter test object is observed, the scotoma is called relative (Harrington, 1956).

In tumours changes in the visual field are caused by involvement of the retina and by the associated retinal detachment. The defect corresponds to the site of maximal damage to the retina. If the tumour breaks through into the vitreous, the neurofibrils appear to be forced aside rather than destroyed. In the latter event, there ought to be a

peripheral loss of function of the retinal area from which these fibres originate, which is not the case (Scott, 1957). Choroidal tumours situated anteriorly cause peripheral depression or sector defects in the visual field. Tumours in the posterior pole may cause scotomata. If an associated retinal detachment is present, the visual field may assume some of its characteristics. In general, the deeper parts of the scotoma or the sector defects then correspond to the portion of the retina that is in contact with the tumour or that is situated at the site of the highest part of the tumour mass. This is surrounded by a zone of retinal detachment which causes a defect with sloping margins, not to be distinguished from a simple retinal detachment. For this reason, perimetry is of limited value for the differential diagnosis of retinal detachments and choroidal tumours with a secondary retinal detachment. However, in case of a tumour in the posterior pole, relatively often a visual field defect without breakthrough to the periphery occurs. This is rare in a simple retinal detachment. In case of a tumour such a breakthrough can only take place in case of a secondary retinal detachment situated inferiorly (Harrington, 1956; Reed and Drance, 1972).

In metastases, defects in the visual field, next to blurred vision constitute the main symptoms (Abramson, 1984). Freedman and Folk (1987) established a defect of the visual field in 18 out of 58 patients with choroidal metastases (31%). The defect is described as either relative (Harrington, 1971) or as absolute in over half the cases (Van Dijk, 1978; Brink et al., 1988). Especially if the tumour invades the choriocapillaris an absolute central scotoma occurs due to early degeneration of rods and cones (Ferry, 1967). In most cases, such a scotoma rapidly increases in size.

Sometimes, small tumours in the contralateral eye escape notice. Early detection may be possible by means of an accurate bilateral examination of the visual field (Manor et al., 1978).

Successive perimetric examinations may be useful for the differential diagnosis of metastases and melanomas, because the size of the defect in most cases increases more slowly in melanoma cases (Manor et al., 1978). However, in general perimetric examination contributes little to the diagnosis of uveal metastases or to the determination of the extent of choroidal or retinal involvement.

The correlation of the lesion with alterations of the visual field is not strong. This is probably due to the fact that in early phases the nutrition of the external retinal layers is not severely affected by the choroidal lesion. In later stages there is no good correlation because of the frequent occurrence of an associated retinal detachment (Thompson et al., 1961).

1.4.8 Electrophysiology

1.4.8.1 Electro-oculography (EOG)

Between the cornea and the back of the eye a difference in electrical potential of 6 mV exists with the cornea positive to the posterior pole. This is called the standing potential. By applying electrodes near the canthus on both sides of the eye potential differences caused by eye movements can be registered indirectly. This registration is called the

electro-oculogram (EOG). The EOG consists of at least two independent potentials: a light-independent potential, the above-named standing potential, and a light-dependent one. Electro-oculography measures changes in potential caused by alterations in the adaptation state of the eye. During dark adaptation, the light-dependent potential decreases slightly. The lowest value, the socalled dark trough, is measured (Dt: the mean of the measurements at the 6th, 8th, 10th and 12th minutes). After illumination this potential increases slowly and reaches a peak: the light peak (Lp: the mean of the maximum values; if no real Lp is present the mean of the registrations between the 19th and 22th minutes is taken). After the light peak, the corneal positive oscillations vary in voltage in a damped sinusoidal manner (François et al., 1957; Pinckers, 1979; Berson, 1981).

The pigment epithelium is probably responsible for the light-independent component of the EOG. The light-sensitive part depends on the activity of the photoreceptors and the inner nuclear layer of the retina (Berson, 1981).

An important EOG criterion is the Arden ratio, which is defined as the quotient of light peak and dark trough. This Lp/Dt ratio in general is higher than 1.8 in normal test subjects (Arden et al., 1962; Pinckers, 1979).

Very little is known about the EOG in metastases. It is mentioned only incidentally in a few published case histories as one of the examinations performed (Ponte and Lauricella, 1977; Hayreh et al., 1982; Lodato et al., 1983). We ourselves have constructed a diagram to differentiate with the aid of the EOG alone between lesions suspected of being a malignant melanoma of the choroid or the ciliary body, choroidal naevi, choroidal metastases and rhegmatogenous retinal detachments. We concluded that no correct classification of metastases is possible with this method. As a rule, a lowered Lp/Dt ratio with a normal dark trough was found in metastases (Brink et al., 1989/1990).

1.4.8.2 Electroretinography (ERG)

Illumination of the retina is followed by hyperpolarization of the sensory elements in the retina, causing a change in electric potential. This mass response is called the electroretinogram (ERG).

The ERG consists inter alia of an early cornea-negative a-wave and a cornea-positive b-wave. The a-wave is composed of a rod and a cone component. The b-wave is largely determined by the Müller fibres but the bipolar cells also play a part. The receptors are dependent on the choroidal circulation. If this is impaired, the a- and b-waves decrease. The Müller fibres are supplied by retinal vessels. Impairment of this circulation leads to a decreasing b-wave.

ERG components registered at the retina can also be measured at the cornea with a similarly shaped wave. The ERG is usually recorded by means of a contact lens electrode on the anaesthesized cornea. The patient is seated in front of an illuminated sphere and various light stimuli are offered during different adaptation conditions. Separate stimulation of the rods and of the cones is possible (François and De Rouck, 1973; Berson, 1981).

In the literature, ERG data of patients with metastases are described only very summarily. The recordings are generally described as subnormal or abnormal (Sundmark, 1958; Straub, 1961; Farnarier et al., 1972; Ponte and Lauricella, 1977; Hayreh et al., 1982; Lodato et al., 1983).

1.4.9 Biopsies and punctures

Various methods of establishing a cytological or histological diagnosis of an intraocular lesion without sacrificing the eye exist. Ophthalmological biopsy was performed as early as 1895 (von Grosz, 1929).

The biopsy method currently most widely used is fine needle aspiration biopsy.

Cytopathological techniques have played an important part in the diagnostics of ocular diseases (Green, 1984). According to a number of authors, ***fine needle aspiration biopsy*** of solid intraocular tumours may be regarded as a reliable and relatively safe diagnostic technique. Owing to lack of large groups and long follow-up, it cannot yet be applied as a routine examination. Its diagnostic use is considered to be restricted to the following indications:

1. patients with a possible neoplastic intraocular lesion with major diagnostic uncertainties;
2. patients who clinically have an intraocular metastasis without a primary non-ocular malignancy being known and without another metastasis accessible to biopsy being present;
3. patients who desire a histopathological confirmation of the clinical diagnosis before agreeing to the treatment proposed (Augsburger and Shields, 1984).

Biopsy should only be performed if it affects the therapeutic management (Jakobiec et al., 1979).

At needle biopsy the approach to an intraocular tumour depends inter alia on the localization of the lesion. Mostly, a 22 to 30 gauge needle is used which is attached to an aspiration syringe. For iridal and iridociliary tumours shorter and finer needles are used than for lesions of the posterior segment.

When the media are clear, the tumour is punctured with direct visualization, with or without use of an operation microscope, indirect ophthalmoscopy and fundus contact lens. In case of opaque media echography is used.

In posterior uveal melanomas and sometimes in choroidal metastases the pars plana over 90° outside the tumour quadrant is used as the puncture site. The vitreous humour situated between the pars plana and the tumour then acts as a buffer to stop any tumour cells on the biopsy needle. In choroidal metastases, if tumour dissemination in the orbit is not a matter of concern, the tip of the needle is sometimes introduced directly into the tumour tissue from the scleral side after preparing a lamellar scleral bed at the tumour site. In iridal and iridociliary tumours, the chosen puncture site is the limbus, 30 to 45° removed from the tumour quadrant. In this case, the aqueous humour serves as a buffer zone. A limbal route is also used in ciliary melanomas in aphakic eyes.

After the needle tip is inserted into the tumour, cells are aspirated by abruptly retracting the piston of the syringe. Apart from tumours with a liquid consistency, as a rule no tissue is seen in the syringe. The entire specimen is localized inside the needle. The piston is released, the needle is introduced farther into the tumour and another aspiration is carried out. This procedure may be repeated several times. Subsequently, the needle is retracted slowly in a straight line. If the puncture site bleeds, the bleeding is stopped by means of digital pressure on the globe. The puncture opening in the sclera is closed with a pre-placed suture, a lamellar scleral bed with interrupted sutures.

In preparation for the cytological examination, a new syringe is attached to the used needle and 1-2 ml of a sterile saline solution or 50% alcohol is aspirated. In this way

the cellular specimen is sucked into the lumen of the syringe and small aspirations may become visible. This syringe is sent immediately to the pathologist (Jakobiec et al., 1979; Augsburger and Shields, 1984; Karcioglu et al., 1985).

The evaluation of the biopsy specimen requires not only an ophthalmologically specialized pathologist but also an experienced cytopathological team (Jakobiec et al., 1979).

The cytological diagnosis of malignancy or benignancy made by means of this needle biopsy method can be confirmed histologically in 94.3% of the cases. The cytology in metastases is often insufficiently clear to indicate the precise nature of the primary tumour. In melanomas, the cell type of the punctures may not correspond well with the histology (Augsburger et al., 1985).

At aspiration biopsy, some intraocular bleeding virtually always occurs after withdrawal of the needle. It is always mild and clears up spontaneously. A rhegmatogenous retinal detachment caused by the hole in the retina is never observed, nor has traction on the retina ever been described (Jakobiec et al., 1979; Augsburger and Shields, 1984). Dissemination along the needle tract, subconjunctival tumour growth or growth in the orbit was not observed by Augsburger and Shields (1984), nor were systemic metastases. After enucleation and histological examination, Augsburger (1985) found tumour cells along the needle tract in only a few cases. Karcioglu et al. (1979), however, encountered clusters of tumour cells in the tract in one-half and Glasgow et al. (1988) even in over one-half of the cases. To what extent this also meant tumour growth was not clear. Tumour cells in the needle tract were found in a larger percentage of the cases after transscleral needle biopsy than after indirect biopsies (Glasgow et al., 1988). Tumour growth was then also observed more often (Jensen and Andersen, 1959).

Decrease of the visual acuity due to the biopsy was never described (Augsburger et al., 1985).

In tumours with subretinal fluid, ***aspiration of the subretinal fluid*** can be performed by puncture of the fluid space after scleral depression. This is considered to be a good examination method in case of doubt concerning the nature of the tumour (Sternberg et al., 1984). Meisner used this technique as early as 1923. Bec (1968) advised against this technique in connection with the risk of implantation metastases, but other investigators did not encounter this complication (Sternberg et al., 1984). In choroidal metastases, this method has been applied successfully several times (Rathschüler and Romanelli, 1971; Sternberg et al., 1984).

In tumours of the anterior uvea with cells in the aqueous humour, ***vitrectomy*** or ***puncture of the anterior chamber or vitreous humour*** may be useful (Font et al., 1967). This method has been used a few times in metastases (Char et al., 1980; Engel et al., 1981; Scholz et al., 1983). So far, however, insufficient data are available to establish the usefulness and safety (Char et al., 1980).

Iridectomy or ***iridocyclectomy*** may be useful in visible iridal lesions (Sanders, 1952; Font et al., 1967; Bec, 1968; Barbee et al., 1971).

Transscleral incision biopsies of posterior uveal tumours directly through the sclera result in a good histological diagnosis (Sanders, 1952). However, tumour dissemination at the biopsy site and in the orbit occurs frequently (Bec, 1968; Augsburger and Shields, 1984).

Constable et al. (1980) described chorioretinal biopsy under hypotension. However, this entails a considerable risk of an intraocular haemorrhage with all its consequences (Foulds et al., 1985).

1.4.10 Radioactive phosphorus (^{32}P) and other isotopes

In ophthalmological tumour diagnostics, radioactively labelled phosphorus (^{32}P) is the principal isotope used (Desjardins, 1986). The examination is based on the principle that malignant tumour cells take up and incorporate more ^{32}P than normal tissue. The beta-radiation at the site of the tumour can be quantified with a counter and compared with a control site (Shields, 1983). Only metabolically active tumours give a positive test result.

Thomas et al. (1952) were the first to apply this method for the diagnosis of intraocular tumours. Using a small Geiger counter, measurements were carried out at the tumour site and in other parts of both eyes, 30, 60 and 90 minutes after intravenous injection of ^{32}P. The eye was then enucleated and the measurement repeated. They concluded that with this method, identification of intraocular tumours could be improved. The examination was limited to tumours situated anteriorly in the eye (Thomas et al., 1952; Dunphy, 1957).

Since a number of non-malignant conditions such as inflammatory lesions also showed an increased uptake of the isotope, the test was modified by also measuring 24 hours after administration of ^{32}P. A relative decrease was then established in inflammatory processes, an increase in malignant lesions (Eisenberg et al., 1954; Terner et al., 1956).

The ^{32}P test fell into disuse because of inaccuracy in posteriorly located tumours. Hagler et al. (1970) modified the test. In tumours of the posterior pole, they opened the conjunctiva and carried out transscleral measurements instead of measuring transconjunctivally, as was usual. They once more emphasized the importance of correct localization of the lesion before the measurement. This requires a diameter larger than 6 mm (Ruiz and Howerton, 1975; Desjardins, 1986). In opaque media, echography may be applied for correct localization of the lesion (Shields, 1978).

The indication for the ^{32}P uptake test is differentiation between benign and malignant lesions and especially the differential diagnosis of melanoma versus naevus and melanoma versus haemangioma. Differentiation between melanomas and metastases is not possible (Ruiz and Howerton, 1975; Shields, 1978; Gysin, 1979; Desjardins, 1986).

The accuracy of the differentiation between benign and malignant lesions is high, over 95% (Jarrett, 1976; Shields, 1978; Goldberg et al., 1980; Desjardins, 1986).

A transconjunctival measurement is regarded as positive if the increase amounts to over 30%; with transscleral measurement, the increase has to be over 60% (Hagler et al., 1970; Chua, 1974). Other investigators apply other limits, e.g. a lower limit of 40% (Lommatzsch et al., 1984), of 50% (Shields, 1978) or of 100% (Ruiz and Howerton, 1975). The transscleral method therefore is more sensitive than the transconjunctival one. An increase of over 100% occurs only in malignancies.

The measurement at the site of the lesion is compared with a control site where no lesion is present. Initially, the other eye was used for this purpose (Eisenberg et al., 1954a) but later, use was made of a normal part of the same eye (Ruiz and Howerton, 1975).

For 6 weeks after an operation the test is unreliable and may give a false-positive result, especially with transconjunctival measurement This occurs in inflammations and, less frequently, in haemorrhages and haemangiomas (Eisenberg et al., 1954, Hagler et al , 1970, Chua, 1974, Lommatzsch, 1977, Shields, 1977b/1978, Van Dijk, 1978, Lommatzsch et al , 1984)

False-negative results as a rule are to be attributed to technical errors such as incorrect localization of the tumour and poor standardization of the equipment (Chua, 1974) When the tumour is in the resting phase or if there are benign cells, haemorrhages or necrosis between the tumour and the probe, a false-negative test result may also be obtained False-negative values are found particularly often in malignant lesions of the ciliary body, probably owing to the thick tissue layer between the tumour and the probe (Goldberg et al , 1980) For iridal tumours, also, the method is not suitable (Hagler et al , 1970, Gysin, 1979, Lommatzsch et al , 1984)

No major complications of the ^{32}P uptake test are known Theoretically, spread of tumour cells is possible due to manipulation during the measurement This has not been demonstrated (Shields, 1978, Desjardins, 1986) Retinal and vitreous haemorrhages may occur, as may occlusion of the central retinal artery (Kanski, 1984) No oncogenic side effects on haematological cells are known (Shields, 1978)

The first description of the ^{32}P uptake test in metastases was published by Thomas et al (1952) As mentioned before, differentiation from melanomas is not possible

Slowly growing and relatively acellular tumours such as metastases of a scirrhous breast carcinoma may give a negative or unclear result (Chua, 1974) Larger numbers of patients with metastases were described by Jarrett (1976), Lommatzsch (1977), Shields (1978), Lommatzsch et al (1984) and Desjardins (1986)

Use of gamma cameras for the diagnosis of intraocular tumours has the advantage that the technique concerned is noninvasive, that images are obtained rather than counts, and that the test can be repeated and may have prognostic value (Packer, 1984) The isotopes used include quinoline labelled with Iodine-125 and Iodine-123, which have an affinity for pigmented structures An amelanotic melanoma cannot be localized with these isotopes and heavily pigmented benign lesions show a positive uptake Moreover, they have short half-lives (Leopold et al , 1964, Packer et al , 1977)

Localization of tumours with labelled melanin precursors could make an important contribution Although in that case amelanotic melanomas would show no uptake, and benign proliferative lesions would give a false-positive value, it is possible to differentiate between uveal melanomas on the one hand and metastases and haemangiomas on the other Metals prove to have an affinity for melanin Therefore radioactive indicum-111 bleomycin, gallium-67 citrate, lead-203 tris and technetium-99 ferroascorbate inter alia have been tested as isotopes for tumour diagnostics However, these isotopes in general showed insufficiently selective uptake and the success was limited (Wilson and Boyd, 1976, Packer et al , 1977, Van Dijk, 1978, Packer, 1984)

1.4.11 Transillumination

Transillumination may provide useful information for the evaluation of suspected intraocular tumours. The principal techniques are:

- transpupillary transillumination: the light source is placed in the conjunctival cul-de-sac at the level of the tumour. It is then determined ophthalmoscopically whether or not the lesion is pervious to light;
- transscleral transillumination: the light source is held against the sclera across from the tumour. This method is used for exact determination of the tumour base for, inter alia, the ^{32}P uptake test. In tumours situated posteriorly, a conjunctival incision is necessary;
- transillumination with ophthalmoscopy: the light source is placed at the site of the lesion which is then inspected with the ophthalmoscope.

The transmission of light is in principle blocked by pigmented lesions or blood. Non-pigmented tumours and serous detachments allow light to pass (Shields, 1983; Arné and Mathis, 1986).

In the differential diagnosis of uveal melanomas, a diaphanous lesion is suggestive of a metastasis. A lightly pigmented melanoma, however, may present the same image (Ferry, 1967; Reese, 1976; Ferry, 1978; Arné and Mathis, 1986). In smaller tumours, also, a normal transmission of light may occur (Dunphy et al., 1958).

1.4.12 Immunological techniques

Char and Christensen (1980) determined the level of immune complexes in the serum of patients with a choroidal tumour. Values higher than 25 μg/ml were classified as abnormal. Such high values were measured in nine out of 11 patients with choroidal metastases and in ten out of 43 patients with a choroidal melanoma (of whom six patients also suffered from an autoimmune disease, which affects the immune complex level). They concluded that immune complexes cannot be used as the sole diagnostic criterion, but that combination with a carcinoembryonic antigen (CEA) assay is useful for the diagnosis of intraocular tumours.

Char (1977) described a number of immunological techniques. Leukocyte migration inhibition assay (a test for cell-mediated immunity) in vitro gave a distinctly different result in metastases than in melanomas. With delayed hypersensitivity skin tests with a soluble melanoma antigen, the results were significantly more often positive in melanomas than in metastases of the uvea. The rosette assay is an immunological test for T-cellular immunity. This test, also, gave distinctly different values in metastases than in melanomas.

Donoso et al. (1984) in a patient with a histologicaly confirmed choroidal metastasis without a known primary tumour used monoclonal antibodies that bound selectively to the tumour tissue.

1.4.13 Histological examination

The group of patients with uveal metastases in which histopathological examination was performed constitutes a selected population. Often, enucleation was performed because of complications, for example in the form of unbearable pain in secondary glaucoma, or on the erroneous diagnosis of malignant melanoma (Ferry, 1973).

Tumour emboli reach the eye via branches of the ophthalmic artery. Histological examination sometimes reveals malignant cells in the blood vessels (Castro et al., 1982).

Uveal metastases arise as emboli of malignant tumour cells that get stuck in the small blood vessels of the choroid. These cells appear primarily to proliferate in the venules. Once the vessel is blocked, a further increase of cells takes place, which cells break through the vessel wall and invade the perivascular space. From here, the cells may invade other vessels. When the perivascular space is reached, the tumour infiltrates further between the layers of the choroidal stroma, choosing the line of least resistance (Cordes, 1944; Duke-Elder and Perkins, 1966) (see Chapter 1.2.2).

The fast growth of cells round the blood vessels may cause erosion and lead to a haemorrhage in the metastasis and the environment of the lesion (Cordes, 1944). Consequently, there are many reports of recent or old haemorrhages found at histological examination (Sattler, 1926).

The impairment of the circulation may cause necrosis through ischaemia (Cordes, 1944). It may be due to an intratumoral haemorrhage or to excessive growth of malignant tumour cells (Castro et al., 1982). Jensen (1970) reported necrosis at histological examination in one-half of the patients with a uveal metastasis. The necrotic areas are usually sharply delimited (Sattler, 1926).

Only a moderate lymphocytic infiltration occurs in the choroid directly adjacent to the lesion (Sattler, 1926). Polymorphonuclear leukocytes may be encountered at the margin of the area with necrotic tumour cells (Castro et al., 1982). In the metastatic tissue many choroidal vessels are destroyed (Sattler, 1926).

A desmoplastic reaction may be observed in the stroma of certain metastases and is particularly distinct in scirrhous breast carcinoma. Calcifications of blood vessel walls are sometimes striking phenomena (Castro et al., 1982).

Sometimes, miliary metastatic deposits are encountered in the choriocapillaris. Small diffuse tumours appear to infiltrate the normal choroid and to displace it; histologically there are then often multiple foci (Shields, 1983). Bruch's membrane as a rule remains intact. The overlying retina is involved only rarely (Cordes, 1944; Duke-Elder and Perkins, 1966).

Jensen (1970) described rupture of Bruch's membrane in four out of 19 patients with a uveal metastasis. In melanomas, a rupture is described more frequently (Castro et al., 1982).

In iridal metastases, malignant cells sometimes tend to grow along the anterior edge of the iris. Such diffuse tumours may constitute a lesion that is only one or two cell layers thick (Shields, 1983).

A choroidal metastasis may invade the optic nerve and the sclera and perforate to extraocular structures (Sattler, 1926; Cordes, 1944; Ginsberg et al., 1970; Daicker and Gysin, 1980; Gartner, 1985). Episcleral expansion of uveal metastases is rare, however, and described only incidentally (Corrado, 1928; Hoffmann, 1933; Cohen, 1937; Cordes, 1944; Maxwell, 1954; Casanovas, 1966). Jensen (1970) described scleral invasion in three

out of 19 patients with uveal metastases The extraocular extension often takes place via blood vessels and nerves (Sattler, 1926). Ginsberg et al. (1970) collected data from the literature on 117 patients with metastatic infiltrations of the optic nerve In 39% of the cases infiltration in the optic nerve was caused by growths from choroidal and retinal metastases

The histopathological picture of a metastatic uveal lesion depends on the primary tumour which has generated the metastasis. However, just as in metastases elsewhere in the body, lack of cellular differentiation may result in loss of characteristic features of the tumour type in question In such cases it is frequently impossible to determine the primary cancer solely on the basis of the histopathological examination of the ocular metastasis (Hogan and Zimmerman, 1962; Duke-Elder and Perkins, 1966, Castro et al., 1982, Spencer, 1986)

Better-differentiated metastatic lesions may retain certain histological and histochemical features of the primary tumour Special staining methods or electron microscopy may be necessary (Shields, 1983)

Many metastases produce intracellular mucus If this cannot be demonstrated with routine haematoxylin or eosin staining, use of various histochemical dyes may render further diagnostics possible in many cases As a rule the mucus production is minimal, but sporadically it may be massive (Jakobiec et al , 1987)

The growth pattern and the cellular characteristics of metastases are often identical to those of the primary tumour (Ferry, 1967)

Metastases of breast cancer are in general reasonably well differentiated and retain features of an adenocarcinoma Typical aspects are solid epithelioid nests or glandular structures As a rule there are alveoli of different sizes with large round or polygonal cells with a large nucleolus The stroma between the alveoli is sometimes scarce In other cases, however, big masses of fibrous tissue are present (Duke-Elder and Perkins, 1966; Shields, 1983, Spencer, 1986)

Some lesions produce mucus, which can be demonstrated using alcian blue, colloidal iron and mucicarmine (Spencer, 1986).

The choroidal tissue is compressed and atrophic Degenerative changes of the stroma manifest themselves with disintegration of chromatophores and release of tumour pigment (Sattler, 1926, Cordes, 1944; Duke-Elder and Perkins, 1966; Castro et al., 1982)

Uveal metastases of bronchial carcinomas are often not differentiated, but exceptionally they may show an epithelioid appearance (Spencer, 1986). Metastases of oatcell carcinomas contain small, closely packed anaplastic cells without an alveolar pattern (Shields, 1983). Sometimes, a biphasic pattern of large and small cells may be present (Spencer, 1986) Bronchial adenomas (carcinoid) may have a glandular structure (Shields, 1983)

Malignant cutaneous melanomas which metastasize to the uvea may sometimes be difficult to differentiate from primary malignant melanomas of the uvea. However, unlike the primary uveal tumours in which different cell types may be found, metastases as a rule consist entirely of epithelioid cells Also, naevus cells at the tumour base are rarely described in metastases. Tumour cells in the uveal vessels are never encountered in

primary melanomas, but are sometimes found in metastases (Font et al., 1967; Albert et al., 1972).

Although metastases of a malignant cutaneous melanoma frequently are not pigmented, microscopy as a rule will reveal signs of pigment production (Spencer, 1986).

In uveal metastases, mitoses are usually more abundant and there is a more pronounced stromal reaction than in the primary uveal melanoma. An important feature of metastases is the large amount of connective tissue that may be present (Hogan and Zimmerman, 1962; Jensen, 1970).

Metastases from the digestive tract produce much mucus. Metastases of a carcinoma of the prostate often retain an adenoid or glandular pattern (Spencer, 1986).

1.5 Differential diagnostics

1.5.1 Introduction

The diagnostics of uveal metastases is complicated. Even before a primary malignancy elsewhere in the body is known, an intraocular metastasis may have occurred, and this tumour may assume different forms (Hutchison and Smith, 1979; Arné and Mathis, 1986). The clinical context and the course of the condition are of great importance for the correct diagnosis (Arné and Mathis, 1986). If in a patient with an ocular tumour a malignancy elsewhere in the body is known, the physician should be alert to the possibility of an intraocular metastasis (Shields, 1983, Hunyor, 1984).

As described in the preceding chapter, in the diagnostics of uveal metastases use is made of a large number of examination techniques because there exists no single method with which the ophthalmological diagnosis can be made with 100% certainty. It is only by histopathological examination of the tumour tissue that the clinical diagnosis can be confirmed. However, pigmentation of the uvea and compression of the tumour tissue may mask characteristic cellular patterns in metastases (Jensen, 1970). The cytological picture of metastases of a bronchial carcinoid may be similar to that of an amelanotic melanoma (Font et al., 1966) and the histological differentiation between primary uveal melanomas and uveal metastases of a malignant cutaneous melanoma is difficult (Font et al , 1967). Consequently, the diagnosis of uveal metastases may pose a problem not only to the clinician but sometimes to the pathologist as well An extensive description of the differential diagnostics is therefore necessary.

What conditions have to be considered concerning the differential diagnosis of uveal metastases depends on the localization of the tumour in the eye (Michelson et al., 1979; Shields, 1983). Where choroidal metastases are concerned, differential diagnosis of (amelanotic) malignant melanoma, (amelanotic) naevus, haemangioma and posterior scleritis is of particular importance. Choroidal metastases have also to be differentiated from other multifocal little-pigmented lesions (Arné and Mathis, 1986). Table 1.5.1.1 presents a survey of some conditions that are mentioned in the differential diagnosis of choroidal metastases

Metastases of the iris and of the ciliary body have to be differentiated, apart from inflammatory conditions such as tuberculosis, sarcoidosis and syphilis from, in particular, other, benign and malignant tumours of the iris (Mayer and Nassar, 1958). The most relevant in the differential diagnosis are amelanotic melanoma, leiomyoma, granulomatous inflammation and endophthalmitis (Shields, 1983: Table 1.5.1.2). In older literature emphasis is laid on inflammatory processes, particularly tuberculosis (Mérigot de Treigny, 1921; Lopes d'Andrade, 1949).

Table 1.5.1.1 Differential diagnostics of choroidal metastases

Stephens and Shields, 1979	*Shields, 1983*
Amelanotic and pigmented melanoma	Amelanotic naevus
Haemangioma	Amelanotic melanoma
Choroiditis with retinal detachment	Haemangioma
Cytomegalic inclusion retinitis	Posterior scleritis
Lymphoid hyperplasia of the uvea	Osteoma
Leukaemia	Retinitis and choroiditis
Lymphoma	Rhegmatogenous retinal detachment
Reticulum cell sarcoma	Harada's disease
	Uveal effusion syndrome
	Central serous chorioretinopathy

Arné and Mathis, 1986	*Wharam and Schachat, 1989*
Amelanotic naevus	Melanoma
Amelanotic melanoma	Osteoma
Haemangioma	Haemangioma
Posterior scleritis	Posterior scleritis
Osteoma	Harada's disease
Viral and mycotic infections	Uveal effusion syndrome
Rhegmatogenous retinal detachment	Disciform scar
Harada's disease	Subretinal haemorrhage
Congenital hypertrophy of pigment epithelium	
Toxic retinopathy	
Diffuse lymphoid hyperplasia of the uvea	
Reticulum cell sarcoma	
Leukaemia	
Multiple uveal melanocytomas	

Table 1.5.1.2 Differential diagnostics of iridal metastases (Shields, 1983)

Amelanotic melanoma
Leiomyoma
Granulomatous iritis
Endophthalmitis
Ectopic lacrimal gland
Juvenile xanthogranuloma
Foreign body

The diagnosis of uveal metastasis is often erroneously not made. Ferry (1973) and Ferry and Font (1974) described 227 patients with histologically confirmed metastases to the eye and orbit. In only 82 patients (36.1%) the clinical diagnosis, made preoperatively or prior

to autopsy, proved to be correct. In 57 of these patients the primary tumour was known. In 127 patients (55.9%) a different diagnosis was made, including 'intraocular tumour' 43 times and malignant melanoma 31 times (Table 1.5.1.3).

Table 1.5.1.3 *Preoperative or ante mortem clinical diagnosis in 227 patients with metastases to ophthalmic structures* *

Diagnosis	Number of patients	
	N	%
Metastasis	82	36.1
Intraocular tumour	43	18.9
Malignant tumour	31	13.7
Glaucoma	17	7.5
Orbital mass	13	5.7
Retinal detachment/tumour	5	2.2
Miscellaneous	18	7.9
Not stated	18	7 9

** Ferry, 1973; Ferry and Font, 1974; three patients (1.3%) metastasis in optic nerve only; 28 patients (12.3%) metastasis in orbit only; 30 patients (13.2%) apart from uveal metastasis also metastasis in optic nerve and/or orbit*

In a study by the same authors, regarding iridal metastases, the clinical diagnosis was correct in only ten out of 26 patients (38%) (Ferry, 1973; Ferry and Font, 1975). In nine of these ten patients the presence of a primary tumour elsewhere in the body was known (Table 1.5.1.4).

Table 1.5.1.4 *Preoperative or ante mortem clinical diagnosis in 26 patients with metastases to the anterior segment* *

Diagnosis	Number of patients	
	N	%
Metastasis	10	38 5
Iridocyclitis with secondary glaucoma	5	19.2
Malignant melanoma	4	15.4
Intraocular tumour	4	15.4
Chronic glaucoma	1	3.8
Not stated	2	7.7

** Ferry, 1973; Ferry and Font, 1975*

In case of intraocular tumours, the possibility of uveal metastases should always be kept in mind. However, several intraocular conditions may mistakenly be regarded as metastases. Michelson et al. (1979) described 13 such pseudometastases of the choroid, including six inflammatory processes (Table 1.5.1.5). In nine of the 13 patients, a malignancy elsewhere in the body was known, and this constituted the main cause of the erroneous diagnosis, as also mentioned earlier by Algan et al. (1965).

Table 1.5.1.5 Conditions mistaken for uveal metastases (Michelson et al., 1979)

Clinical diagnosis
Malignant choroidal melanoma
Choroidal haemangioma
Subretinal granuloma (possible sarcoidosis)
Subretinal granuloma (rubella retinopathy)
Cytomegalic inclusion retinitis (twice)
Presumed ocular histoplasmosis syndrome
Serous detachment of the retinal pigment epithelium
Excentric haemorrhagic exudative chorioretinopathy (disciform)
Choroidal effusion secondary to scleritis
Subfoveal haemorrhage secondary to thrombocytopenic purpura
Aphakic choroidal detachment
Myelinated nerve fibers

Accordingly, the diagnosis of uveal metastases is frequently missed but also erroneously made in a number of cases. The differential diagnosis of metastases of the uvea is therefore very important. In this chapter a number of conditions that have to be differentiated from uveal metastases will successively be described. Extensive attention will be paid to the findings in the principal differential-diagnostic conditions: melanomas, naevi and haemangiomas of the uvea. The aetiology and therapy of these conditions will also briefly be discussed.

The discussion of a number of other lesions will be restricted to their main differential-diagnostic features. A subdivision is made into lymphoproliferative conditions, other intraocular tumours, inflammatory diseases, intraocular haemorrhages, detachments of the retina, pigment epithelium and choroid and miscellaneous symptoms and disorders.

1.5.2 Malignant melanoma

The amelanotic malignant melanoma of the uvea is the main lesion that has to be differentiated from a uveal metastasis (Shields, 1983).

In 1 to 2% of the patients of whom an eye was enucleated on the diagnosis of malignant melanoma, histopathological examination proved the lesion to be an intraocular metastasis (Ferry, 1964; Howard, 1969; Shields and Zimmerman, 1973; Colombo and Carnevali, 1985). Zero to 2% of the iridal 'melanomas' prove to be metastases (Ferry,

1965; Shields, 1983). On the other hand, 4% of all metastases reportedly are mistakenly enucleated as melanomas (Shields and McDonald, 1973).

Metastases of breast cancer are correctly diagnosed in 93% of the cases. Metastases of a pulmonary carcinoma, on the other hand, are mistaken for a melanoma in 59% of the patients. In most patients of whom an eye with an intraocular metastasis is enucleated on the erroneous diagnosis of melanoma, the lesion proves to be a metastasis of a pulmonary carcinoma. This holds particularly true of mushroom-shaped tumours (Jarrett, 1976; Ossoinig and Harrie, 1983; Verbeek, 1985).

The incidence of uveal melanomas is four to nine per 1.000.000 of the population (Lommatzsch et al., 1985; Egan et al., 1988; Mahoney et al., 1990). The sex distribution is approximately 1:1 (Wilder and Paul, 1951; Paul et al., 1962) although sometimes a slightly higher incidence in females (Bonnin, 1986) or in males (Mahoney et al., 1990) is reported Among non-white races the condition is rare (Wilder and Paul, 1951; Paul et al., 1962, Scotto et al , 1976, Margo and McI ean, 1984) The melanoma is diagnosed as a rule in the sixth and seventh decades and occurs rarely in children and adolescents (Wilder and Paul, 1951, Paul et al , 1962; Barr et al , 1981, Egan et al., 1988). Patients with iridal melanomas are on the whole 10 to 20 years younger than patients with choroidal melanomas (Duke and Dunn, 1958, Rones and Zimmerman, 1958; Geisse and Robertson, 1985).

Uveal melanomas reportedly rarely coexist with other extraocular malignancies (Algan et al , 1965; Lischko et al , 1989) Jensen (1963) in 4 to 6% of the patients described a second independent malignancy in addition to the uveal melanoma, which is higher than the frequency of multiple malignancies in other tumours Char (1989) describes a percentage of 6 to 10% in melanomas, and Hart (1962) even of 14%. In one case, the malignant uveal melanoma was described as a third (Morgan et al., 1973) and in one other case as a fourth primary tumour (Pheasant et al , 1979)

Turner et al. (1989) believed that the prevalence of malignancies was increased in patients with a melanoma, that gynaecological tumours, in particular, occur more frequently and that a connection may exist between cutaneous and uveal melanomas. A common aetiological factor for the occurrence of uveal and cutaneous melanomas may exist (Gilbert et al , 1987, Lischko et al., 1989). According to other authors, however, this association is unusual (de Bustros et al., 1985) In patients with cutaneous melanomas, uveal naevi, on the other hand, are said to occur more frequently (Albert et al., 1983). Oosterhuis et al (1982) described the 'familial atypical multiple mole melanoma syndrome' (FAMMM syndrome) which occurs very rarely.

In some articles, an association of uveal melanoma with breast cancer is described (Algan et al., 1965, Henkind and Roth, 1971). Holly et al. (1991), however, were unable to demonstrate a connection between earlier malignancies and a possibly increased risk of uveal melanomas.

Histologically, uveal melanomas are subdivided into spindle cell, epithelioid and mixed cellular tumours (Jakobiec, 1978) In older literature necrotic and fascicular tumours are distinguished as well (Callender, 1931; Wilder and Paul, 1951). Mixed cellular and spindle cell B melanomas are the most frequent forms (Paul et al., 1962).

In one-half of the patients with uveal melanomas, histological examination shows a tumour invasion of the sclera to be involved (Jensen, 1963). Extraocular extension is

described in 10 to 23% of the patients (Byers and MacMillan, 1935; Starr and Zimmerman, 1962; Jensen, 1963; Shammas and Blodi, 1977).

Metastasization is mainly to the liver and, less frequently, to the bone, the lungs and the subcutaneous tissue and occurs in one-half of the patients. If metastases develop, the average survival is less than one year (Einhorn et al., 1974; Lommatzsch and Dietrich, 1976; Char, 1978; Bedikian et al., 1981; Jensen, 1982). At the time of enucleation of the affected eye, metastases elsewhere in the body are described in 0.5% of the patients (Zimmerman and McLean, 1979).

The reported survival of patients with uveal melanomas varies considerably. The prognosis depends strongly on the cell type and the tumour size. The 10-year survival rate is 50 to 70% (Wilder and Paul, 1951; Packard, 1980; Jensen, 1982; McLean et al., 1982). The nature of the treatment (in the form of brachytherapy or enucleation) is reported not to affect the survival rate (Augsburger et al., 1986; Adams et al., 1988).

There are several therapeutic possibilities in malignant melanoma of the uvea. The main ones are enucleation in tumours with posterior localization (Zimmerman and McLean, 1979; Manschot, 1980), local resection, particularly in lesions of the ciliary body (Peyman et al., 1984; Damato and Foulds, 1986), iridectomy in iridal melanomas (Rones and Zimmerman, 1958), irradiation, either by means of radioactive plaques (brachytherapy): Ruthenium-106 (Lommatzsch, 1986), Cobalt-60 (Zografos et al., 1988; Augsburger et al., 1990) and Iodine-125 (Packer et al., 1984) or with protons (Gragoudas et al., 1985) or helium ions (Char et al., 1990) and photocoagulation in very small tumours (Meyer-Schwickenrath, 1980; François, 1982).

Signs and symptoms. The principal complaint of patients with uveal melanomas is deterioration of the visual acuity. Defects in the visual field are described frequently. Sometimes, metamorphopsia, micropsia, photopsia, anisocoria, muscae volitantes or veils occur (Jensen, 1963; Gailloud, 1975; Arné and Mathis, 1986).

In 67% of the patients with an uveal melanoma loss of visual acuity, mostly pronounced, is reported: 19 to 38 5% are said to have no more light perception and only 27 to 37% a visual acuity better than finger counting (Martin-Jones, 1946; Jensen, 1963; Karickhof, 1967). According to Augsburger et al. (1990), 60% of the patients have a visual acuity over 5/10. In 21% of the patients visual field defects constitute the initial complaint. In combination with deterioration of the visual acuity this occurs in 77 to 100% of the patients (Karickhof, 1967; Mosselman, 1975).

Only 3% of the patients with uveal melanomas are reported to have no complaints, the tumour being a fortuitous finding (Jensen, 1963). However, in more recent literature it is stated that the melanoma is a fortuitous finding in 17% of the patients (Augsburger et al., 1990).

In choroidal melanomas the symptoms as a rule have been present for longer than in choroidal metastases. Of the patients with melanomas, 40% have had symptoms for longer than one year, which never occurs in metastases (Jensen, 1970).

Melanomas of the ciliary body cause symptoms such as metamorphopsia and visual field defects only when the tumours are large (Alberti and Halama, 1987). Loss of vision is caused by displacement or deformation of the lens. Foos et al. (1969) described a shallow anterior chamber and unilateral cataract in these patients.

Melanomas of the iris are detected either fortuitously (20%: McGalliard and Johnston, 1989) or as the result of a unilateral glaucoma or inflammation (Dhermy, 1979). The pigmented iridal lesion often has been known for years Visual acuity is usually normal· 74% have an eyesight of 20/20 or better (Duke and Dunn, 1958). Cataract is reported to occur in 66% of the melanomas, as against only 12% of the metastases (Jensen, 1970)

Pain occurs in 12 to 24% of the patients with uveal melanomas and is a first symptom in 6% (Jensen, 1963; Mosselman, 1975) Pain is said to be more frequent in choroidal metastases than in choroidal melanomas (Ferry, 1978; Gartner, 1985).

Shields et al (1987) described elevation of the intraocular pressure in only 3% of all uveal melanomas. Other authors, however, report glaucoma in 20 to 48% of the patients Risk factors mentioned are a localization in the iris, with or without involvement of the ciliary body, and in melanomas localized posteriorly, the size of the tumour (Kirk and Petty, 1956, Duke and Dunn, 1958; Jensen, 1963; Yanoff, 1972; Foulds and Lee, 1983, Rohrbach et al , 1988, McGalliard and Johnston, 1989) Melanomas of the ciliary body frequently cause ocular hypotension (Foos et al , 1969)

Diffuse uveal melanomas cause glaucoma in 61% of the patients, while 9% have a red eye and 15%, an inflammation (Font et al , 1967)

Almost all melanoma patients with glaucoma are reported to have uveitis, and closure of the angle of the anterior chamber by posterior peripheral synechiae (Kirk and Petty, 1956) Fraser and Font (1979) report an inflammation in 4 9% of the patients with a melanoma of the ciliary body or choroid, in ciliary body tumours this was usually episcleritis, in necrotic choroidal melanomas, panophthalmitis Although necrosis frequently occurs in iridal metastases, it is rare in melanomas of the iris (Mayer and Nassar, 1958)

In 3 to 10% of the patients with a choroidal melanoma, a vitreous haemorrhage is described This is said to be characteristic of a melanoma (Noble and Marsh, 1984; Bonnin, 1986, Gragoudas et al , 1987) In case of sudden loss of visual acuity due to a vitreous haemorrhage, the possibility of this tumour should be considered (Gass, 1963). Fraser and Font (1979) described a hyphaema and subretinal haemorrhages.

Prominent episcleral vessels are described in 5 to 25% of the patients with a uveal melanoma (Jensen, 1963, Danis, 1979) In melanomas of the ciliary body this phenomenon is said to occur nearly always (Foos et al., 1969).

Rubeosis ir dis is observed in 5% of the choroidal melanomas (Schulze, 1967).

Ophthalmoscopy and slit lamp examination. Malignant melanoma of the choroid may manifest itself in various ways (Shields, 1985).

Jensen (1963) reported that 93% of the uveal melanomas originated from the choroid, 4% from the ciliary body and 3% from the iris.

Melanomas may be encountered throughout the eye, unlike choroidal metastases which are frequently limited to the macular area (Hungerford, 1985; Augsburger et al., 1990) Nevertheless, most choroidal melanomas are said also to be localized temporally in the posterior pole (Jensen, 1963, Shields and Young, 1980, Shields, 1983). In contrast to choroidal metastases, melanomas are rarely observed round the optic disk (Hart, 1962; Howard, 1965; Augsburger et al., 1990).

Bilateral melanomas are very rare (Lerman, 1966; Shammas and Watzke, 1977;

Shields and Young, 1980; Shields, 1983). Multiple melanomas in one eye, also, have virtually never been described (Kreibig, 1935; Rosen and Moulton, 1953).

According to Jensen (1963) 5% of the melanomas have a flat shape, 64% are dome-shaped, 24% are mushroom-shaped and 2%, diffuse (other shapes 5%).

Choroidal melanomas in general have a prominence of 5 to 8 mm with a base of 12 mm on average (Peyster et al., 1985; Poujol and Chaintron, 1988; Augsburger et al., 1990). Mostly, melanomas are more elevated than metastases (Bonnet and Jambon-Genet, 1948; Slezak, 1966, Ferry ,1978; Gartner, 1985). However, in metastases the base of the tumour is relatively larger than in melanomas with a simular prominence (Poujol and Chaintron, 1988). Dome-shaped metastases may be difficult to differentiate from amelanotic melanomas (Gass, 1974; Arné and Mathis, 1986).

Breakthrough of Bruch's membrane and protrusion into the vitreous may bring about the mushroom shape that is typical of melanomas. In such cases even the retina may be perforated (Norton, 1969; Scheffer, 1973; Gass, 1974; Char, 1989). With the passage of time such mushroom shapes occur more frequently, especially in amelanotic or slightly pigmented choroidal melanomas (Hayreh, 1974, Shields, 1985).

Melanomas are more sharply delimited than metastases (Bonnet and Jambon-Genet, 1948, Ferry, 1978) Flat melanomas may sometimes be delineated poorly (Hayreh, 1974). Norton (1969), Scheffer (1973) and Hunyor (1984) described a flat greyish-brown marginal zone round the tumour or a kind of halo In mushroom-shaped tumours the central, most protruding part is not or only slightly pigmented, while the peripheral portion contains more pigment (Hayreh, 1974).

The pigmentation of the melanoma varies, but most lesions are pigmented to some extent (Reese, 1951; Bonnin,1986). Jensen (1963) described the melanoma as white to yellowish in 15% of the cases, as grey in 20%, as yellowish-brown in 13%, as brown or dark in 26% and as spottily pigmented in 26%. Twenty-five per cent of the melanomas reported are relatively amelanotic (Char, 1989) Prominent tumours, in particular, display much pigment (Shields, 1976). The tumour surface may be white, sometimes with grey pigment patches, or have a pink haze due to vascularization (Hayreh, 1974).

Suggestive of a melanoma are widespread alterations of the overlying pigment epithelium with areas of orange pigment deposits on the tumour surface (Gass, 1974). Histologically, these are predominantly lipofuscin pigment-laden cells (macrophages or pigment epithelium cells· Gass, 1974; Shields et al , 1976). In melanomas this is described in 47 to 85% of the cases (Smith and Irvine, 1973; Shields, 1976), especially in flat lesions (Hayreh, 1974).

During growth of the melanoma, large dilated blood vessels may become visible on the tumour surface, especially in little-pigmented tumours (Reese, 1951; Norton, 1969; Gass, 1972/1974, Hayreh, 1974) These vessels are described less frequently in metastases (Gass, 1974).

Melanomas even at an early stage show alterations in the pigment epithelium. These lesions are associated with a variable degree of exudation between the tumour and the retina (Gass, 1972). Cystoid oedema of the retina is sometimes described (Scheffer, 1973, Gass, 1974; Schatz et al , 1978).

A retinal detachment is observed in 25 to 87% of the tumours (Jensen, 1963; Karickhoff, 1967; Font et al., 1968; Schatz et al., 1978; Peyster et al., 1985; Augsburger et al., 1990). Sometimes, a bullous retinal detachment is described (Norton, 1969).

Retinal breaks are very rare (Peyman et al , 1976). According to Shields (1976), the extension of the retinal detachment is usually larger in metastases.

Haemorrhages in uveal melanomas are reported to be observed only rarely (Danis, 1979). In 3 to 10% of the melanomas an intraocular haemorrhage is reported, usually in the form of a vitreous haemorrhage, sometimes as a hyphaema or subretinal haemorrhage (Martin-Jones, 1946, Jensen, 1963; Noble and Marsh, 1984). The cause of a vitreous haemorrhage may be invasion of the retina by the tumour (Gass, 1974). Massive haemorrhages may occur in necrotic tumours (Shields and Young, 1980). Sub- or intraretinal haemorrhages are sometimes observed (Hunyor, 1984) and may be due to haemorrhages from the choriocapillaris or from the large vessels on the tumour surface (Zimmerman, 1963; Scheffer, 1973; Gass, 1974). A haemorrhagic retinal detachment may mask the tumour Haemorrhages are observed particularly often in melanomas localized in the macular area (Gass, 1974) Although a spontaneously recurring hyphaema is said to be almost pathognomonic of iridal metastases, it is also encountered in melanomas of the iris (Ferry, 1973)

Three per cent of all uveal melanomas are situated in the iris (Jensen, 1963; Noor Sunba et al., 1980) They are predominantly solitary and may or may not be pigmented. Frequently, an ectropion uveae is present with distortion of the pupil (Foulds, 1985; Shields, 1985) The lesion is predominantly present in the inferior or infero-temporal region of the iris (Jensen, 1963, Dhermy, 1979, Territo et al , 1988), but it may be found in any part (Zimmerman, 1963)

The lesion is generally small and placoid The margin may be sharply or poorly defined The degree of pigmentation is highly variable (Zimmerman, 1963; Foulds, 1985): 58% have a pale colour and 42% are darkly pigmented (Foulds, 1985) Heterochromia of the iris is often present (Shields and Young, 1980, Shields, 1983) In 58% of the tumours, abnormal vessels are observed (Foulds, 1985)

Melanomas of the ciliary body in an early phase are difficult to discern (Naumann, 1980). Mostly they are detected by accident (Shields, and Young, 1980) At the time of presentation they are usually large (Gass, 1974; Shields, 1985). Frequently, part of the choroid or the iris is also involved in the process (Gass, 1974). The iris may be pushed forward by the tumour and the root of the iris may be displaced (Foulds, 1985).

The shape is generally convex, but a diffuse ring melanoma has sometimes been described (Gass, 1974, Lommatzsch, 1989). The surface is smooth, sometimes irregular (Gass, 1974) Ciliary melanomas are often dark or of a mottled greyish-brown colour. Abnormal vessels are described, sometimes with blood on the tumour surface (Foulds, 1985) A retinal detachment occurs only at a late stage and in that case the choroid is often also involved in the process (Gass, 1974).

A metastasis of the ciliary body may show great similarity to a diffuse melanoma (Foulds, 1985).

Suckling and Donaldson (1970) state that melanomas and metastases may be distinguished from each other with the aid of infrared photography. According to Sautter et al. (1974), however, this is not possible.

Fluorescein angiography. The fluorescence of choroidal melanomas is indistinguishable in timing and progression pattern of the patterns seen with choroidal metastases (Davis and Robertson, 1973). The fluorescein-angiographic picture of melanomas is variable (Oosterhuis and Van Waveren, 1968; Wessing, 1968; Gass, 1972). In general, melanomas stain in the arterial or arteriovenous phase in vague confluent patches, sometimes even before the retinal arteries. In late phases, diffuse staining takes place. Atrophy of the retinal pigment epithelium causes hyperfluorescence. The fluid beneath the retinal detachment, if present, stains to a greater or lesser extent. Areas with hyperpigmentation and lipofuscin remain dark (Norton et al., 1964; Wessing, 1968/1977; Gass, 1974; Hayreh, 1974; Fishman, 1977; Theodossiadis et al., 1978; Bonnin, 1986). Necrotic areas are hypofluorescent but some staining occurs later (Wessing, 1977). Large blood vessels in the tumour, separate from the retinal circulation, the socalled 'double-blood supply', are seen more often than in metastases (Gass, 1972; Davis and Robertson, 1973; Wessing, 1977). Hyperfluorescent spots are observed in late phases, especially at the margin of the tumour.

Cystoid degeneration and oedema of the retina which stain with fluorescein are sometimes described. Occasionally, dilatation of the retinal capillaries with micro-aneurysms is established. The tumour is frequently surrounded by a hypofluorescent margin. If breakthrough of Bruch's membrane occurs, the protruding part of the tumour remains hypofluorescent with clearly staining tumour vessels and leakage in the vitreous.

An amelanotic melanoma is usually large and mushroom-shaped, with prominent vessels. The pink pigmented parts stain more than the white areas. The fluorescence is progressive and in the late phases diffuse. The greyly pigmented parts of the tumour mask the background fluorescence (Gass, 1972/1974; Davis and Robertson, 1973; Hayreh, 1974; Fishman, 1977; Wessing, 1977; Schatz et al., 1978; Theodossiadis et al., 1978; Danis, 1979).

For the diagnosis of melanomas of the ciliary body, fluorescein angiography is not very useful, because of the peripheral localization of the tumour (Fries and Char, 1990).

Melanomas of the iris show an early, mottled fluorescence in the direct vicinity of the lesion. Leakage occurs from the central margin and from the otherwise normal radial iridal vessels (tumour iritis). Leakage at the pupillary margin is frequently described. Such fluorescence is reported never to occur in iridal metastases (Demeler, 1981). However, Kottow (1978) does describe a fluorescence at the tumour margin in metastases. In melanomas the blood vessels run in a crisscross fashion. Parts of the iris that are not affected by the tumour show no fluorescence.

Echography. Echographically, a melanoma displays a dome-shaped tumour or a characteristic mushroom shape. The initial retinal spike is followed by lower regular internal echoes brought about by the densely packed cellular structure and are frequently accompanied by an orbital shadow. Tumour infiltration in the choroid causes a choroidal excavation. Large tumour vessels cause echographic vascularity (Ossoinig and Blodi, 1974; Ossoinig and Harrie, 1983; Coleman et al., 1974; Verbeek, 1985; Poujol, 1986).

If necrosis or haemorrhage occurs in the tumour, a higher and more irregular echo pattern appears (Verbeek, 1985).

Extraocular extension of the melanoma may be established by means of echography

(Ossoinig and Harrie, 1983; Guthoff, 1988).

The differential diagnostics of choroidal metastases may be difficult in individual cases, especially in metastases of oatcell carcinomas of the lung (Verbeek, 1981/1985).

According to several authors, computer echography renders possible the differentiation of spindle cell B and mixed epithelioid melanomas (Thijssen and Verbeek, 1981; Coleman and Lizzi, 1983).

Computed tomography. The melanoma is characterized by an elevated, hyperdense, sharply delimited lesion with, as a rule, a slight to moderate enhancement after administration of contrast (Mafee et al., 1985; De Keizer et al., 1986; Desjardins, 1986). Making the differential diagnosis between melanoma and metastasis by means of the CT scan may be difficult (Alsbirk and Halaburt, 1983).

Magnetic Resonance Imaging (MRI). Melanomas in general are hyperintense in relation to the vitreous in T_1 weighted images and hypointense in T_2 weighted images because of the relative short T_1 and T_2 relaxation times. However, melanomas which remain hypointense in T_1 weighted images have also been reported (Sobel et al., 1985; Chambers et al., 1987; Haik et al., 1987; Mafee et al., 1987; Wollensak et al., 1988). The image is probably brought about by the paramagnetic properties of melanin. An increase of pigment leads to short T_1 and T_2 relaxation times. Consequently, a melanoma containing little pigment may show a different image. In such cases, differentiation from metastases may be a problem (Gomori et al., 1986). Unlike melanomas, metastases display an hyperintensive image in T_2 weighted images (Chambers et al., 1987).

Perimetry. Jensen (1963) reports visual field defects in 64% of patients with a uveal melanoma. According to Van Dijk (1978), the visual field defect is absolute in 86% of the cases. In large tumours with a secondary serous retinal detachment, perimetry is of limited value. It is considered quite useful, on the other hand, for the diagnosis of small pigmented tumours with little prominence. The melanoma, namely, rapidly causes destruction of the sensory cells and of the deeper layers of the choroid (Oosterhuis et al., 1981). According to Flindall and Drance (1969), the visual field defect in melanomas often extends to the periphery owing to rupture of the neurofibrils. This is in contrast to what Scott (1957) observed in choroidal tumours. Characteristic of melanomas are the intensity and the steep margin of the visual field defect. This in contrast to the relative scotoma and the sloping edge in a simple retinal detachment (Harrington, 1956; Aulhorn, 1966; Arné and Mathis, 1986).

According to Gass (1977) and Shields (1977), perimetry is of limited value for the differentiation of melanomas from naevi. While a visual field defect is frequently encountered in a melanoma, exceptions are possible and defects are frequently described in naevi as well.

The progression of the visual field defect in general is less rapid in melanomas than in metastases (Manor et al., 1978).

Electro-oculography (EOG). An abnormal EOG with a low ratio is frequently described in melanomas. According to most authors, the EOG registration is independent of the size of the tumour (Staman et al., 1980; Markoff et al., 1981; Brink et al., 1989/1990), although according to Jones et al. (1981), the ratio is inversely proportional to the prominence. Differentiation from naevi and retinal detachments is possible (Bohar and Farkas, 1976; Staman et al., 1980; Graniewski-Wijnands and Van Lith, 1981; Markoff et al., 1981; Ulrich et al., 1981; Brink et al., 1989/1990; Thaler et al., 1989). The EOG does not contribute to the differential diagnostics of melanomas from metastases of the choroid (Brink et al., 1989/1990).

Electroretinography (ERG). The ERG in melanomas of the choroid is subnormal to abnormal. The a- and b-waves are distinctly lower in the eye containing the tumour than in the normal eye. The larger the tumour, the more the amplitude is decreased. In tumours without associated retinal detachment, the ERG is described as normal to subnormal. In a large retinal detachment, the ERG is absent (Sundmark, 1958; Straub, 1961; Bohar and Farkas, 1976; Ponte and Lauricella, 1977; Ulrich et al., 1981).

Biopsies and punctures. In melanomas, use is made of biopsy methods as mentioned in Chapter 1.4.9. In most cases differential diagnosis from metastases is possible. In metastases of malignant cutaneous melanomas and of bronchial carcinoids, assessment of the biopsy may give problems, however (Font et al., 1966; Font et al., 1967).

^{32}P and other isotopes. The diagnostics of melanoma constitutes one of the main indications for the ^{32}P uptake test (Jarrett, 1976; Lommatzsch, 1977; Shields, 1977/1978; Goldberg et al., 1980; Lommatzsch et al., 1984; Desjardins, 1986). Cell typing by means of this test is not possible (Terner et al., 1956; Gysin, 1979).

No distinction of metastases from melanomas is possible by means of the ^{32}P uptake test (Van Dijk, 1978; Gysin, 1979). Of tumours in an anterior position, metastases in general present lower values than melanomas (Thomas et al., 1954).

Uveal melanomas can be distinguished from metastases with the aid of labelled melanin precursors. In amelanotic tumours, however, no differentiation is possible (Packer et al., 1977).

Monoclonal antibodies against cutaneous melanomas labelled with radioactive technetium (^{99}mTc) have been used in the diagnostics of uveal melanomas. The specificity is high but the sensitivity depends on the tumour size, the site of the lesion and the proportion and amount in which the antibody is incorporated (Bomanji et al., 1987).

Transillumination. In melanomas, a shadow or a reduced transparancy to light is virtually always described (Van Dijk, 1978; Jensen, 1963). However, in little-pigmented melanomas, diaphanous tumours are also described and differentiation from metastases is not possible (Jensen, 1963; Ferry, 1967/1978; Arné and Mathis, 1986).

Immunological techniques. In melanomas, extensive research has been carried out into immunological techniques for tumour diagnostics. Their use, however, is still in a phase of development (Cochran et al., 1985; Folberg et al., 1985; Dieckhues, 1986; Damato et al., 1987; Ringens et al., 1989; Scheiffarth et al., 1989).

1.5.3 Naevus

The terms naevus and benign melanoma are synonyms for benign melanocytic tumours of the uvea (Zimmerman, 1965; Gass, 1974). Naevi may be present from birth and rarely grow faster than the normal uveal tissue, and therefore they may be regarded as hamartomas (Gass, 1974).

Histologically, naevi are aggregations of melanocytes (Gass, 1974). Cytologically, naevoid cells are identical to cells normally present in the choroid. Plump polyhedral cells and spindle cells are observed in particular. Differentiation from spindle cell A melanomas is not always possible (Gass, 1974). Melanomas are said to originate from pre-existent naevi (Yanoff and Zimmerman, 1967), although the transformation of naevi into malignant melanomas has only rarely been described clinically (Gass, 1974).

Choroidal naevi are observed clinically in 1 to 5% of normal eyes, and at histopathological examination, in 10 to 20% (Hale et al., 1965; Gass, 1974). Naevi of the ciliary body are clinically rare and histologically occur in 3% of the normal population (Gass, 1974).

Naevi are described more frequently in females than in males. In Negroes, they are observed less frequently than in Caucasians, but the difference is less than for malignant melanoma. The incidence of naevi increases from the fourth decade and the age is 59 years on average at the time of detection (Tamler and Maumenee, 1959; Naumann et al., 1966; Gass, 1977). In young patients, choroidal naevi often contain little pigment, so they are rarely detected. The growth is probably maximal in the prepubertal years. In adults there occurs no or only a very slow increase in size and marked growth suggests a malignant melanoma (Tamler, 1970; Gass, 1974).

The differentiation of iridal naevi from iridal melanomas is often difficult. Naevi may remain stationary in size for years and then begin to grow (Gass, 1974). Of pseudomelanomas of the uvea, one-quarter of the cases prove to be naevi (Shields et al., 1980a), of iridal lesions this proportion is 31% (Shields et al., 1983).

Treatment is necessary only if serous detachments of pigment epithelium or retina, which sometimes occur, fail to disappear spontaneously. Areas of leakage may be treated with laser photocoagulation (Gass, 1974; Folk et al., 1989).

Signs and symptoms. Naevi in general cause no symptoms. Symptoms manifest themselves when a serous retinal detachment occurs in naevi localized in the macular area (Gass, 1974). However, Karickhoff (1967) described a decrease of visual acuity in 21% of the patients with naevi. A defect in the visual field was present in 7.5% of the patients. Naevi of the iris are nearly always asymptomatic (Dhermy, 1979).

Ophthalmoscopy and slit lamp examination. Choroidal naevi are flat or slightly elevated oval or round grey tumours with well-defined, although not sharply delimited margins (Gass, 1974, Hayreh, 1974). They are in general 1 to 3 disk diameters large with a prominence of 0.05 to 1 mm. Diameter and elevation of the lesions may vary greatly. They may be so elevated that a suspicion of malignant melanoma arises (Naumann et al., 1966; Gass, 1974/1977).

The typical colour of a naevus is slate-grey, but it may vary markedly, depending on the thickness of the lesion, the amount of melanin, pigment characteristics of the patient and changes of the overlying pigment epithelium. The lesion may be completely pigmented or only partly and have a dark centre with a light margin or vice versa. Mostly, naevi are evenly coloured. Focal areas of pigment loss and clustering of pigment, either in the form of dark patches or as orange pigment, do occur but are rare. Sometimes, whitish granular material is observed on the surface of the lesion (Smith and Irvine, 1973; Gass, 1974/1977; Oosterhuis and Von Winning, 1979). If naevi are amelanotic and multiple, as in neurofibromatosis, differentiation from metastases may be difficult (Font and Ferry, 1972).

Drusen occur frequently in choroidal naevi (in about one-quarter to one-half of the cases); they are described particularly often in larger and more prominent lesions. These drusen become confluent to form large areas of exudative detachment of the pigment epithelium. Leakage of serous fluid may lead to a limited serous retinal detachment which may resolve spontaneously. Cystoid retinal degeneration and oedema are rare (Naumann et al., 1966/1977; Gass, 1972/1974; Hayreh, 1974). Ruptures may develop in Bruch's membrane which may be associated with formation of neovascularization membranes in the sub-pigment epithelial space. Especially when located in the macular area these may give rise to haemorrhages and localized or disciform haemorrhagic detachments of pigment epithelium and retina. In the early phases, haemorrhages may look black and be mistaken for fast-growing malignant melanomas (Gass, 1974).

Naevi may occur throughout the fundus, but are encountered particularly often in the posterior pole. They are described with the least frequency in the anterior part of the choroid and the ciliary body (Reese, 1951; Naumann, 1966; Gass, 1974). Arné and Mathis (1986) stated that 90% of the naevi were situated behind the equator. Thirty per cent of the patients have one naevus in one eye, 3.5% more than one lesion in both eyes and 7%, multiple lesions in one eye (Gass, 1977).

Naevi of the ciliary body are discovered only rarely. In general they are relatively flat or slightly elevated (Gass, 1974).

Naevi of the iris are usually slightly elevated tumours situated in the anterior iridal stroma They only become visible at the young adult age because of the pigmentation developing at that time. As a rule, no changes of the shape of the pupil develop, although this has been described in large naevi. Iridal naevi may be multiple (Gass, 1974).

Fluorescein angiography. The fluorescence depends on the localization of the naevus. More superficially localized lesions cause an early shadowing of the choroidal staining which disappears with complete staining of the choroid. Naevi in the deeper layers of the choroid are poorly visible and only show the late masking of the background fluorescence in a variable degree. The size of the area of hypofluorescence roughly corresponds to that of the tumour. Hayreh (1974), however, reported that in the preretinal arterial phase a much larger area was seen than at ophthalmoscopical examination. This

area rapidly grew smaller after complete filling of the choroidal vasculature. Naevi have no vascularization of their own (Gass, 1972/1974; Hayreh, 1974; Fishman, 1977; Wessing, 1977; Bischoff, 1985; Bonnin, 1986).

Drusen frequently become visible in the first few minutes of staining and then stain progressively more. Retinal cysts may be present. They show no leakage, disappear with the retinal vascular fluorescence and are specific of naevi in older patients (Gass, 1972/1974; Wessing, 1977).

Choroidal neovascularizations may be visible in the form of intensely staining membranes (Gass, 1974).

Sometimes, a spotty or granular staining resembling that of a melanoma is observed in the arterial or arteriovenous phase. Possibly, only part of the pigmented area stains (Rubinstein, 1967; Wessing, 1977). Areas with whitish pigmentation remain non-fluorescent (Oosterhuis and Von Winning, 1979).

In naevi of the iris only minimal changes develop in the normal vascular pattern and permeability of the iris (Gass, 1974).

Echography. For echographic differentiation of intraocular lesions a prominence of 2 to 2.5 mm is necessary (Coleman et al., 1974; Ossoinig and Blodi, 1974). Since uveal naevi are less than 2 mm prominent, echography is of very limited value (Gass, 1977). A choroidal excavation has been described occasionally (Fuller et al., 1979).

Because ***CT scanning*** and ***MRI*** require a minimal prominence of 3 mm for visualization of the lesion, these examination techniques are not suitable for the differential diagnosis of naevi (Chambers et al., 1987; Mafee et al., 1987; Wollensak et al., 1988). In exceptional cases naevi are imaged, however. Liu et al. (1989) described a patient with a choroidal lesion with a prominence of 2.3 mm that was visible in the CT scan. At MRI, a hyperintense image was seen in T_1 weighted images, and the intensity decreased in T_2 weighted images. Consequently, the lesion was mistaken for a malignant melanoma; it proved to be a naevus, however.

Perimetry. According to certain investigators, defects in the visual field are encountered only rarely in naevi. They only develop when the choroidal nutritional supply of the retina is affected. If a scotoma develops, the depth is virtually always relative and it is localized at the site of the lesion (Reese, 1951; Karickhoff, 1967; Van Dijk, 1978).

Some authors described a relative scotoma in 38 to 85% of the patients with a naevus of the choroid. These defects are observed in particular in elevated lesions, and they are associated with visible changes of the pigment epithelium. If a retinal detachment is or has been present, the defect of the visual field may be larger than the size of the lesion (Tamler and Maumenee, 1959; Flindall and Drance, 1969; Gass, 1974). Absolute scotomas have been reported in naevi but they occur only rarely (Naumann et al., 1966a; Flindall and Drance, 1969; Oosterhuis and De Wolff-Rouendaal, 1981).

According to Gass (1977) and Shields (1977), perimetry is of limited value for the differentiation of a naevus from a melanoma. While in melanoma a visual field defect is usually established, exceptions are possible, and in naevi defects are also observed frequently. An absolute scotoma is more indicative of a melanoma, a relative scotoma of a

naevus (Oosterhuis et al., 1981).

Electro-oculography (EOG). In general, the light peak/dark trough ratio is normal in naevi cases (Staman et al., 1980; Jones et al., 1981; Markoff et al., 1981). The dark trough is not abnormal. Differentiation from melanomas, metastases and retinal detachments solely by means of EOG is possible in 73% of the cases (Brink et al., 1989/1990).

^{32}P uptake test. In 98 to 100% of naevi, the ^{32}P uptake test gives a negative result. If the result is positive, a melanoma with a low degree of malignancy may be involved (Shields, 1978, Van Dijk, 1978, Oosterhuis et al , 1980).

Transillumination. At diaphanoscopy, naevi show the same image as melanomas (Van Dijk, 1978) Hale et al (1965) performed transillumination in 200 eyes with a uveal naevus and reported sharply delimited, opaque lesions

1.5.4. Haemangioma

The cavernous haemangioma of the choroid is a benign hamartoma which manifests itself either as a solitary tumour in patients without other vascular malformations, or as a diffuse thickening of the choroid in the Sturge-Weber syndrome (Gass, 1974). For the differential diagnostics of uveal metastases, the solitary haemangioma is of particular importance

Uveal haemangiomas do not occur frequently (MacLean and Maumenee, 1960) Haemangiomas of the ciliary body and of the iris are rare (Reese, 1951, Duke Elder and Perkins, 1966a)

At histopathological examination large, dilated, thin-walled vessels are observed which at the edges blend into the normal choroidal tissue (Gass, 1974). The tumour contains hardly any connective tissue. Between the tumour and the retina a membrane may be present which contains calcifications Ossification is frequent (Reese, 1951). Jones and Cleasby (1959) and Gass (1974) describe an extensive proliferative change of the pigment epithelium, and metaplasia and cystoid degeneration of the retina

Growth of the tumour is probably maximal during the normal growth period of the individual. In adulthood, the size of the lesion shows hardly any change (Gass, 1974). In case of rapidly growing and multiple localizations, the possibility of uveal metastases should be considered (Chisholm and Blach, 1973, Hutchison and Smith, 1979).

Although according to a number of authors haemangiomas are rarely detected before the third decade, and the patients are between 40 and 59 years old in 85% of the cases (Gass, 1974; Jarrett et al , 1976), according to other authors they are diagnosed more often in young people (Reese, 1951; Jones and Cleasby, 1959). The mean age is 48 to 51 years (Gass, 1974; Anand et al., 1989) Patients with haemangiomas of the Sturge-Weber syndrome are much younger, 8 years old on average (Witschel and Font, 1976). Interestingly, haemangiomas in 70% of the cases are observed in males (Gass, 1974;

Jarrett et al., 1976; Anand et al , 1989) and particularly in Caucasians (Gass, 1974). Witschel and Font (1976) described an equal distribution over the sexes in solitary tumours, but a larger proportion of males in diffuse haemangioma.

If a haemangioma is detected fortuitously, without retinal detachment or signs of an earlier retinal detachment, it requires no treatment. If the tumour is situated outside the fovea and a retinal detachment is present, the tumour may be treated with laser photocoagulation at the site of diffuse leakage on the tumour surface. This will nearly always result in absorption of the subretinal fluid and correction of the retinal detachment. The treatment does not affect the tumour size (Jarrett et al., 1976; Gass, 1974; Bonnin, 1986). Sanborn et al., (1982), Greber et al. (1985) and Zografos et al., (1989) describe various radiotherapeutic techniques used in the treatment of uveal haemangiomas.

Signs and symptoms. Ninety per cent of the patients with a choroidal haemangioma have symptoms varying from blurred vision and metamorphopsia to severe deterioration of the visual acuity or blindness Ten per cent of the patients are asymptomatic. As a rule, symptoms only develop when, at an older age, a serous retinal detachment occurs which extends from the margin of the lesion to the macular area In haemangiomas situated in the macular area or in large tumours symptoms are reported earlier If the tumour is localized in the macular area, a disturbance of the central visual acuity sometimes occurs before significant alterations manifest themselves in the overlying pigment epithelium or retina. The visual acuity varies from 20/15 to no light perception and on average is 6/30 (Gass, 1974; Anand et al , 1989). Witschel and Font (1976) report total blindness in 60% of the patients.

Glaucoma, uveitis, cataract, corneal degeneration and intraocular haemorrhages have been described as well as dilated episcleral vessels (Reese, 1951; Jones and Cleasby, 1959) Hayreh (1974), however, denies that uveitis and cataract occur. Witschel and Font (1976) report an increased intraocular pressure in 40% of the solitary and 76% of the diffuse haemangiomas.

In haemangiomas of the ciliary body a hyphaema is sometimes described (Daily, 1931; Reese, 1951).

Ophthalmoscopy and slit lamp examination. Characteristic of the choroidal haemangioma is a round or oval, slightly elevated, orange-red tumour with a vague margin (Gass, 1974)

Most haemangiomas are located in the macular area or close to the optic disk and then may cause early symptoms (Reese, 1951, Gass, 1974; Jarrett et al., 1976; Witschel and Font, 1976, Bonnin, 1986, Anand et al., 1989)

Haemangiomas are distributed evenly over the right and left eyes (Gass, 1974; Witschel and Font, 1976), although Anand et al (1989) report a predilection for the right eye and Bottoni et al. (1990) one for the left eye. A bilateral solitary haemangioma is encountered only sporadically (Schepers and Schwart, 1958; Shields, 1983). Multiple haemangiomas in one eye have been described only rarely (Shields, 1983; Zografos et al., 1989).

The tumour is usually less than 4 to 5 disk diameters large. Large haemangiomas may be difficult to distinguish from amelanotic melanomas and metastases (Gass,

1972/1974; Jarrett et al., 1976). Haemangiomas are said never to show the mushroom shape typical of melanomas (Shields, 1983). Arné and Mathis (1986) described haemangiomas with a multifocal appearance. The margins of the lesion are blurred and poorly delimited (Bonnin, 1986). The colour is pinkish, orange-red or fleshy. There may be small pigment patches on the tumour surface (Gass, 1974; Jarrett et al., 1976; Arné and Mathis, 1986). Orange lipofuscin pigment is not observed in haemangiomas (Smith and Irvine, 1973). Because the colour often resembles that of the surrounding normal fundus and the lesion is usually only slightly elevated, choroidal haemangiomas are easily overlooked if no use is made of binocular indirect ophthalmoscopy. If there are no or only minimal signs of change of pigment epithelium or retina, the tumour is detected only by accident (Gass, 1974). Some haemangiomas may blanch on manual compression of the eye (Gass, 1974).

Biomicroscopy is important for the perception of changes of pigment epithelium and retina. In adults, the retina is typically thickened and cystoid and retinoschisis may be present. The mottled yellow material that accompanies the cystoid alterations lies in the depth or beneath the degenerated retina (Gass, 1974). Retinal oedema is frequently observed, usually at a distance from the tumour. Presence of cystoid macular oedema in a nasally localized tumour according to a number of authors indicates a haemangioma (Jarrett et al., 1976; Bonnin, 1986). Approximately one-third of the patients have a permanently damaged macula owing to the cystoid retinal degeneration and oedema, circinate retinopathy, distinct pigment disturbances and sometimes, a macular pucker (Gass, 1974). Serous detachment of the surrounding retina is often present (Gass, 1972; Jarrett et al., 1976). A retinal detachment is described in 76 to 78% of the patients and is total in 7%. This retinal detachment is rarely bullous and almost never separated from the tumour. Sometimes, there are signs of previous retinal detachment (Gass, 1974; Anand et al., 1989). The retinal detachment may mask the tumour (Bonnin, 1986).

Intraretinally, haemorrhages may develop. Reportedly, small calcifications in the retina occur in 20% of the haemangiomas (Reese, 1951; Witschel and Font, 1976; Bonnin, 1986). Bonnin (1986) describes the frequent development of alterations of the retinal capillaries. Prominent choroidal vessels, as in melanomas, are not observed in haemangiomas (Hayreh, 1974). The choroidal vascular pattern (Karel and Peleska, 1972) and dilatation of the retinal or choroidal vessels may be visible (Jones and Cleasby, 1959).

Haemangiomas of the ciliary body or the iris are uncommon (Daily, 1931; Keller, 1962; Heath, 1964; Oksala et al., 1964; Duke-Elder, 1966; Bruck, 1969).

Fluorescein angiography. Characteristic aspects of the haemangioma are a coarse vascular fluorescence pattern in the pre-arterial and arterial phases corresponding to the location of the tumour, the extensive areas of fluorescence secondary to the diffusion of the dye from the surface and the multiloculated pattern of fluorescein accumulation in the outer retina, characteristic of polycystic degeneration and oedema, during later stages. In the absence of visible cystoid retinal oedema, the diagnosis of haemangioma allegedly is doubtful (Norton and Gutman, 1967; Gass, 1974; Hayreh, 1974; Schatz, 1978).

The tumour as a rule stains even before the retinal arteries, simultaneously with the surrounding choroid (Hayreh, 1974; Wessing, 1977; Schatz, 1978; Wessing and Foerster, 1983; Bonnin, 1986). For a few seconds there occurs a sponge-like configuration of areas that do or do not stain. This fades because of the fluorescein leaking into the perivascular space, which stains the entire tumour (Wessing and Foerster, 1983). In the venous phase,

a uniform fluorescence of the entire tumour is described (Bottoni et al., 1990). Pink areas stain more than white areas (Hayreh, 1974).

Dilated vascular canals fill in early phases (Rosen, 1969; Fishman, 1977; Schatz, 1978; Bottoni et al., 1990), but according to other authors they are not visible (Hayreh, 1974). Gass (1974) describes the separate vascular structures with clearly frayed vascular walls, unlike the smooth vascular walls in melanomas. The delimitations in the fluorescein angiographic image are far sharper than in the ophthalmoscopic image (Bonnin, 1986) although, according to Wessing (1977), there is, on the contrary, a smooth blending into the normal choroid. Frequently, a hypofluorescent zone at the margin of the lesion is observed. This might be caused by the common proliferative changes in the pigment epithelium (Gass, 1974) or by displacement of the normal choroidal melanocytes (Bonnin, 1986).

In haemangioma, hyperfluorescent spots may be seen which accordingly are not characteristic of melanomas but only of prominent choroidal tumours (Bonnin, 1986) and which, according to other authors, do not occur in metastases (Fishman, 1977). Sometimes there are signs of changes of the permeability of the retinal capillaries at the margin of the lesion (Gass, 1974; Hayreh, 1974), although according to Loewer-Sieger and Oosterhuis (1971) these constitute an argument against the diagnosis of haemangioma. Multilake areas, as in haemangiomas, and late fluorescence in areas with cystoid retinal oedema, as also seen in melanomas, are said not to be described in metastases (Davis and Robertson, 1973).

The early pre-arterial fluorescence brought about by the large vascular canals and the later multilocular staining due to cystoid degeneration of the overlying retina have rarely been described in other tumours (Gass, 1972/1974).

Echography. Haemangiomas have a broad base and are mostly 0.5 to 3 mm prominent. They are rarely larger than 5 to 6 mm (Chang et al., 1978; Anand et al., 1989). Allegedly, a mushroom shape never occurs (Shields and Tasman, 1977).

The large congested vessels with intervascular septa, owing to the large tissue interfaces, give a high reflectivity, of 95 to 100%. Because of the predominantly regular tissue structure, the infrastructure of the tumour is usually regular (Ossoinig and Harrie, 1983; Neetens et al., 1984; Verbeek, 1985; Poujol, 1986; Bigar, 1988). Sporadically, the reflectivity is described as relatively low (Coleman, 1973).

Since the haemangiomatous tissue echographically is highly similar to the normal surrounding choroid, a choroidal excavation will almost never occur (Chang et al., 1978; Neetens et al., 1984; Poujol, 1986), but it has occasionally been described (Fuller et al., 1979). Echographic vascularity is hardly ever seen, probably because there is no blood flow in the tumour or the lesions are too small (Neetens et al., 1984; Verbeek, 1985; Guthoff, 1988). However, Ossoinig and Blodi (1974) frequently describe a distinct vascularity.

In haemangiomas of longer standing calcium deposits may be demonstrated, owing to which the lesion echographically is sometimes no longer to be distinguished from an osteoma (Guthoff, 1988).

Computed tomography. Haemangiomas can be visualized by means of the CT scan only after administration of contrast medium (De Keyzer et al., 1985; Mafee et al., 1985).

Roentgen examination may be useful because of possible calcifications which, however, are only present in tumours of long standing (MacLean and Maumenee, 1960).

Magnetic Resonance Imaging (MRI). In haemangiomas a hypodense tumour is described in T_1 weigthed images as against a hyperdense lesion in T_2 weighted images (Haik et al., 1987b; Mafee et al., 1987). Anand et al. (1989) in these cases describe a hyperdense image in T_1 and an isodense image in T_2 weighted images.

Perimetry. A haemangioma with cystoid retinal alterations causes a defect in the visual field at the site of the tumour and when a retinal detachment is present, at the site of the detachment. Defects of nerve fibre bundles secondary to a choroidal haemangioma have rarely been described (Gass, 1974). If a haemorrhage occurs in the nerve fibre layer of the retina it may cause a sector defect (Reese, 1951). According to MacLean and Maumenee (1960), visual field defects occur frequently in haemangiomas and are more extensive than the size of the tumour itself. The scotoma is usually relative but sometimes absolute (Witschel and Font, 1976).

Electro-oculography (EOG). A low ratio and a normal dark trough are described at EOG examination (Graniewsky-Wijnands et al , 1981).

^{32}P uptake test. The ^{32}P uptake test usually, but not always, gives a negative result (Gass, 1974). A positive result is described in 8 to 10% of the haemangiomas (Van Dijk, 1978; Shields, 1978; Lanning and Shields, 1979; Oosterhuis et al., 1980; Desjardins, 1986).

Transillumination. Choroidal haemangiomas allow easy passage to light. Sometimes there is a vague circular defect in the transillumination at the tumour margin. This corresponds to a comparable zone of hypofluorescence at fluorescein angiography (Gass, 1974; Jarrett et al., 1976).

1.5.5 Lymphoproliferative diseases

Practically all parts of the eye and the ocular adnexa may be involved in lymphoproliferative diseases. Most frequently, lesions are encountered in the orbit and conjunctiva. The intraocular structures are only sporadically affected clinically (Shields, 1983). Lymphoid tumours may resemble amelanotic melanomas, metastases or intraocular infections (Shields, 1983). Uveal localizations are seen more frequently in patients with leukaemia than in patients with a malignant lymphoma (Gass, 1974).

1.5.5.1 Leukaemia

In patients with leukaemia the eye may be involved in the pathological process through infiltration of tissue by leukaemic cells or through secondary complications such as haemorrhages and infections (Allen and Straatsma, 1961; Kincaid and Green, 1983; Nelson et al., 1983; Shields, 1983; Leonardy et al., 1990). Ocular abnormalities occur about as often in acute as in chronic leukaemia (Allen and Straatsma, 1961; Schachat et al , 1988; Leonardy et al., 1990). However, according to Gass (1974), the most evident lesions are seen in the acute forms.

Histopathologically, the choroid is infiltrated in 66% of the patients, the ciliary body in 13% and the iris in 3% (Leonardy et al., 1990). Clinically, however, infiltration of ocular structures is established in only 3% of the patients with leukaemia (Schachat et al , 1989).

Histopathologically, variable numbers of neoplastic cells are observed in the uvea, with separation of choroidal vessels and thickening of the choroid, most pronounced in the posterior pole. If the ciliary body is involved in the disease process, it shows only slight thickening and the architecture little abnormality (Shields, 1983; Leonardy et al., 1990). It has been asserted that a relationship exists between the ophthalmological involvement on the one hand and the leukocyte count and severity of the systemic disease on the other (Leonardy et al , 1990).

Ocular signs and symptoms may constitute the first indications for the diagnosis of leukaemia. In the majority of the patients this diagnosis is already known, however. If the choroid is affected, blurred vision is an important symptom. Although histopathologically, infiltrates occur frequently in terminal stages of leukaemia, it is doubtful whether they also frequently cause symptoms (Gass, 1974; Shields, 1983; Abramson, 1984; Stewart et al., 1989; Leonardy et al., 1990).

If the iris is involved, complaints about blurred vision, photophobia and pain are frequent Conjunctival and episcleral injection can regularly be observed. Iridal infiltrates may have features in common with granulomatous iritis, endophthalmitis or iridal metastases. The iris may show diffuse thickening, often with small poorly delimited nodules extending to the pupillary margin. Diffuse infiltrations cause discolouring of the iris and heterochromia.

Vascular congestion may cause a vascular rupture and consequently, a hyphaema. The infiltration may be so extensive that tumour cells layer out into the anterior chamber and there form a pseudohypopyon. Infiltrates of the angle of the anterior chamber may lead to a secondary glaucoma. An increased intraocular pressure occurs in 9% of the patients with leukaemia (Johnston and Ware, 1973; Gass, 1974; Kincaid and Green, 1983; Shields, 1983; Shields et al., 1987, Schachat et al., 1988).

Ophthalmoscopically, well-defined white preretinal lumps and masses may be observed. Secondary leukaemic alterations such as haemorrhages and cottonwool spots due to anaemia and thrombocytopenia are described more frequently than in infiltrates (Schachat et al., 1989). Intraocular haemorrhages develop in 11 to 45% of the patients with leukaemia (Leonardy et al., 1990). Although in many patients the uvea is involved in the process, the alterations are often not visible at ophthalmoscopy. In extreme cases, the fundus at the site of the infiltration may have an intensive yellow-pink colour (Gass, 1974; Naumann, 1980). Sporadically, alterations occur in the retinal pigment epithelium in the

form of focal areas of brown pigment. At ophthalmoscopy this may give a leopardskin-like image as described in choroidal metastases and uveal effusion. Apart from choroidal infiltrations, the disk and retina are also sometimes involved. The infiltrate may grow so large that it becomes a localized or diffuse choroidal tumour. This occurs most frequently in acute lymphatic leukaemia. A serous retinal detachment is described regularly (Gass, 1974; Kincaid and Green, 1983; Shields, 1983; De Laey and De Gersem, 1989).

Fluorescein angiography may be useful for the detection of areas of damage to the pigment epithelium situated beneath a serous retinal detachment. No characteristic fluorescein angiographic image exists. If the pigment epithelium is affected, mottled irregular areas may be present which cannot be differentiated from inflammatory choroidal cellular infiltrations with multiple sites of leakage from the underlying choroid (Gass, 1972/1974). In leukaemic infiltration of the choroid, multiple fluorescent spots are described which then fade again and progressive diffusion occurs which in late phases delimits an extensive area of serous detachment. The image may greatly resemble that of Harada's disease, sympathetic ophthalmia, toxicosis or other signs of occlusion of the choriocapillaris (De Laey and De Gersem, 1989).

Echographically, a thickening of the uvea is described in leukaemia, often with a high reflectivity (Poujol and le Roy, 1983).

Puncture of the anterior chamber and other techniques of obtaining cellular ocular material may be of diagnostic importance (Shields, 1983; Schachat et al., 1988).

Ophthalmological therapy consists of atropine and steroids to combat the symptoms in case of involvement of the anterior segment and radiotherapy of the eye for local tumour treatment (Johnston and Ware, 1973; Shields, 1983; Schachat et al., 1988).

1.5.5.2 Lymphoma

Apart from reticulum cell sarcoma, lymphomas of intraocular structures are rare (Shields, 1983). Forms described include intraocular Hodgkin lymphoma (Primbs et al., 1961) and the Burkitt lymphoma (Karp et al., 1971). Choroidal infiltration by malignant lymphocytic lymphomas is rarely observed (Weisenthal et al., 1988). Raised intraocular pressure is described in 27% of the patients (Shields et al., 1987).

Reticulum cell sarcoma (RCS, diffuse histiocytic lymphoma, non-Hodgkin lymphoma) is probably less rare than is assumed. Intraocular manifestations may occur isolatedly but in most cases are associated with involvement of the central nervous system and less often with visceral lymphomas. The mean age is about 60 years. The condition is said to occur more frequently in females (Freeman et al., 1987). The interval between the earliest symptoms and the diagnosis is two years in general. The condition is often bilateral (Shields, 1983; Freeman et al., 1987; Siegel et al., 1989; Schachat, 1990).

The clinical picture of RCS depends on whether the vitreous humour, the retina, the papilla or the choroid is affected most. Ophthalmological symptoms may precede other symptoms. A painless deterioration of the visual acuity is frequent. Slit lamp examination reveals characteristic corneal precipitates and retrolental vitreous cells, probably secondary to the retinal involvement. The vitreous cells may be so dense that ophthalmoscopy is not possible. If the retinal or choroidal involvement is more pronounced and there is little reaction of the vitreous, the picture may give the impression of retinitis or posterior

uveitis. In that case, yellow infiltrates may be observed that appear to lie deep in the retina (Shields, 1983; Schachat, 1990). Sometimes, instead of more diffuse lesions, solitary subretinal or choroidal masses are seen. These lesions may be mistaken for choroidal metastases (Barr et al., 1975; Stephens and Shields, 1979; Raju and Green, 1982; Shields, 1983; Strempel, 1983; Siegel et al., 1989). Several authors describe a large serous retinal detachment in RCS (Barr et al., 1975; Simon and Friedman, 1980; Char et al., 1988/1988a). In general, choroidal lesions are observed more often in systemic RCS (with lymphadenopathy and visceral involvement). If the central nervous system is involved in the disease, the optic nerve and retina are affected more frequently (Klingele and Hogan, 1975; Shields, 1983).

Extensive affection of the iris occurs less frequently. It may resemble granulomatous iritis or an iridal metastasis. Iridal lymphomas may sometimes spontaneously bring about a hyphaema. Closure of the angle of the anterior chamber may lead to a secondary glaucoma (Collyer, 1972; Shields, 1983).

Needle biopsy of the vitreous humour to obtain cellular material may be of diagnostic importance in RCS (Shields, 1983; Freeman et al., 1987; Char et al., 1988/1988a). Echographically, a patient with a solitary low-reflective tumour of an RCS, with 6.5 mm prominence, has been described with choroidal excavation, vascularity and orbital shadow suggestive of a malignant melanoma (Fredrick et al., 1989). Sullivan and Dallow (1989) described an echographic image of a ring/annular tumour in the ciliary body.

In uveitis of unknown origin in patients of more advanced age, the possibility of RCS should be considered (Shields, 1983; Siegel et al., 1989).

The treatment of RCS consists of radiotherapy, possibly corticosteroids and systemic chemotherapy (Margolis et al., 1980; Shields, 1983; Freeman et al., 1987; Char et al., 1988/1988a).

1.5.5.3 Benign reactive lymphoid hyperplasia

Benign reactive lymphoid hyperplasia (BRLH) is a pseudotumour which may affect the uvea with or without simultaneous involvement of the conjunctiva or the orbit. In case of uveal localization the diagnosis is sometimes difficult because the lesion may resemble a diffuse choroidal neoplasm or an inflammatory process. For the differential diagnosis a diffuse malignant melanoma, metastasis, reticulum cell sarcoma, leukaemia, sympathetic ophthalmia and posterior scleritis should be considered (Crookes and Mullaney, 1967; Gass, 1967; Ryan et al., 1972; Shields, 1983; Ben-Ezra et al., 1989; Verbeek et al., 1990).

Although initially a reactive inflammatory genesis was postulated (Hogan and Zimmerman, 1962), it is currently believed that the condition is a low-grade tumour with diffuse infiltrates of mature lymphocytes with lymphoblastic features. (Uveal) lymphoid infiltration accordingly would be a more appropriate name (Jakobiec et al., 1987a).

In general the condition occurs in middle-aged persons (average 55 years). BRLH is described more frequently in Caucasians and in males, and is mostly unilateral (Ryan et al., 1971/1972).

A characteristic element is a mostly painless deterioration of the visual acuity. If

the orbit is also involved, ocular protrusion may develop Glaucoma is reported in 67% of the cases, iridocyclitis in 57% (Ryan et al , 1972)

In involvement of the iris, a diffusely thickened iridal stroma is described, sometimes associated with Tyndall's phenomenon, cells in the aqueous humour and keratitic precipitates Occasionally, a spontaneous hyphaema is reported The picture may show similarity to a granulomatous inflammation or a diffuse iridal neoplasm Sometimes, a localized nodular iridal tumour is described, as in an iridal melanoma or metastasis At fluorescein angiography, a non-specific early vascularization and late hyperfluorescence are seen Needle or excision biopsy may be necessary before a definite diagnosis can be made (Shields et al , 1981, Shields, 1983)

BRLH of the ciliary body rarely occurs as a solitary lesion It is usually described as part of a panuveal involvement In extensive infiltrates a narrow-angle glaucoma may develop The lesion may show similarity to chronic cyclitis or a ring melanoma of the ciliary body (Gass, 1967, Shields, 1983)

A BRLH of the posterior uvea is characterized by a diffuse or nodular amelanotic thickening of the choroid In one-half of the patients a serous retinal detachment is present with displacement of the subretinal fluid at movements of the head (Gass, 1967, Ryan et al , 1972, Shields, 1983) Changes of the pigment epithelium are possible Ophthalmoscopy then reveals golden-brown foci on the amelanotic tumour surface, which foci contain macrophages with lipofuscin and melanin (Shields et al , 1976, Shields, 1983). Jakobiec et al (1987a) described BRLH cases with multifocal, sometimes confluent, cream-coloured choroidal infiltrates with an indistinct margin without changes of the pigment epithelium or retinal detachment At fluorescein angiography, staining of the lesions was seen without leakage into the sub-pigment epithelial or subretinal space Shields (1983) describes fluorescein-angiographic images with early mottled hyperfluorescence of the choroidal mass with late staining and many aspecific hyperfluorescent foci

Desroches et al (1983) described echographic images with an elevated mass in the posterior pole without choroidal excavation or vascularity with a low regular reflectivity In other cases, thickening of the choroid was observed with sometimes, an episcleral extension (Jakobiec et al , 1987a) At CT scanning, a thickened choroid may be imaged (Desroches et al , 1983, Jakobiec et al , 1987a)

Treatment consists of systemic and sometimes, retrobulbar corticosteroids. Radiotherapy is also possible (Shields, 1983, Jakobiec et al , 1987a, Ben-Ezra et al , 1989) Given early diagnosis and treatment, the prognosis of the visual acuity is excellent as is the prognoses quoad vitam (Shields, 1983)

1.5.6 Other intraocular tumours and related tumour-like lesions

1.5.6.1 Leiomyoma

Leiomyomas of the uvea are rare tumours derived from smooth muscle tissue. Probably, all uveal leiomyomas are of mesectodermal origin. Clinically, the differential diagnosis, especially from malignant melanomas and metastases, is extremely difficult or impossible. By optic microscopy, the cells frequently cannot be distinguished from melanoma cells, either. Electron microscopy is then required for a definite diagnosis (Reese, 1963; Jakobiec et al., 1977; Ishigooka et al., 1989; Shields et al., 1989; White et al., 1989). With regard to many tumours described in the literature as leiomyomas, the correctness of the diagnosis is doubted (Reese, 1963). Of all iridal tumours, 9 to 14.5% reportedly are leiomyomas (Reese, 1963; Ashton and Wybar, 1966). Brovkina and Chichua (1979) described 30 out of 55 surgically removed iridal tumours as leiomyomas. Shields et al. (1983) diagnosed only one out of 158 pseudomelanomas of the iris as a leiomyoma.

Jakobiec et al. (1976) described an extremely rare choroidal leiomyoma which had been enucleated on the erroneous diagnosis of malignant melanoma.

Leiomyomas of the ciliary body are encountered nearly exclusively in females. The mean age is 31 years. Patients over 50 are rarely described (Burk et al., 1989; Shields et al., 1989). At slit lamp examination, dilated episcleral vessels, uveitis, neovascularization of the iris, pupillary deformations, lens dislocations, cataractogenous opacities and a tendency to rapid growth can be observed (Ishigooka et al., 1989). A retinal detachment may develop.

At fluorescein angiography, hyperfluorescence in the venous phase with late irregular fluorescence or a diffuse staining of the tumour is observed. At echography, a low-reflective spherical tumour is described with a choroidal excavation, similar to a melanoma. The tumours are generally large: on average with a prominence of 6 mm and a base of 9 mm. The CT scan may display a solid ciliary mass, MRI shows a slight hyperdensity in relation to the vitreous humour in T_1 and hypo- or hyperdensity in T_2 weighted images. Of the ^{32}P uptake test, pathological results are regularly described.

A noticeable aspect of leiomyomas of the ciliary body is the fact that at diaphanoscopy the site of the lesion transilluminates more clearly than the vicinity of the tumour. This has also been described in an adenoma of the non-pigmented ciliary epithelium and in a nodular posterior scleritis.

With the various examination techniques, differentiation of the leiomyoma from other tumours is not possible. The occurrence at an early age and the diaphanoscopical image, however, are possibly pathognomonic of leiomyomas (Dunbar, 1956; Jakobiec et al., 1977; Burk et al., 1989; Ishigooka et al., 1989; Mafee et al., 1989; White et al., 1989).

Leiomyomas of the iris are flesh-coloured, yellowish-pink or brown, but nearly always unpigmented. The lesions are often prominent with a sharp delimitation from the normal iridal tissue. On the tumour surface blood vessels may be discerned. Some ectropion uveae is regularly described. The tumours may be localized anywhere in the iris, but there is a predilection for the lower, especially the temporal part of the iris and

the iridociliary zone. The tumour may be a localized lesion or infiltrate the iridal stroma as far as the angle of the anterior chamber (Erdbrink and Harbert, 1955; Reese, 1963; Ashton and Wybar, 1966; Duke-Elder, 1966; Brovkina and Chichua, 1979; Waubke, 1983; Shields et al., 1989).

At fluorescein angiography, usually at the same time as the iridal vessels, a spotty staining of the lesion is observed and sometimes, a vascular tumour network, without diffuse staining. Fluorescence at the pupillary margin as a rule is only seen opposite to the tumour (Brovkina and Chichua, 1979).

The treatment of leiomyoas of the iris and the ciliary body consists of local excision of the tumour. Metastases have not been described. The prognosis quoad vitam is excellent (Ashton and Wybar, 1966; Waubke, 1983; Ishigooka et al., 1989; Jakobiec et al., 1989).

1.5.6.2 Tumours of the non-pigmented ciliary epithelium

Tumours of the non-pigmented epithelium of the iris and the ciliary body are rare (Shields et al., 1983). The neuroepithelial tumours and tumour-like lesions are subdivided into congenital and acquired tumours. The medullo-epithelioma belongs to the congenital tumours and is subdivided in its turn into the primary and the teratoid tumours, of which both benign and malignant forms exist. The acquired, more differentiated tumours include the adenoma and the adenocarcinoma (Zimmerman, 1971; Andersen et al., 1982).

Medulloepitheliomas are rare, slowly growing tumours of the non-differentiated unpigmented epithelium of the ciliary body and very rarely of the optic nerve or retina. The mean age is 5 to 7 years and the patients are practically never older than 14 years. The tumour occurs with equal frequency in both sexes and is always unilateral.

Deterioration of the visual acuity is described in 25 to 40% of the patients, pain in 30%. About 30 to 50% of the patients have cataract and 32 to 50%, glaucoma. Rubeosis iridis is observed in over 80% of the patients, although Broughton and Zimmerman (1978) reported this only a few times. A retinal detachment is seen in 5 to 10% of the patients and 18% have a leukokoria. Occasionally, a hyphaema or vitreous haemorrhage is described (Broughton and Zimmerman, 1978; Canning et al., 1988). The tumour may fill the entire ovular cavity (Sirsat et al., 1972). The diagnosis can be made after aspiration of vitreous humour containing free-floating cysts (Orellana et al., 1983).

In general, medullo-epitheliomas grow slowly. Locally, however, they may show a malignant behaviour. Allegedly, two-thirds of the tumours are benign, most of them containing keratoid elements (Canning et al., 1988). Broughton and Zimmerman (1978), however, classified two-thirds of the tumours as malignant. All these tumours contained cells that resembled cells as encountered in retinoblastoma. An extraocular extension is described in 18 to 25% of the tumours. The tumour is said to behave more malignantly in adults. Distant metastases develop rarely and occur only in patients with extrascleral spread (Orellana et al., 1983). Treatment consists of enucleation or, in localized tumours, local excision. The prognosis quoad vitam generally is excellent (Canning et al., 1988).

In young children with poor eyesight, a mass in the ciliary body, unilateral glaucoma and/or cataract, a medullo-epithelioma has to be considered for the differential

diagnosis.

The tumour is also sometimes called diktyoma (Orellana et al., 1983).

Adenomas of the non-pigmented ciliary epithelium cannot be distinguished from malignant melanomas of the ciliary body and are often enucleated on that clinical diagnosis. The tumour is also sometimes called benign epithelioma. Although the tumour is cytologically benign, it may grow slowly and cause subluxation of the lens, cataract or secondary glaucoma (Reese, 1976; Shields et al., 1983). The mean age of the patients in whom the tumour is observed is 43 years (Andersen, 1962; Shields et al., 1983). The tumour may be accompanied by decrease of the visual acuity, pain and mild iridocyclitis (Fanta, 1977).

Echography shows a solid mid-reflective tumour (Shields et al., 1983). The ^{32}P uptake test may be positive (Lommatzsch et al., 1979). Patrinely et al. (1983) described an adenoma at the site of an iridocoloboma in a child aged 2.5 years. This was probably a hamartomous tumours.

Adenocarcinomas of the non-pigmented ciliary epithelium, also sometimes called malignant epitheliomas, are very rare slowly growing tumours. They are diagnosed at the mean age of 59 years and are distributed equally over the sexes. Forty per cent of the patients have an ophthalmological anamnesis of injury or inflammation. Malignant transformation of a reactive hyperplasia may have occurred. Subluxation of the lens and glaucoma may be observed (Kuchynka, 1979; Dryja et al., 1981; Rodrigues et al., 1988; Grossniklaus et al., 1990). The tumour has to be differentiated from a metastasis of a carcinoma of the prostate and from colloid breast cancer. Histologically, this distinction is difficult to make (Jakobiec et al., 1987; Grossniklaus et al., 1990). The treatment consists in enucleation or local excision. The prognosis is unknown. Extraocular extension is regularly observed, metastasization may occur (Grossniklaus et al., 1990).

1.5.6.3 Tumours and tumour-like lesions of the pigment epithelium of the iris, ciliary body and retina

Hypertrophy, hyperplasia and benign melanoma of the pigment epithelium according to Gass (1974) are different names for one and the same condition which is probably congenital and should be regarded as a hamartoma of the pigment epithelium. Arné and Mathis (1986), on the other hand, make a clear distinction between hypertrophy and hyperplasia.

The ***hypertrophic lesions of the retinal pigment epithelium*** may occur at any age and in both sexes. They cause no symptoms, are mostly unilaterally located and situated temporally in 70% of the cases. Defects in the visual field develop only rarely. These are mostly absolute in older and relative in young patients (Buettner, 1975). The lesions are flat, sharply delimited and pigmented, brown, greyish-brown or black. The pigmentation may be irregular and a hypopigmented halo is often present. The overlying retina as a rule shows no abnormalities. In larger lesions hypopigmentation occurs. In contrast to

metastases of the choroid, hypertrophic lesions are less numerous, flat, display no growth and may show the above-mentioned halo. Hyperfluorescence is caused by pigment defects and the halo. No leakage is observed. The EOG and ERG are normal, as is the ^{32}P uptake test. There is no connection with systemic diseases or ophthalmological pathology (Buettner, 1975; Purcell and Shields, 1975; Arné and Mathis, 1986).

Hyperplasia of the retinal pigment epithelium nearly always develops as a reaction to an earlier inflammation. The condition appears as solitary or multiple, heavily pigmented and sometimes elevated lesions with irregular margins (Arné and Mathis, 1986). At fluorescein angiography, a well-delimited masking of the background fluorescence is observed (Hayreh, 1974; Bonnin,1986).

Hypoplasia of the retinal pigment epithelium is probably congenital and is characterized by a flat, sharply delimited lesion which is usually round to oval in shape, of a white colour with focal hypopigmentation. Histopathologically, pigment granules are absent in a predominantly normal but somewhat flattened pigment epithelium. The lesion may be confused with unpigmented naevi, metastases or other nodular lesions of the choroid (Gass, 1974).

The ***adenoma of the pigment epithelium*** (benign epithelioma) is described as accounting for 1.4% of all primary tumours of the iris (Ashton and Wybar, 1966). It may also be present in the ciliary body (Lieb et al., 1990). It presents as a predominantly black mass in the iridal stroma, which causes slight deformation of the iris without an ectropion of the pigment epithelium. The pupillary reactions are mostly unimpaired. Pale lesions may occur. In general there is only little melanin production. Inflammation in the affected area is observed frequently, lenticular opacities are sometimes seen (Garner, 1970; Lowe and Greer, 1971).

Patients with an ***adenocarcinoma of the retinal pigment epithelium*** (malignant epithelioma) on the whole are older than patients with benign epitheliomas. The condition is divided equally over both sexes. It is a rare low-grade malignant tumour which almost never causes metastases and as a rule does not cause infiltration outside the choroid or the lamina cribrosa. There is only little inflammation and nearly always there is production of melanin so that the fundus is heavily pigmented. The fluorescein angiogram reveals mottled fluorescence. Echographically, an elevated low- to mid-reflective lesion is described with a distinct choroidal excavation without vascularity. The tumour may show great similarity to a melanoma (Garner, 1970; Minckler and Allen. 1970).

1.5.6.4 Combined hamartoma of the retina and retinal pigment epithelium

The combined hamartoma of the retina and the retinal pigment epithelium is a rare, benign, congenital lesion. It may represent an ocular manifestation of a phakomatosis (Font et al., 1989; Palmer et al., 1990). The hamartoma grows endophytically and is variably pigmented with abnormal-appearing retinal blood vessels due to contraction of the inner surface of the lesion, leading clinically to distortion of the retina. The lesion occurs

as often in females as in males The patients are mostly adolescents or young adults, with a mean age of 15 years Juxtapapillary lesions are said to develop mostly at older ages. Multiple and bilateral tumours are rarely observed.

Sixty per cent of the patients experience a painless loss of visual acuity. In numerous patients the eyesight is poorer than finger counting Strabismus is present in 18% of the patients, in 10% the lesion is detected fortuitously Most of these tumours are situated round the disk and macula Peripherally localized lesions are rarely encountered The colour is greenish-blue, grey or black Nearly all patients have tortuosity of the retinal vessels in and round the lesion The majority of the patients show some depigmentation and elevation and vitreoretinal alterations or formation of an epiretinal membrane A subretinal or vitreous haemorrhage may develop At fluorescein angiography, an early hypofluorescence, depending on the degree of pigmentation, is seen with tortuosity and abnormal retinal capillaries In the majority of the patients, accumulation of dye and leakage from tumour vessels are observed (Gass, 1973, McLean, 1976, Laqua and Wessing, 1979, Schachat et al , 1984, Font et al , 1989)

1.5.6.5 Retinoblastoma

The retinoblastoma is a malignant congenital tumour arising from the nuclear cell layers of the retina Sixty per cent of the tumours occur sporadically and are unilaterally located Forty per cent is autosomal dominant hereditary and nearly always bilateral (Sanders et al , 1988) The incidence in the Netherlands is 1 15 560 inhabitants (Schipper, 1980) Virtually all tumours are diagnosed before the fifth year of life (Tamboli et al , 1990), the mean age is 17 to 20 months Retinoblastoma is the most frequent malignant intraocular tumour in children (Howard and Ellsworth, 1965, Pendergrass and Davis, 1980, Ellsworth, 1989) Sex and race do not affect the frequency of occurrence (Ellsworth, 1989, Tamboli et al , 1990)

The first sign of retinoblastoma is usually a white pupillary reflex (leukokoria) Strabismus is seen in 20% of the patients Depending on the site in the retina where the tumour develops, either a tumour bulging into the vitreous is observed or a subretinally growing lesion which causes a retinal detachment A retinoblastoma has a creamy-pink colour, often with neovascularization on the tumour surface The tumour stroma is frequently found to contain microaneurysms and teleangiectatic vessels Large afferent vessels to the tumour have been described, as well as exudates on the tumour surface or in the macular area An atrophic pigment ring round the tumour is seen in 10% of the patients In retinoblastomas, a spontaneous hyphaema, superficial haemorrhages and vitreous haemorrhages have been described Necrosis may cause inflammation (Howard and Ellsworth, 1965, Schipper, 1980, Ellsworth, 1989) Clinical glaucoma is reported in 23% of the patients (Yoshizumi et al , 1978) In 84% of the patients there are several tumours per eye, with an average number of five Cell clusters may detach themselves from the tumour and be found floating in the vitreous or as implantation metastases Together with intratumoral calcifications, they are pathognomonic of retinoblastoma (Schipper, 1980, Ellsworth, 1989)

Fluorescein angiography reveals a capillary network permeable to fluorescein Within the depth of the tumour, vessels may be observed (Gass, 1974). Echographically, either a solid tumour is described or, in extensive necrosis, a more cystic lesion A retinoblastoma is markedly high-reflective and produces strong shadowing. Intratumoral

calcifications and vascularity may be observed. A choroidal excavation is not described (Shields et al., 1976a, Chang et al , 1978; Ossoinig, 1974; Ellsworth, 1989). Kerman and Fishman (1987) described mushroom-shaped retinoblastomas. Calcifications may also be seen in the CT scan (Char et al., 1984; Haik et al., 1987a; Mafee et al., 1989). With MRI the tumour can be demonstrated and differentiated well; a hyperdense lesion is described in T_1 and a hypodense lesion in T_2 weighed images (Mafee et al., 1989). Of the ^{32}P uptake test, pathological results are described (Ellsworth, 1989)

Ingrowth into the choroid is practically always present. Expansion via the optic nerve to the meninges is possible and carries a poor prognosis. Metastasization is to the brain and bone marrow, not to the lungs (Schipper, 1980, MacKay et al., 1984; Ellsworth, 1989, Kopelman et al., 1987) The five-year survival rate is 91% (Tamboli et al., 1990). A retinoblastoma may be accompanied by osteosarcomas elsewhere in the body (Sanders et al., 1988)

The treatment of the retinoblastoma is irradiation, either external or by brachytherapy, which may or may not be combined with chemotherapy. Enucleation is indicated in a limited number of cases About 1% of the tumours show spontaneous regression (Schipper, 1980, Ellsworth, 1989).

1.5.6.6 Osteoma

The osteoma is a benign tumour of the choroid which histopathologically shows bone formation The pathogenesis is not completely known. There are indications that the tumour arises from an embryonal tumour remnant and is primarily congenital. Bilateral tumours may occur familially Osteoma-like lesions may also develop due to secondary calcification of haemangiomas, inflammatory lesions, injuries and Harada's disease (Cunha, 1984; Gass, 1979/1987, Shields et al , 1988; Noble, 1990). The tumour is encountered with equal frequency in both eyes Virtually all the patients are females of about 20 years of age (Gass, 1979; Shields, 1983) The osteoma has also been described in older patients, however (Wiesner et al., 1987; Menchini et al., 1990). Hormonal factors may play a part in the growth of the lesions (McLeod, 1988, Noble, 1990).

Symptoms are blurred vision, metamorphopsia and paracentral scotomas. Most patients have a good visual acuity (Gass, 1979).

Clinically, an osteoma is a sharply delimited, sometimes lobulated lesion with a scalloped or geographic border. The size at the base ranges from 1.5 to 15 disk diameters and the prominence from 0 5 to 2 mm Osteomas are typically solitary with a para-papillary localization; they may surround the optic nerve head completely. Extension to the macular area is nearly always present. The colour depends on the degree of thinning and depigmentation of the pigment epithelium If the epithelium is affected only slightly, the colour is orange-red Mostly, however, depigmentation of the overlying pigment epithlium develops and then the tumour has a yellowish-white appearance often with orange pigment on the surface. Bundles of vascular branches across the lesion have been described which resemble those of choroidal neovascularizations. A retinal detachment is frequently encountered Cystoid oedema or degeneration of the retina is not observed. Sometimes, drusen or a haemorrhagic macular detachment are described (Gass, 1979).

At fluorescein angiography, if the pigment epithelium is affected only little, a normal or only slightly masking of the choroidal fluorescence is observed. However, in yellowish-white tumours, there is hyperfluorescence due to prompt perfusion of the

capillary network. In late phases the fluorescence fades. A spotty staining sometimes occurs. Choroidal neovascularization, if present, causes early leakage. On the tumour surface hyperfluorescent drusen may be observed. The retinal circulation is normal (Gass et al., 1978; Gass, 1979). Echographically, a highly reflective, irregular tumour with a marked orbital shadow is described (Gass, 1979; Ossoinig and Harrie, 1983; Shields et al., 1988; Cennamo et al., 1990).

At roentgen examination, CT scanning of the orbit and MRI, the calcified tumour may be visualized (Shields et al., 1988; DePotter et al., 1991).

The ^{32}P uptake test gives a pathological result (Coston and Wilkinson, 1978; Gass, 1979).

Spontaneous decalcification of the lesions is possible (Trimble et al., 1988). Sites of leakage of exudates may, if desired, be treated with laser photocoagulation (Gass, 1979; Rose et al., 1991).

Osteomas owing to their colour and the occasionally multifocal appearance may resemble metastases, but they are more sharply delimited from the environment (Gass, 1979; Arné and Mathis, 1986; Menchini et al., 1990).

1.5.6.7 Melanocytoma and other melanocytic uveal tumours

Melanocytomas (magnocellular naevi) are benign tumours. They may develop wherever in the eye there are melanocytes present, inter alia in the iris, the ciliary body and the choroid. The most frequent localization is on or immediately adjacent to the optic nerve head (Reidy et al., 1985). Melanocytomas of the uvea are rare and difficult to distinguish from other pigmented naevi. Sometimes they are mistaken for a melanoma (Zimmerman, 1965; Howard and Forrest, 1967).

Unlike melanomas, melanocytomas are reported with a high frequency in ethnic groups with hyperpigmentation of ocular structures such as Negroes. Mostly they are discovered at routine examinations of middle-aged people, without a distinct sex predilection. Characteristically they are unilaterally located, but sometimes bilaterally (Frangieh et al., 1985; Reidy et al., 1985).

Melanocytomas are asymptomatic unless the lesion is large and/or shows necrosis. However, perimetry in the majority of the cases reveals an enlarged blind spot (Reidy et al., 1985). Eckhardt and Hutz (1990) describe a large absolute scotoma. Sometimes there is an afferent pupillary defect in the affected eye, probably due to compression of the nerve fibre layer by the tumour. The tumour is ink-black, flat and mostly localized excentrically on the optic nerve head. The margins of the tumour frequently show a fuzzy aspect due to infiltration into the surrounding nerve fibre layer, but they may also be sharp. Growth is usually absent (Joffe et al., 1979; Reidy et al., 1985). If progressive increase of the tumour size occurs, it may be mistaken for a melanoma (Mansour et al., 1989).

At fluorescein angiography, hypofluorescence is observed, probably brought about by the pigmentation of the tumour. No pathognomonic image exists (Reidy et al., 1985). Echographically, a solid tumour with a smooth surface and about 2 mm prominence which was highly reflective has once been described (Lauritzen et al., 1990).

The management of this benign tumour is observation. Malignant degeneration has been described (Reidy et al., 1985).

Melanocytomas of the iris may undergo malignant transformation. Pigmentation of

the angle of the anterior chamber may lead to a secondary glaucoma (Cialdini et al., 1989). At fluorescein angiography, no staining of the lesion is observed (Shields et al., 1977; Hodes et al., 1979, Cialdini et al., 1989).

Melanocytomas of the ciliary body show no preference for any particular quadrant and, although benign, they may infiltrate adjacent tissues. Fluorescein angiography, echography and the ^{32}P uptake test do not contribute to the differential diagnosis. Shields et al. (1980) described a melanocytoma of the ciliary body which showed growth but caused no complaints about visual acuity. At echography, a low- to mid-reflective tumour was observed which was compatible with the diagnosis of melanoma. The ^{32}P uptake test gave a pathological result.

The literature contains reports of a few cases of bilateral diffuse benign melanocytomas of the uvea in association with a systemic malignancy. Such lesions may be mistaken for intraocular metastases (Barr et al , 1982, Mullaney et al., 1984; De Wolff-Rouendaal, 1985, Arné and Mathis, 1986). In all probability, a syndrome is concerned here in which the uvea shows a reaction to the malignancy elsewhere in the body or to the same 'oncogenous' stimulus which causes that malignancy (Barr et al., 1982). The patients' ages range from 57 to 78 years. In most patients there is loss of visual acuity and bilateral diffuse darkly pigmented lesions are described. A nodular shape is also possible, however No lesion has a prominence of over 3 mm. A serous retinal detachment and cataract occur very frequently Dilatation of episcleral vessels is described regularly and glaucoma may also develop. At fluorescein angiography in the arteriovenous phase, multiple irregular areas of hyperfluorescence are observed which correspond to small orange spots on the tumour surface. Echography reveals a thickening of the uvea or a highly reflective nodular tumour with a choroidal excavation. Histopathologically, a diffuse flat infiltration of the uvea is described with polygonal and spindle-shaped naevus cells and intrascleral spread Sometimes, atypical cells are encountered. As a rule there is focal necrosis Most patients die shortly after the ophthalmological diagnosis, probably due to the systemic malignancy elsewhere in the body. This malignancy may be of various types, such as a carcinoma of the lung, ovary, pancreas, colon, uterus or gall bladder (Machemer et al., 1966, Curtin, 1974; Font, 1976; Ryll et al., 1980, Barr et al., 1982; Mullaney et al., 1984, De Wolff-Rouendaal, 1985; Gass et al , 1990).

1.5.7 Inflammatory disorders

On the one hand, uveal metastases may be associated with inflammatory phenomena, especially if the metastasis is localized in the iris (Duke and Kennedy, 1958; Ferry, 1967; Reese, 1976; Stephens and Shields, 1979) Ferry and Font (1975) described iridocyclitis in 40% of the patients with metastases in the anterior segment. The inflammation may be so pronounced that endophthalmitis develops (Levine and Williamson, 1970; de Bustros et al , 1985).

On the other hand, various inflammatory disorders may resemble uveal metastases (Shields, 1983, Arné and Mathis, 1986, Wharam and Schachat, 1989). It is especially in the older literature that inflammations are frequently mentioned in this connection. Sattler (1926), for instance, lists tuberculosis, foci of choroiditis and septic metastases in his differential diagnostics of choroidal metastases. Michelson et al (1979) described a patient

with a possible focus of toxoplasmosis in the choroid and a patient with a subretinal granuloma in rubellar retinopathy as pseudometastatic lesions. Endophthalmitis in rare cases may resemble an iridal metastasis, and create a hypopyon similar to the pseudo-hypopyon that may be formed by metastatic cells (Shields, 1983). If a uveitis fails to respond to treatment, the possibility of intraocular metastases should be considered, at any rate if weight loss or coughing is also involved (Scholz et al., 1983).

1.5.7.1 Uveitis

Choroiditis with an exudative retinal detachment is part of the differential diagnosis of choroidal metastases (Daicker, 1981; Shields, 1983). Granular lesions in particular may show distinct similarities to an intraocular tumour (Keller, 1962). If no primary tumour or metastases elsewhere are known, the differential diagnosis may be difficult (Takahashi et al., 1984).

In case of suspicion of tuberculosis or sarcoidosis, an iridal metastasis may not be diagnosed correctly (Bonamour and Bonnet, 1956; Abramowicz, 1969; Talegaonkar, 1969; Scholz et al., 1983; Spencer, 1986).

Tuberculosis of the choroid is rare nowadays. Clinically, its distinction from tumours such as metastases or malignant melanomas may be difficult. Ophthalmoscopy, fluorescein angiography, echography and ^{32}P uptake testing frequently leave uncertainty (Guthoff, 1988). Jaensch (1951) was of the opinion that the ophthalmoscopic image of a choroidal metastasis resembled that of disseminated tuberculosis of the choroid. Poujol and le Roy (1983) described a choroidal tuberculoma which echographically showed similarities to a melanoma with choroidal excavation.

Granulomatous ***sarcoidosis*** of the choroid is rare. At ophthalmoscopy, a non-pigmented yellowish subretinal mass is seen with an overlying retinal detachment which causes decrease of the visual acuity. The intraocular lesion is usually solitary and may be the first sign of sarcoidosis. However, bilateral and multiple localizations are also described. Especially if the choroidal infiltrates are situated in the macular and paramacular regions, subretinal fluid is present and the visual acuity is decreased, the differential diagnosis of choroidal metastases may be difficult. At perimetry, a scotoma may be found (Wessing, 1968; Michelson et al., 1979; Marcus et al., 1982; Olk et al., 1983; Campo and Aaberg, 1984; Ryckewaert et al., 1988).

At fluorescein angiography in the early phases a block of the choroidal fluorescence is observed. In the arteriovenous phase, a minimal abnormal hyperfluorescence is seen at the site of the lesion followed by hyperfluorescent spots on the surface. In the late phases the choroidal mass beneath the retinal detachment stains intensely and homogeneously. The retinal vasculature is normal (Marcus et al., 1982; Olk et al., 1983). The fluorescein-angiographic image in sarcoidosis may show similarities to that of choroidal metastases. The echographic finding of a homogeneous mid-reflective tumour is also described both in metastases and in sarcoidosis (Campo and Aaberg, 1984). Olk et al. (1983) reported that a lesion in sarcoidosis may be visualized by means of CT scanning with image intensifying after administration of contrast medium.

Treatment consists of systemic administration of corticosteroids (Marcus et al., 1982; Campo and Aaberg, 1984).

In *syphilis*, also, a lesion suggestive of an intraocular tumour is possible (Tamesis et al., 1990).

In *cryptococcosis* discrete yellow choroidal or chorioretinal lesions can be observed (Clarkson and Green, 1989; Holland, 1989).

The *juvenile xanthogranuloma*, a chronic granulomatous inflammatory reaction of unknown aetiology, is a rare benign intraocular tumour. It may be accompanied by yellow skin lesions. Ophthalmologically, an involvement of the iris and the ciliary body occurs most frequently. The condition is distributed evenly over both sexes and nearly all patients are young children, most of them younger than one year (Sanders, 1962; Zimmerman, 1965a; Treacy et al., 1990). However, juvenile xanthogranuloma has been described in adults between 26 and 38 years (Zimmerman, 1965; Smith et al., 1969; Brenkman et al., 1977; Bruner et al., 1982). The lesions develop virtually always unilaterally (Zimmerman, 1965; Hadden, 1975). A localization of juvenile xanthogranuloma in the iris may lead to an opacification of the cornea and cause complaints such as photophobia and epiphora. In involvement of the ciliary body a red eye and signs of inflammation have been described (Dhermy, 1979). Minckler et al., (1978) described a pathological result of the ^{32}P uptake test.

In young children the possibility of juvenile xanthogranuloma has to be considered in the presence of an asymptomatic diffuse or localized iridal tumour, unilateral glaucoma, spontaneous hyphaema, a red eye with signs of uveitis or iridal heterochromia (Sanders, 1962; Zimmerman, 1965).

Treatment consists in corticosteroids or radiotherapy (Treacy et al., 1990).

Harada's syndrome involves an inflammation of inter alia the uvea, retina and meninges. It is part of the Vogt-Koyanagi-Harada syndrome in which lesions of ears and skin are also described. In Harada's syndrome, uveitis with exudative retinal detachment is predominant. The condition may have a viral aetiology and is probably a cell-mediated autoimmune process (Ohno et al., 1977; Lubin et al., 1981).

Harada's syndrome usually develops between the ages of 20 and 40 years, occurs as frequently in males as in females and is observed particularly in patients with marked pigmentation. Inflammation of the anterior segment and vitreous opacities are encountered virtually always and cataract and glaucoma are described frequently. In 96% of the cases both eyes are involved (Ohno et al., 1977; Perry and Font, 1977).

The principal complaint is deterioration of the visual acuity, followed by headache, tinnitus, metamorphopsia, photophobia, vertigo and depigmentations of the skin (Shimizu, 1973).

Ophthalmoscopically, the condition is characterized by diffuse bilateral granulomatous uveitis with involvement of the choriocapillaris. Focal areas of chorioretinal scarring develop with a distinct reaction of the retinal pigment epithelium. Depigmentation of the retinal pigment epithelium and the choroid causes the ophthalmoscopical image of a 'sunset glow fundus'. A retinal detachment develops from the macular area and extends towards the periphery. Many bullous detachments may occur. There is hyperaemia of the optic nerve head with subretinal fluid in the peripapillary space. Progressive signs of inflammation of the vitreous humour may develop (Lubin et al.,

1981). The picture may be deceptive, owing especially to choroidal detachment (Arné and Mathis, 1986). In addition, subretinal neovascularization is possible (Ober et al., 1983). The ophthalmoscopic image may greatly resemble that of choroidal metastases (Gass, 1987; Wharam and Schachat, 1989).

At fluorescein angiography in the arteriovenous phase, many discrete fluorescent dots are seen at the level of the retinal pigment epithelium. These dots increase in number but their size does not change. Dye accumulates beneath the pigment epithelium. In the venous phases, a diffuse background fluorescence develops. There is an increased permeability of the optic disk capillaries. The retinal vessels, on the other hand, appear normal (Shimizu, 1973; Lubin et al., 1981).

The condition responds well to administration of corticosteroids (Lubin et al., 1981).

Acute multifocal ischaemic choroidopathy (AMIC), also called acute multifocal posterior placoid pigment epitheliopathy (AMPPPE), is a primary affection of the choroid with obstruction of precapillary choroidal arterioles which is probably caused by a vasculitis (Deutman, 1983). Its aetiology is not known but may be viral (Deutman et al., 1972; Ryan and Maumenee, 1972). The condition should be included in the differential diagnostics of choroidal metastases (Daicker, 1981). AMIC develops at an average age of 31 years, independently of sex or race and often bilaterally. The symptoms consist of acute painless deterioration of visual acuity without photopsia. The eyesight ranges from finger counting to 20/20 and in practically all cases returns to normal after 2 to 12 weeks, with or without treatment with corticosteroids. Frequently, cells in the vitreous humour or iritis are observed (Annesley et al., 1973; Tessler and Schlaegel, 1989; Williams and Mieler, 1989).

At ophthalmoscopy, yellowish-white placoid lesions, about one disk diameter in size, are observed at the level of the choroid and the pigment epithelium. The macula in particular is affected, but the lesions may extend farther to the periphery and fuse. Sometimes retinal oedema, small retinal haemorrhages, anterior uveitis or diffuse episcleritis develop (Gass, 1968; Annesley et al., 1973; Tessler and Schlaegel, 1989; Williams and Mieler, 1989). At fluorescein angiography in the early phases, hypofluorescent spots are seen similar to the cream-coloured lesions at ophthalmoscopy which in later phases show hyperfluorescence. There is a sharp delimitation between fluorescent and non-fluorescent areas. Filling defects of the choriocapillaris may be demonstrated (Annesley et al., 1973; Deutman and Lion, 1977; Tessler and Schlaegel, 1989).

The EOG and the ERG are abnormal at early stages (Deutman et al., 1972).

1.5.7.2 Retinitis

Patients with a malignancy often have reduced resistance and are more susceptible to infections.

Michelson et al. (1979) described two patients with ***cytomegalovirus retinitis*** in whom the lesions were suspected of being metastases. In contrast to metastases of the choroid, cytomegalovirus retinitis, as its name indicates, involves the retina in particular. Multiple and bilateral yellowish-white areas of retinal necrosis may be present. The lesions have irregular margins and often exhibit retinal haemorrhages.

Fungal retinitis may also resemble a choroidal metastasis, but is usually accompanied by signs of inflammation (Shields, 1983, Arné and Mathis, 1986). Cryptococcosis has already been discussed in the chapter on uveitis (Chapter 1.5 7.1).

1.5.7.3 Posterior scleritis

Posterior scleritis is an uncommon condition. Existing signs of anterior scleritis or a history of collagen and vascular diseases may constitute indications for the diagnosis. The main cause of posterior scleritis is rheumatoid arthritis Posterior scleritis occurs twice as frequently in females as in males This applies in particular if an exudative macular detachment has developed or a circumscribed area of swelling is established. Annular ciliochoroidal effusion and choroidal folds are observed more often in males Posterior scleritis occurs at an average age of 38 years If a circumscribed mass is present, the age is 47 years on average Posterior scleritis occurs bilaterally in 10 to 33% of the cases (Benson, 1988)

The main symptoms are pain, deteriorating eyesight and a red eye and, in severe cases, proptosis and diplopia The patient may also be asymptomatic, however. Most patients have some degree of anterior scleritis Watson (1982) and Benson (1988) in one-quarter of the cases describe cells in the anterior chamber or the vitreous humour due to uveitis, and an increase in the intraocular pressure may also be observed

A local posterior scleritis may present the ophthalmoscopical picture of a choroidal tumour (Chang et al , 1978, Arné and Mathis, 1986, Bonnin, 1986) The similarities may be very pronounced in metastases with intrascleral or even extrascleral spread (Bailliart et al , 1968, Yeo et al , 1983) In posterior scleritis the lesion shows the same orange-red colour as the surrounding normal retinal pigment epithelium and a normal choroidal vascular pattern The swelling is surrounded by concentric choroidal folds or retinal striae Cystoid macular oedema, an exudative macular detachment, a bullous and/or peripheral retinal detachment and an annular choroidal detachment may be encountered (Benson, 1988)

If the scleritis leads to a retinal detachment, a defect in the visual field related to this detachment may be recorded (Harper, 1960) If subretinal fluid is present, this may at fluorescein angiography bring about a mottled choroidal background fluorescence, following which bright multiple pinpoint areas of hyperfluorescence develop that grow larger In later phases leakage of dye is observed The same pattern may also be observed in choroidal metastases However, characteristic features of posterior scleritis are the choroidal folds observed at angiography (Bonnin, 1986, Benson, 1988).

At echography, a flattening of the posterior pole is observed with a diffuse thickening of the posterior coats of the eye and retrobulbar oedema (Benson, 1988) The differentiation from malignant tumours is difficult The scleritis may exhibit pronounced prominence with the same acoustic properties as a melanoma (Chang et al , 1978, Finger et al., 1990) or a highly reflective lesion with an irregular ultrastructure which may be mistaken for a metastasis (Ossoinig and Harrie, 1983, Benson, 1988).

In the CT scan a scleral thickening may be established which grows more pronounced after administration of contrast medium (Benson, 1988). The ^{32}P uptake test may give positive as well as negative results (Chang et al., 1978; Shields, 1978; Benson, 1988).

Thus, posterior scleritis may present a picture like that of a choroidal metastasis

and vice versa. Signs of intraocular inflammation may be useful for the differential diagnosis (Chang et al., 1978; Arné and Mathis, 1986; Bonnin, 1986). Important indications of posterior scleritis are pain, cells in the anterior chamber or vitreous humour, the orange colour, choroidal folds and retinal striae as well as the presence of a retrobulbar oedema at echography indicative of oedema (Benson, 1988).

Treatment consists of systemic or retrobulbar corticosteroids or antiprostaglandins such as aspirin (Benson, 1988).

1.5.8 Intraocular haemorrhages and detachments of the retina, retinal pigment epithelium and choroid

1.5.8.1 Vitreous haemorrhage

A vitreous haemorrhage, whatever its cause, sometimes assumes a globular configuration and may then show the appearance of a melanoma. Ophthalmoscopically, the haemorrhage is mobile and the correct diagnosis can as a rule be made without difficulty (Shields, 1977b).

An organized haemorrhage may show the echographic image of an acoustically dense mass. However, there is no connection of the lesion with the sclera. The reflectivity is very low (Neetens et al., 1984).

1.5.8.2 Retinal detachment, subretinal haemorrhage and retinoschisis

Retinal detachments are predominantly of rhegmatogenous origin. Ophthalmoscopically, they can as a rule be recognized easily by the break in the retina, the folded aspect of the retina and the absence of displacement of subretinal fluid during movements of the head. In intraocular tumours and also in choroidal metastases in which retinal detachments are frequently described, breaks in the retina occur rarely (Albert et al., 1967; Howard, 1968; Shields, 1977b; Pau, 1979; Stephens and Shields, 1979; Arné and Mathis, 1986; Freedman and Folk, 1987). If the subretinal fluid is cloudy, the lesion may be mistaken for an amelanotic tumour (Gass, 1972).

The defect in the visual field in retinal detachment is nearly always relative, has a sloping edge and is reasonably uniform in density. In bullous detachments a sharp edge is possible. The scotoma as a rule shows an extension to the periphery (Harrington, 1956; Reed and Drance, 1972).

At fluorescein angiography, some hypofluorescence is sometimes seen, due to masking of the background fluorescence. As a rule no hyperfluorescence or late staining of the lesion is seen. In retinal detachments of longer standing some hyperfluorescence may be observed due to secondary defects in the retinal pigment epithelium (Gass, 1972; Fishman, 1977).

In bullous retinal detachments, echography shows a highly reflective membrane that is connected with the disk or the ora serrata. The surface is smooth and concave. The subretinal space is acoustically empty except if a haemorrhagic detachment has occurred. If the haemorrhagic detachment was caused by a tumour, this tumour may be difficult to

distinguish from an organizing haemorrhage (Coleman and Jack, 1973; Shields and Tasman, 1977; Chang et al., 1978; Verbeek, 1985).

Electro-oculographically, both a low dark trough and a low ratio are reported in retinal detachment (François et al., 1957; Brink et al., 1989). The retinal detachment can be clearly distinguished from melanomas and metastases, even if these tumours are associated with a similar secondary detachment (Brink et al., 1989/1990).

An organized ***subretinal haemorrhage*** may present as an elevated lesion which, because of its shape, may be mistaken for a haemangioma or neoplasm. At echography in the early phase a low-reflective irregular tumour is observed. With time the lesion becomes more highly reflective. Since in general the haemorrhage does not displace the choroid, no choroidal excavation develops (Chang et al., 1978).

With MRI shorter T_2 relaxation times are observed than in choroidal metastases (Wollensak et al., 1988). The ^{32}P uptake test shows no abnormalities (Shields, 1978).

In ***retinoschisis*** a peripheral splitting of the retina without a break is observed. A schisis constitutes a smooth thin-walled bullous lesion with extensive peripheral cystic degeneration. Bilateral presence has been described. The schisis is most frequently localized peripherally in the inferotemporal quadrant (Shields, 1977b).

A schisis is regularly mistaken for a melanoma or a slightly pigmented tumour, especially if the condition is accompanied by retinal cysts, intraretinal haemorrhage and proliferations of the pigment epithelium, or if the lesion contains cloudy fluid (Gass, 1972; Arné and Mathis, 1986).

At fluorescein angiography, some hypofluorescence is sometimes observed due to masking of the choroidal staining. If a break is present in the outermost layer of the retina with a retinal detachment of long standing, hyperfluorescence may occur secondarily to loss of pigment from the pigment epithelium. As a rule, however, fluorescein angiography shows no hyperfluorescence or late staining (Gass, 1972; Fishman, 1977).

At echography, a linear echo is obtained extending from the ora serrata. Unless a secondary retinal detachment occurs, it rarely reaches the optic nerve. The space behind this echo is acoustically clear (Shields and Tasman, 1977).

1.5.8.3 Detachment of the retinal pigment epithelium, haemorrhage below the pigment epithelium and age-related disciform macular degeneration

A ***detachment of the retinal pigment epithelium*** varies in size from a minimal lesion to a detachment that extends over nearly the entire posterior pole. Only large lesions cause diagnostic problems and then have to be included in the differential diagnosis of choroidal metastases (Shields, 1977b; Michelson et al., 1979; Arné and Mathis, 1986). Characteristic features of detachments of the pigment epithelium are sharply delimited round or kidney-shaped elevations with a smooth surface. The colour varies from orange to yellow or white, depending on the loss of pigment from the pigment epithelium. On the surface, pigment clumps may be present. Large detachments in general occur in older patients with intraocular drusen which can then be observed in the other eye as well. Gass (1972),

Shields (1977b) and Arné and Mathis (1986) described the rarely observed detachment of the pigment epithelium as a complication after choroiditis due to a suspected histoplasmosis.

At fluorescein angiography, a pathognomonic image is observed. In the early phases, the dye diffuses beneath the detached pigment epithelium and stains the underlying fluid. This causes an area of hyperfluorescence which corresponds exactly to the detachment. This staining persists long. Sometimes, there is a diffuse leakage of dye into the subretinal space through a rupture in Bruch's membrane (Gass, 1972; Fishman, 1977).

A ***central serous chorioretinopathy*** (retinitis or retinopathia centralis serosa) may cause blurred vision and metamorphopsia such as may also occur in choroidal metastases. Usually the visual acuity is not severely affected. Ophthalmoscopically, only serous fluid below the fovea is observed without signs of a choroidal tumour. Rarely, a large bullous retinal detachment is described. This may be accompanied by a creamy-white detachment of the retinal pigment epithelium. Its appearance may show clear similarities to that of a metastasis. Neovascularization may occur directly below or in the immediate vicinity of the central fovea. These abnormal vessels may pierce Bruch's membrane and pass into the subretinal space. At fluorescein angiography one or several small foci of leakage of fluorescein may be observed, probably due to increased capillary permeability and/or a defect in Bruch's membrane. EOG is normal (Deutman, 1971; Gass, 1973a; Shields, 1983; Abramson, 1984; Watzke, 1989).

Vitelliform dystrophy of the fovea (Best's disease) is an autosomal dominant inherited usually bilateral macular condition affecting the retinal pigment epithelium. Predominantly a gradual decrease of visual acuity occurs. Classically an egg-yellow round slightly elevated lesion surrounded by a dark border is described. Multiple structures in the posterior pole can occasionally be observed. At fluorescein angiography hypofluorescence at the site of the lesion is observed. In case of atrophy of the pigment epithelium areas of hyperfluorescence occur. EOG is almost always subnormal (Deutman, 1971/1989).

A ***haemorrhage below the pigment epithelium*** in most cases presents with a sudden loss of visual acuity (Reese, 1961). A haemorrhagic detachment of the pigment epithelium and retina may be brought about by a rupture of neovascular structures in the subpigment epithelial space, such as occurs in patients with age-related macular degeneration or early degenerative alterations of the choroid (Gass, 1972). In the posterior pole, a generally unilateral, dark round thickening is seen which may resemble a melanoma. After about two weeks, a red halo of subretinal blood develops at the margin of the lesion (Reese, 1961; Gass, 1972). At fluorescein angiography, a hypofluorescence is observed, the fluorescein being absorbed by the extravascular haemoglobin. As a rule, absorption takes place after 10 days to 2 weeks (Fishman, 1977; Shields, 1977b). The lesion may be difficult to distinguish from a tumour (Silva and Brockhurst, 1976; Shields, 1977b; Arné and Mathis, 1986).

Age-related macular degeneration (Kuhnt Junius) is the principal cause of blindness in the Western world and should be included in the differential diagnosis of choroidal metastases (Daicker, 1981; Michelson et al., 1987). About its aetiology only little is known. The patients are mostly over 50 years of age and the disorder frequently

occurs bilaterally. Most patients exhibit only drusen in the fundus. Decrease of visual acuity is caused by subretinal neovascularizations and the resulting serous and haemorrhagic detachment of pigment epithelium and retina at the site of the macula. A choroidal neovascularization membrane presents the image of a round to oval grey-green lesion. The ultimately formed fibrovascular disciform scar may be mistaken for a tumour (Gass, 1987; Bressler et al., 1988).

At fluorescein angiography a hypofluorescence at the site of the lesion is observed in all phases as well as an intense late hyperfluorescence that corresponds to the neovascularization membrane beneath the retinal pigment epithelium and retina (Shields, 1983).

If collagenous tissue has formed between the retina and the choroid, this homogeneous mid-reflective tissue may echographically resemble a melanoma (Bigar, 1988). A choroidal excavation may be present (Shields, 1983). Guthoff (1988) described this pseudotumour as a lesion with an irregular infrastructure, with areas of both low and high reflectivity. The prominence rarely exceeds 3 mm.

The ^{32}P uptake test gives a normal result (Van Dijk, 1976; Shields, 1983a).

1.5.8.4 Choroidal detachment and choroidal haemorrhages

A ***choroidal detachment*** frequently occurs after an injury or intraocular surgery with low intraocular pressures, but it may also be associated with uveitis or a retinal detachment or as part of a uveal effusion (Fishman, 1977; Shields, 1977b; Chang et al., 1978; Arné and Mathis, 1986). A choroidal detachment has to be distinguished from choroidal metastases (Michelson et al., 1979).

At ophthalmoscopy, a smooth round or lobulated brown mass is seen at the periphery which may present as a tumour. As a rule it does not extend farther back than a few millimeters behind the equator, and the detachment is frequently annular. Differentiation from a tumour is more difficult in a haemorrhagic detachment. An overlying detachment of the pigment epithelium may make the lesion appear to be solid (Gass, 1972; Fishman, 1977; Kelley, 1977; Shields, 1977b; Arné and Mathis, 1986).

At fluorescein angiography a shadow at the site of the lesion may be observed. Neither in serous nor in haemorrhagic detachment is hyperfluorescence, abnormal permeable vessels or staining observed (Gass, 1972; Fishman, 1977; Kelley, 1977).

Echography as a rule shows a convex elevation of the retina and choroid delimited anteriorly by the ciliary body and posteriorly by the site of the vortex ampullae. The suprachoroidal space is acoustically empty or, in case of a haemorrhagic detachment, shows diffuse echoes (Shields and Tasman, 1977; Chang et al., 1978).

MRI in a serous detachment shows a hyperintensity in T_1 weighted images and a moderately hyperdense image in T_2 weighted images (Mafee et al., 1987). The ^{32}P uptake test is normal (Shields, 1978). A serous detachment of the choroid is diaphanous, a haemorrhagic detachment gives a shadow (Gass, 1972; Fishman, 1977; Arné and Mathis, 1986).

A choroidal detachment disappears spontaneously, although this may take several months (Kelley, 1977).

If an exudative detachment of the choroid and ciliary body occurs without a clear cause, this is called an ***idiopathic ciliochoroidal effusion***. This condition frequently

develops bilaterally and in healthy subjects, mostly in middle-aged males. The aetiology is probably an anomaly of the sclera with hypotrophy of the vorticose veins impairing outflow from the uvea (Schepens and Brockhurst, 1963; Gass and Jallow, 1982; Gass, 1983).

The uveal effusion syndrome, which may include increased albumin in the cerebrospinal fluid and a raised intracranial pressure, has to be differentiated from choroidal metastases (Schepens and Brockhurst, 1963; Kreiger et al., 1969; Michelson et al., 1979; Gass and Jallow, 1982; Wharam and Schachat, 1989).

Frequently, gradual loss of the superior field of vision is noticed, sometimes blurred eyesight and metamorphopsia. Dilated episcleral vessels and cells in the vitreous humour are observed often. The ocular pressure is normal (Gass and Jallow, 1982).

Clinically, a partial or circular flat or bullous choroidal detachment with an exudative retinal detachment is observed. The serous fluid is displaced by movements of the head. Frequently, a separate clumping of brown pigment is seen in the retinal pigment epithelium and on the surface of the detachment orange pigment may be present. Oedema of the optic nerve occurs in 10 to 20% of the patients (Schepens and Brockhurst, 1963; Shields, 1977b, Gass and Jallow, 1982)

At fluorescence angiography, a retarded perfusion of the choroid is often described The above-mentioned depigmentation of the pigment epithelium and leopardskin-like clumping of pigment may be demonstrated (Gass and Jallow, 1982).

Owing to the serous nature of the detachment, echographic differentiation from a choroidal tumour is possible. A thickening of the choroid is observed, or a smooth circumferential convex elevation of the choroid and ciliary body (Coleman and Jack, 1973; Gass and Jallow, 1982, Guthoff, 1988)

The ERG is subnormal (Gass and Jallow, 1982), the ^{32}P uptake test gives a normal result (Shields, 1983a).

In localized ***suprachoroidal haemorrhages***, ophthalmoscopy reveals a darkly pigmented lesion in the posterior pole, localized in the suprachoroidal space. No vitreous haemorrhage or retinal detachment occurs, choroidal vessels run a normal course and the intraocular pressure is normal. Choroidal folds are observed, however. The condition is encountered rarely, mostly shortly after intraocular surgery and especially in myopic patients, it may present as a melanoma

Fluorescein angiography reveals a pattern that resembles that of the surrounding choroid with relative hypofluorescence at the margins and choroidal folds. There is no block of the choroidal fluorescence or double circulation (Hoffman et al., 1984, Augsburger et al., 1990a). At echography an acoustically very low-reflective lesion is observed without choroidal excavation, vascularity or orbital shadow (Neetens et al., 1984). At echography, the base of the lesion ranges from 7 to 14 millimeters and the prominence from 1.5 to 5.5 millimeter (Augsburger et al., 1990a).

An ***intrachoroidal haemorrhage*** of recent date gives a hypodense image in both T_1 and T_2 weighted images. A chronic haemorrhage is hyperdense in T_1 and T_2 weighted images (Mafee et al , 1987).

The lesion disappears spontaneously after one to two months (Augsburger et al., 1990a).

A ***subfoveal haemorrhage*** due to thrombocytopenic purpura may be mistaken for a choroidal metastasis (Michelson et al., 1989).

1.5.9 Miscellaneous disorders and phenomena

Cysts and *pseudocysts* of the iris and ciliary body may be mistaken for an intraocular malignant tumour (Reese, 1950; Yanoff and Zimmerman, 1965; Duke-Elder and Perkins, 1966b; Shields et al., 1984).

Shields (1983) mentions a ***foreign body*** in the differential diagnosis of iridal metastases. Lipper et al., (1981) described a patient with a painful eye and a large yellow choroidal mass with exudates and a flat retinal detachment. At fluorescein angiography, an early staining was observed followed by a distinct hyperfluorescence and leakage into the retina. Echography showed a low-reflective tumour. The eye was enucleated on the diagnosis of malignant melanoma. At histopathological examination it proved to be a chorioretinal inflammatory process due to a foreign body. Ferry (1964) also described such a pseudomelanoma.

A ***toxic retinopathy*** may be the consequence of protracted treatment with, for instance, thioridazine hydrochloride (Mellaril^{R}) and manifests itself as depigmented zones (Meredith et al., 1978). These more or less characteristically alternating zones of pigmentation and thinning have to be differentiated from choroidal metastases (Arné and Mathis, 1986).

Simpson (1961) described a retinal vascular occlusive image characterized by acute impairment of the central and paracentral visual acuity with ***retinal oedema*** as a differential diagnosis from choroidal metastases.

A ***chorioretinal coloboma*** is a predominantly congenital defect in the eye and is rarely mistaken for an intraocular tumour (Pagon, 1981; Brown, 1989).

A ***vorticose vein*** in an area of a delimited choroidal detachment echographically may show a low-reflective tumour, with the rapid movements of the spikes being mistaken for vascularity (Till and Hauf, 1981). Buettner (1990) described a patient in whom a varix of a vorticose vein was taken for a melanoma.

Michelson et al. (1987) in their article on pseudometastases refer to a woman with breast cancer in whom ***myelinated nerve fibres*** were mistaken for a choroidal metastasis.

Finally, according to Shields (1983), an ***ectopic lacrimal gland*** should be included in the differential diagnosis of iridal metastases. Such an aberrant lacrimal gland may present as a cystic lesion of the iris and the ciliary body (Hunter, 1960) or as a solid mass (Christensen and Anderson, 1952).

1.5.10 Conclusions

Many examination techniques are used for the differential diagnosis of uveal metastases. Although the differentiation of a metastasis with a more or less typical appearance from, for instance, a characteristic melanoma as a rule causes no problems, it is the atypical lesions that render the diagnosis difficult. With no single examination technique is the correct diagnosis to be made with 100% certainty and histopathologically, also, the diagnosis can sometimes only be made with difficulty.

Since uveal metastases may be detected before a primary tumour elsewhere in the body is known, assumed absence of a systemic malignancy does not exclude the diagnosis of intraocular metastasis. Furthermore multiple and bilateral localizations are not limited to metastases. Complications such as retinal detachment and inflammatory reactions may further impede the differentiation.

Metastases of lung tumours, in particular, may cause diagnostic problems.

The principal lesions from which ***choroidal metastases*** have to be differentiated are (amelanotic) malignant melanoma, naevus and haemangioma. The various lesions are surveyed in Table 1.5.10.1.

The melanoma, the most often diagnosed intraocular tumour, can often be differentiated from a metastasis on the basis of its unilateral and solitary occurrence, the pigmentation and the echographic characteristics. The differentiation of small and amelanotic melanomas from, especially, choroidal metastases of lung tumours may be extremely difficult.

Naevi of the choroid are flat and usually darkly pigmented and show no growth. At fluorescein angiography, no leakage is observed and electro-oculographically, also, naevi can be distinguished from choroidal metastases.

Haemangiomas of the choroid are unilateral and solitary, with an orange-red colour, with in most cases a typically thickened and cystoid retina and a characteristic fluorescein-angiographic pattern. At echography and CT scanning, calcifications may be observed.

Clinically, intraocular structures are only sporadically involved in lympho-proliferative diseases. Uveal infiltration in leukaemia is mostly diffuse, with presence of intraocular haemorrhages and cottonwool spots. The reticulum cell sarcoma, which often occurs bilaterally, is characterized in general by corneal precipitates and cells in the vitreous humour. A nodular lesion in benign reactive lymphoid hyperplasia of the uvea may give rise to diagnostic problems.

Posterior localized tumours such as leiomyomas, adenomas and adenocarcinomas of the retinal pigment epithelium are extremely rare. Hypertrophy and hyperplasia of the pigment epithelium can as a rule be differentiated from metastases owing to the marked pigmentation. Combined hamartomas of the retina and retinal pigment epithelium develop at younger ages than choroidal metastases and can also be differentiated adequately because of the retinal tortuosity and the distorted retina. Osteomas occur predominantly in young adults. Calcifications give a characteristic image at echography and CT scanning. Unlike metastases, retinoblastomas develop at very early ages. Melanocytomas of the uvea are heavily pigmented and occur only exceptionally. Bilateral diffuse benign melanocytomas show similarities to choroidal metastases.

Table 1.5.10.1 Differential diagnosis of choroidal metastases

- Malignant melanoma
- Naevus
- Haemangioma
- Lymphoproliferative diseases
  - Leukaemia
  - Lymphoma (in particular reticulum cell sarcoma)
  - Benign reactive lymphoid hyperplasia
- Other intraocular tumours and related tumour-like lesions
  - Leiomyoma
  - Tumours and tumour-like lesions of the retinal pigment epithelium
    - Hypertrophic lesions of the retinal pigment epithelium
    - Hyperplasia of the retinal pigment epithelium
    - Hypoplasia of the retinal pigment epithelium
    - Adenocarcinoma of the retinal pigment epithelium
  - Combined hamartoma of the retina and retinal pigment epithelium
  - Retinoblastoma
  - Osteoma
  - Melanocytoma
- Inflammatory disorders
  - Endophthalmitis
  - Uveitis
    - Tuberculosis
    - Sarcoidosis
    - Syphilis
    - Cryptococcosis
    - Toxoplasmosis
    - Harada's syndrome
    - Acute multifocal ischaemic choroidopathy (AMIC)
  - Retinitis
    - Cytomegalovirus retinitis
    - Fungal retinitis (cryptococcosis)
    - Subretinal granuloma in rubella retinopathy
  - Posterior scleritis
- Intraocular haemorrhages and detachments of the retina, retinal pigment epithelium and choroid
  - Vitreous haemorrhages
  - Serous and haemorrhagic retinal detachments
  - Retinoschisis
  - Serous and haemorrhagic detachments of the retinal pigment epithelium
  - Age-related macular degeneration (Kuhnt Junius)
  - Central serous chorioretinopathy
  - Vitelliform foveal dystrophy
  - Serous and haemorrhagic detachment of the choroid
  - Uveal effusion syndrome

Table 1.5.10.1 (continued)

Reactive fibrosis due to a foreign body
Toxic retinopathy
Retinal oedema
Chorioretinal coloboma
Vortex vein
Myelinated nerve fibres

In inflammatory disorders the signs of inflammation in general point in the right direction, but these signs may also be observed in metastases. If inflammatory signs are less pronounced and a granulomatous lesion is observed, which occurs, for instance, in tuberculosis or sarcoidosis, the differential diagnosis may be difficult. Harada's syndrome and acute multifocal ischaemic choroidopathy may ophthalmoscopically resemble choroidal metastases as well as certain forms of retinitis. The diagnosis of posterior scleritis is often clear owing to the pain and the redness of the eye. If there are only few symptoms in the presence of an intraocular swelling, the differentiation from metastases may be difficult. However, characteristic features of posterior scleritis are the choroidal folds and the retrobulbar oedema that can be demonstrated by means of echography.

Differentiation of metastases from serous and haemorrhagic detachments of the retina, retinal pigment epithelium or choroid as a rule is not difficult with echography. An intraocular haemorrhage may resemble a tumour, but can nevertheless be distinguished adequately from it.

The other lesions, such as reactive fibrosis in foreign body, toxic retinopathy, oedema in retinal vascular occlusion, dilated vorticose veins and myelinated nerve fibres are only mistaken for choroidal metastases in highly exceptional cases.

Metastases of the ciliary body occur extremely rarely. Since only a few patients have been described, establishing an adequate differential diagnosis for these lesions is difficult. The principal tumour in this connection is the malignant melanoma, which as a rule can be differentiated well owing to its colour, shape and echographic features. Patients with a leiomyoma or a medulloendothelioma in the ciliary body are far younger than patients with metastases. Also, the leiomyoma shows a characteristic image at diaphanoscopy. Naevi, reactive fibrosis and the other tumours in the ciliary body are particularly rare (Table 1.5.10.2).

Iridal metastases occur infrequently and have to be differentiated from amelanotic melanoma, leiomyoma and a number of inflammatory disorders (Table 1.5.10.3).

Melanomas of the iris are solitary and at fluorescein angiography show leakage of dye at the pupillary margin. Since these lesions are treated with local excision, a possible fault in the diagnosis is mostly rapidly cleared up.

Naevi of the iris in general have been known for years to the patient as well as his environment, they show no growth and are mostly flat and pigmented.

If in leukaemia infiltration of the iris occurs, a diffuse image is seen. As a rule, signs and symptoms of inflammation are present.

The other tumours in the iris are extremely rare.

Iridal metastases are frequently accompanied by iridocyclitis. For this reason, inflammatory disorders such as tuberculosis and sarcoidosis have to be included in the differential diagnosis. The juvenile xanthogranuloma is characterized by its onset at a very early age.

A reactive fibrosis round a foreign body may sometimes be mistaken for a tumour.

Table 1.5.10.2 Differential diagnosis of ciliary metastases

Malignant melanoma
Naevus
Lymphoproliferative diseases
Leukaemia
Lymphoma
Benign reactive lymphoid hyperplasia
Other tumours
Haemangioma
Leiomyoma
Medulloendothelioma
Adenoma of the non-pigmented ciliary epithelium
Adenocarcinoma of the non-pigmented ciliary epithelium
Juvenile xanthogranuloma
Cysts and pseudocysts

Table 1.5.10.3 Differential diagnosis of iridal metastases

Malignant melanoma
Naevus
Lymphoproliferative diseases
Leukaemia
Lymphoma (in particular reticulum cell sarcoma)
Benign reactive lymphoid hyperplasia
Other tumours
Leiomyoma
Adenoma of the pigmented epithelium of the iris
Adenocarcinoma of the pigmented epithelium of the iris
Inflammatory disorders
Endophthalmitis
Iritis
Tuberculosis
Sarcoidosis
Syphilis
Juvenile xanthogranuloma
Reactive fibrosis due to foreign body
Cysts and pseudocysts

1.6 Treatment and prognosis

1.6.1 Treatment

The treatment of uveal metastases is virtually always palliative. According to Daicker (1981), in some cases, with a curable primary tumour and a solitary intraocular metastasis, treatment of the ocular tumour may be curative. Treatment aimed at the primary tumour, such as surgical resection and radiotherapy of this malignancy, appear to have little or no effect on the metastases in the choroid (Gillet, 1971). It is therefore necessary to treat the uveal metastases selectively. The choice of treatment depends on the symptoms, the localization and the extension of the intraocular metastasis, the nature of the primary tumour and the chemotherapeutic possibilities (Ferry, 1967; Shields, 1983) Char (1989) emphasizes the importance of the patient's general condition and of the presence or absence of metastases in the central nervous system.

It is the ophthalmologist's duty to endeavour to preserve good visual acuity and to treat complications such as pain and secondary glaucoma (Ferry, 1967).

Although the life expectation of patients with uveal metastases is mostly poor, treatment should be considered to maintain visual function (Gass, 1974).

Therapeutical decisions have to be made in consultation with the medical oncologist in charge. According to Char (1989), treatment should only be decided upon after complete evaluation including CT or MRI examination of the brain

In this chapter, the various possibilities of treatment will be discussed. Reference will be made to the nature and indications of the treatment, the therapeutic effect and the possible complications.

1.6.1.1 Observation

If a patient in whom metastases in the uvea are detected is in a terminal phase of the disease, no treatment should be instituted (Ferry, 1978). Observation is also often indicated in small metastatic lesions (Brady et al , 1982). Stephens and Shields (1979) recommended an expectative policy if the fovea is not threatened by the tumour or a secondary retinal detachment. Brady et al. (1982) described regression of a uveal metastasis in an untreated patient.

If observation of an intraocular tumour is advocated, examinations such as ophthalmoscopical photography, fluorescein angiography and echography may be valuable for determination of alterations of the lesion (Shields, 1983).

If metastases cause visual symptoms or threaten the macula or disk, treatment is necessary (Wharam and Schachat, 1989). Untreated uveal metastases may rapidly increase in size and, partly through the accompanying retinal detachment, may lead in a few days or weeks to severe loss of visual acuity (Orenstein et al., 1972; Brink et al., 1988).

1.6.1.2 Chemotherapy

If intraocular metastases are discovered in cancer patients, this usually also indicates progression of the disease elsewhere in the body. Therefore, systemic treatment is frequently necessary (Aasved and Seim, 1973, Mewis and Tang, 1982).

Choroidal metastases, being localized extracerebrally, may be as sensitive to chemotherapy as other metastases (Orenstein et al , 1972; Char, 1989). A favourable response of the primary tumour to chemotherapy is usually accompanied by regression of coexistent intraocular metastases (Abramson, 1984). Chemotherapy of uveal metastases may therefore be useful (Focosi and Salvi, 1961, Smith, 1976; Turut et al., 1987). Especially if the primary tumour is breast cancer, chemotherapy might be the treatment of first choice (Char, 1989). Gailloud (1975/1978) and Brinkley (1980) also stated that combination chemotherapy may be an alternative for irradiation of the intraocular metastases.

According to Shields (1983) asymptomatic intraocular metastases that can be observed adequately require no specific ophthalmological treatment It is then necessary carefully to check the patient every two to four months for tumour growth and visual loss Saßmannshausen et al (1990) are also of the opinion that in some cases, in peripherally localized metastases, the effect of systemic treatment may be awaited provided ophthalmological follow-up is possible during chemotherapy. If tumour growth occurs during systemic therapy, these authors consider radiotherapy necessary in all cases.

Muller-Grotjan and Liegl (1966) recommend, in the presence of choroidal metastases and metastases elsewhere, to start with cytostatic therapy. If this remains without effect, the chemotherapy should be changed (Kaiser-Kupfer, 1978) According to Meythaler and Herold (1979), multiple-drug chemotherapy is to be preferred in rapidly growing metastases. Stolzenbach and von Domarus (1978) treat patients with uveal metastases from breast cancer and metastases elsewhere with a combination of hormonal and chemotherapy. If this has no effect, treament is changed to radiotherapy of the uvea and combination chemotherapy of second choice. Rottinger et al. (1979) believe that in minimal clinical symptoms and under continuous ophthalmological control the choroidal metastases may be used as a parameter of the efficacy of the chemotherapy. However, most patients develop choroidal metastases during such systemic therapy and therefore are probably resistant to this treatment.

While, therefore, on the one hand there is no consensus on whether the effect of systemic treatment on choroidal metastases should (Stolzenbach and von Domarus, 1978, Shields, 1983, Char, 1989) or should not be awaited (Thatcher and Thomas, 1975; Chu, 1980), on the other hand investigators who, in a number of situations treat uveal metastases with chemotherapy alone, differ on the policy to be conducted.

According to Brady et al (1982), systemic therapy may be followed by stabilization or regression of uveal metastases According to these authors, 50% of the eyes show no progression when the patient receives chemotherapy.

Letson and Davidorf (1982) described six patients with a choroidal metastasis from breast cancer in eight eyes who were treated with chemotherapy alone. Chemotherapy consisted of cyclophosphamide and fluorouracil, often in combination with other cytostatics Eight other patients received radiotherapy alone. The patients treated with

chemotherapy alone had a more generalized metastasization and a poorer prognosis than those subjected to radiotherapy. All patients on chemotherapy showed regression of the tumour with improved visual acuity in five eyes and stabilization of the acuity in the three eyes with normal visual acuity prior to therapy. The mean visual acuity before treatment in eyes with a metastasis was 0.39 (finger counting to 0.8) while after treatment it was 0.58 (0.2 to 1.0). Five of the six patients died after a mean interval of 12 months. No effect of the chemotherapy on the duration of survival was established. In all eight irradiated patients a decrease of the tumour size was observed and in seven patients, improvement of the visual acuity. Letson and Davidorf conclude that chemotherapy alone is as effective as radiotherapy in the treatment of choroidal metastases from breast cancer, without the risk of irradiation cataract. According to these authors, therefore, radiotherapy is indicated only when no stabilization is achieved with chemotherapy (Davidorf et al., 1982). The possibility exists that owing to the effective use of chemotherapy of metastases elsewhere, still undiscovered choroidal metastases are not progressive and escape notice (Letson and Davidorf, 1982).

In a comment on this article by Letson and Davidorf, Mewis and Tang (1982) pointed out that the group of patients treated with chemotherapy alone cannot simply be compared with the irradiated patients. The mean visual acuity before treatment, namely, was 0 39 in the chemotherapy group as against only 0 04 in the radiotherapy group. Of the nine patients with breast cancer whom Mewis and Tang examined themselves and who received chemotherapy alone, five in 6 months showed an increase in size or number of metastases. In three of these patients radiotherapy was necessary to treat (imminent) loss of visual acuity. In four other patients, no progression of the choroidal metastases was observed during chemotherapy. Improvement of visual acuity was reported in only one patient. However, this patient had also been irradiated for an occipital cerebral metastasis. Mewis and Tang accordingly conclude that chemotherapy alone is inadequate for the treatment of choroidal metastases.

Stolzenbach and von Domarus (1978) treated eight patients with choroidal metastases of breast cancer with a combination of hormonal and chemotherapy. These patients had known metastases elsewhere as well. In six of the eight patients a decrease in size of the metastasis was observed and in five patients, improvement of the visual acuity was achieved. The mean visual acuity in the nine eyes of the six patients in whom the metastases went into remission was 0.65 (1/40 to 1 0) before treatment and 0.92 (0.5 to 1.0) after the systemic therapy. An accompanying retinal detachment went into regression in all cases. Other authors also reported positive results of such combined therapy (Aasved and Seim, 1973, Farnarier et al., 1973).

Other authors who reported a positive effect of chemotherapy alone on uveal metastases from breast cancer are Liegl (1960), Gunther (1961), Todter (1961), Schmelzer (1963), Muller-Grotjan and Liegl (1966), Orenstein et al (1972), Brinkley (1980) and Brasseur et al. (1983).

According to Wharam and Schachat (1989), patients with lung cancer as a rule at the time of occurrence of choroidal metastases have already received chemotherapy. Mostly, then, no effect of resumed chemotherapy is to be expected. If the patient has not yet received chemotherapy, the effect of such therapy may be awaited. This applies exclusively to metastases of small cell pulmonary tumours and not to metastases of squamous cell, adeno or large cell tumours of the lung.

Sierocki et al. (1980) had to alter the chemotherapy before remission of iris

metastases and increase of the visual acuity could be achieved in a patient with oat cell carcinoma of the lung. Lloyd (1968) reported a patient with a metastasis of oat cell carcinoma in whom on cyclophosphamide the uveal metastases went into regression although the existing visual field defect remained unchanged. Later on, some growth of the metastasis was observed again. Castro et al. (1982) described a patient with a choroidal metastasis of an oat cell carcinoma in whom the metastasis grew larger and the visual acuity decreased during chemotherapy. By means of radiotherapy, an improvement of the visual acuity could be obtained.

Finally, positive results of chemotherapy have been reported in patients with a choroidal metastasis of a cutaneous melanoma (Stark et al., 1971; Engel et al., 1981), in a patient with a choroidal metastasis of a choriocarcinoma (Keates and Billig, 1970), and in a neonate with iris metastases of a neuroblastoma (Bowns et al., 1983).

In a patient with a metastasis from a thyroid carcinoma, chemotherapy proved ineffective (Farnarier et al., 1973), just as in a patient with a metastasis of a bladder carcinoma (Resnick et al., 1975).

Chemotherapy for uveal metastases may only be administered in consultation with the oncologist and when the patient's general condition is known (Daicker, 1981).

In the discussion of the effect of chemotherapy it should further be kept in mind that use of cytostatics in the treatment of uveal metastases may lead to various side effects and ophthalmological complications (Haye, 1986). On this aspect, several survey articles have been published (Vizel and Oster, 1982; Fraunfelder and Meyer, 1983; Zaal and Polak, 1985; Imperia et al., 1989). Table 1.6.1.2.1 presents a survey of these side effects.

Ferry (1972) described a patient with a choroidal metastasis from a cutaneous melanoma in whom a major inflammatory reaction developed after administration of cytostatics. The probable cause was massive necrosis and haemorrhage in the intraocular tumour. Cytostatic treatment of uveal metastases therefore entails the risk of permanent loss of eyesight and possibly even loss of the eye.

With respect to the complications of simultaneous use of chemotherapy and radiotherapy, the reader is referred to the chapter on radiotherapy of uveal metastases (1.6.2.4).

If in patients with a malignancy which is being treated with cytostatics ophthalmological complaints occur, these may be the consequence of metastases in the uvea as well as of side effects of the systemic cytostatic therapy.

To recapitulate, there is no consensus in the literature on the efficacy or inefficacy of chemotherapy for treatment of uveal metastases or on the policy to be conducted when cytostatic treatment is instituted. Only a few studies on the use of cytostatics in uveal metastases have been published. In general these concerned small groups of patients with breast cancer as the primary tumour.

Table 1.6.1.2 1 Ophthalmological side effects of commonly used cytostatics *

Amsacrine	Blurred vision
Busulfan	Keratoconjunctivitis sicca, hyperpigmentation of the eyelids and conjunctiva, cataract, blurred vision
Chloromethine	Hyperpigmentation of the eyelids and conjunctiva, necrotizing uveitis
Chlorambucil	Keratitis, retinopathy and retinal haemorrhages, papilloedema, oculomotor disturbances with diplopia
Cis-platinum	Retinopathy, papilloedema, retrobulbar neuritis, ERG abnormalities, colour blindness, cortical blindness, blurred vision
Cyclophosphamide	Keratoconjunctivitis sicca, blepharoconjunctivitis, hyperpigmentation of the eyelids, pinpoint pupils, accommodation disorders, blurred vision
Cytarabine	Keratitis, conjunctivitis, decreased visual acuity
Doxorubicin	Conjunctivitis, epiphora
Fludarabine	Papilloedema, optic neuritis, cortical blindness
Fluorouracil	Cicatricial ectropion, hyperpigmentation of the eyelids, hyperaemia, ankyloblepharon, blepharospasm, blepharitis, keratoconjunctivitis, epiphora, chronic canaliculitis, dacryostenosis and fibrosis, epiphora, photophobia, ocular pain, optic neuropathy, circumorbital oedema, nystagmus, oculomotor disturbances, accommodation disorders, blurred vision
Ifosfamide	Blurred vision
Methotrexate	Blepharoconjunctivitis, conjunctival hyperaemia, depigmentation or hyperpigmentation of the eyelids, keratitis, epiphora, cataract, periorbital oedema, optic neuropathy, photophobia, ocular pain, blurred vision
Mitomycin-C	Blurred vision
Mitotane	Cataract, retinopathy and retinal haemorrhages, papilloedema, diplopia, blurred vision
Nitrosoureas	Corneal opacification and oedema, conjunctival hyperaemia, secondary glaucoma, vitreal opacities, retinitis, retinopathy, retinal infarction, optic neuroretinitis, optic atrophy, extraocular muscle fibrosis, internal ophthalmoplegia, diplopia, orbital arteriovenous shunts, orbital pain, blurred vision
Plicamycin	Periorbital pallor
Procarbazine	Hyperpigmentation of the eyelids and conjunctiva, purpura, retinopathy, retinal haemorrhages, nystagmus, accommodation disorders, papilloedema, photophobia, diplopia
Vincristine and vinblastine	Ptosis, lagophthalmos, corneal hypaesthesia, optic atrophy and neuropathy, extraocular muscle paralysis and cranial nerve palsies with diplopia, hemeralopia, cortical blindness, tapetoretinal degeneration, ocular pain

** Dralands, 1972, Fraunfelder, 1976, Griffin and Garnick, 1981; Vizel and Oster, 1982, Fraunfelder and Meyer, 1983, Zaal and Polak, 1985, Imperia et al , 1989, Farmacotherapeutisch Kompas 1990-1991*

1.6.1.3 Hormonal treatment

Uveal metastases occur most frequently in patients with breast cancer. In these patients endocrine therapy is possible (Abramson, 1984).

If in patients with breast cancer specific receptors for oestradiol can be demonstrated, a favourable effect of hormonal treatment may be expected in 50% of the cases. If no such receptors can be demonstrated, only up to 10% of the patients respond. If in addition to the oestradiol receptors the progesterone receptors are also present, the probability of positive effect increases further.

Endocrine treatment may consist inter alia of ovariectomy or antioestrogenic agents such as tamoxifen. More recent methods of treatment are large doses of oestrogens or progestative agents, or of aminoglutethimide. Adrenalectomy and hypophysectomy, formerly widely used, are rarely recommended nowaways because of the pharmaceutical alternatives available.

Hormonal treatment can be combined with chemotherapy. Although combinations of hormonal and chemotherapy lead to higher percentages of remission than single therapies, no evident benefit to the patient in the sense of a longer total duration of remission or longer survival is demonstrable. For this reason, the palliative combination of hormonal and chemotherapy is not a standard treatment (Beex, 1987; Rose and Mouridsen 1984; Lippman et al., 1988).

A few patients have been described with a good response of uveal metastases to systemic hormonal treatment. Cogan and Kuwabara in 1954 published the first positive results of diethylstilboestrol. Other authors also have used such additive therapy in a few cases with good results (Goldmann, 1957; Aasved and Seim, 1973; Farnarier et al., 1973; Meythaler and Herold, 1979).

Hormonal treatment of uveal metastases may be combined with chemotherapy with a positive result (Farnarier et al., 1973; Stolzenbach and von Domarus, 1978). Wharam and Schachat (1989) recommended that if a patient with a choroidal metastasis is not yet receiving systemic treatment, a cytostatic or hormonal therapy may be given, which may have an adequate effect on the eye.

A number of authors stated that for the treatment of uveal metastases hormonal therapy should be combined with radiotherapy (François et al., 1976; Ferry, 1978). About hormonal treatment of patients with breast cancer it may be stated, just as about chemotherapy, that most patients had already been subjected to it, and had developed uveal metastases in spite of this treatment (Thatcher and Thomas, 1975). Thompson et al. (1961) are also of the opinion that hormonal treatment alone of breast cancer metastases in the eye causes no dramatical regression of the lesions.

Just as during chemotherapy it is possible, according to Röttinger et al. (1979), in case of minimal clinical symptoms and under continuous ophthalmological control to use the choroidal metastasis as a parameter of the efficacy of the hormonal treatment.

Ablative endocrine therapies to combat uveal metastases such as surgical or radiological ovariectomy, adrenalectomy or hypophysectomy are reported mainly in older literature; the results varied (Ellis and Scheie, 1952; King, 1954; Blondet et al., 1957; Hotz, 1957; Beringer et al., 1961; Fanta, 1961; Lemke, 1965; Hollwich, 1966; Klien, 1966; Harner et al., 1967; Kaiser-Kupfer, 1978; Meythaler and Herold, 1979).

The only publication on the effect of hormonal treatment on choroidal metastases from breast cancer not confined to case histories was a brief comment by Vesterdal (1973) on an article by Aasved and Seim (1973). Vesterdal described 14 choroidal metastases, all treated with large doses of glucocorticoids. In addition, in seven premenopausal women the ovaries were irradiated and five patients were given androgens. Twelve of the patients retained a visual acuity of 6/6 in at least one eye until death. In one patient, the visual acuity was 6/12 owing to an age-related macular degeneration and another patient had a visual acuity of 6/36 due to, as Vesterdal put it, 'too late ovarial X-ray treatment'. His conclusion was that owing to a late diagnosis the prognosis of the first-affected eye was poor in some cases but the visual acuity in the second eye was preserved in all eyes until the time of death, without cytostatic treatment being necessary.

Ophthalmological side effects of tamixofen are increased corneal opacities and retinopathy (Griffin and Garnick, 1981; Imperia et al., 1989).

Corticosteroids have many possible ophthalmological side effects including discolouring of the sclera, cataract, glaucoma, visual field defects, diplopia, exophthalmos, ocular infections and blurred eyesight (Griffin and Garnick, 1981; Imperia et al., 1989).

To recapitulate, there are major differences of opinion among the various investigators with respect to the indication and the use of hormonal treatment to combat uveal metastases of breast cancer. Both ablative (surgical and physical) and additive (pharmaceutical) hormonal treatments have been applied. On this subject only a few, mostly older, publications are known.

Another tumour metastasis that might be treated hormonally is a choroidal metastasis of prostatic carcinoma (Saraux and Biais, 1969). Dieckert and Berger (1982) described a patient whom they treated with orchidectomy and oestrogens, following which the metastasis disappeared in two months and visual acuity improved from 6/60 to 6/6. They are consequently of the opinion that for an initial choroidal metastasis of a prostatic carcinoma, hormonal treatment is to be preferred. François et al. (1976) recommended both endocrine and radiotherapeutic treatment of this metastasis.

1.6.1.4 Radiotherapy

As far back as the thirties radiotherapy was used in the treatment of uveal metastases (Lemoine and McLeod, 1936; Evans, 1937; Cordes, 1944) and nowadays is generally regarded as an efficacious therapy (Thatcher and Thomas, 1975; Stephens and Shields, 1979; Brady and Shields, 1982; Letson and Davidorf, 1982; Mewis and Young, 1982; Hoogenhout et al., 1989; Lommatzsch, 1989).

This chapter contains a review of the literature on the indications, irradiation schedules, irradiation techniques, effects of irradiation and side effects in radiotherapy of uveal metastases.

Classification of ionizing radiation

There is no essential qualitative difference in the biological efficacies of the various types of ionizing radiation whatever their form or energy (Tables 1.6.1.4.1 and 1.6.1.4.2). There are only quantitative differences in penetrating power and in density of the ionizations brought about. These ionizations are caused by the inelastic scattering of electrons or, in the case of neutron radiation, by collisions with hydrogen nuclei. Quantitative differences depend on the energy. As to roentgen and gamma radiation (photon radiation), the penetrating power is less and the dose in the superficial layers larger when the energy is lower (Duke-Elder, 1972; Lerman, 1980). In high energy electrons, the penetrating depth is directly correlated with the energy [penetrating depth (cm) = energy (MeV)/2] (Khan, 1984).

Table 1.6.1.4.1 Classification of ionizing radiation *

Electromagnetic radiation:	- Roentgen radiation (Bremsstrahlung): produced by an electron beam in an X-ray unit or linear accelerator
	- Gamma radiation: emitted spontaneously by decay of unstable nuclei
Subatomic particles:	- α particle decay (Helium nuclei)
	- ß particle decay (electrons)
	- Neutrons
	- Protons
	- π-mesons
	- Heavy ions

* *Duke-Elder, 1972; Khan, 1984; Richter et al., 1985*

The advantages of use of megavoltage X-ray or gamma-ray beams over low energy roentgen irradiation are the relatively low skin dose with a large dose at greater depth, and the equal degrees of absorption in soft tissues and bone (Tapley, 1973; Lerman, 1980; Khan, 1984).

The density of ionization depends on the type of radiation. Roentgen and gamma radiation deliver energy to the tissue through a large number of ionizations over a large area. High energy electrons deliver their energy by ionizations, the ionization density being of the same magnitude as that of roentgen or gamma radiation. Alpha particles cause tracks of high-density ionizations. Indirectly neutrons cause ionizations through collisions with hydrogen nuclei. Since the biological damage increases with the density of the ionizations produced, alpha radiation is the most effective form. However, its range is small so that this type of radiation has no applications in radiotherapy (Duke-Elder, 1972; Lerman, 1980).

Table 1.6.1.4.2 Classification of ionizing radiation

Energy (MV/MeV)	*Photons*		*Electrons*	
100				
	4-30 MV	Megavoltage therapy	4-45 MeV	Betatron
10		(linear accelerator, betatron,		Microtron
		microtron)		Linear accelerator
	1.25 MV	Co-60 gamma radiation		
1	500-1000 kV	Supervoltage therapy		
	660 kV	Cs-137 gamma radiation		
	150-500 kV	Orthovoltage therapy		
		(deep X-ray therapy)		
0.1	50-150 kV	Superficial X-ray therapy		
	40-50 kV	Contact therapy		
0.01	<20 kV	Grenz ray therapy		

* *Khan, 1984; Richter et al., 1985*

Indications

Radiotherapy of intraocular metastases is necessary if the visual acuity is threatened or if secondary complications such as an accompanying retinal detachment or secondary glaucoma are to be expected (Stephens and Shields, 1979; Mewis and Young, 1982; Shields, 1983; Alberti and Halama, 1987). In addition, irradiation may alleviate ocular pain (de Bustros et al., 1985).

According to Dollfus (1954), metastases from breast and lung cancer are particularly to be considered for radiotherapy. Jaeger et al. (1971) and Lommatzsch (1989) also report that breast cancer metastases respond well to irradiation. Allen (1968) is of the opinion that metastases from primary malignancies sensitive to radiation may be irradiated. However, according to de Bustros et al. (1985) radiotherapy is also used successfully for uveal metastases of primaries less sensitive to radiotherapy, such as malignant melanoma of the skin.

Radiotherapy may also be of diagnostic value: Dickson (1958) described a patient with a uveal 'metastasis' that failed to respond to irradiation. After enucleation it was found to be a melanoma.

Time of irradiation

No consensus exists about the time when radiotherapy should be applied. Some authors state that to begin with, the effect of systemic hormonal or chemotherapy may be awaited (Stolzenbach and von Domarus, 1978; Shields, 1983; Char, 1989). According to Chu (1980), however, postponement of irradiation of ocular metastases may lead to retinal detachment and permanent blindness. Radiotherapy should therefore be administered without delay. Thatcher and Thomas (1975) believe that awaiting the effect of hormonal or chemotherapy leads to unnecessary delay of irradiation. It should be noted in this connection that the two last-mentioned publications originated from radiotherapeutic clinics.

Occasionally, radiotherapy is started only when growth of the metastases is established photographically or echographically (Alberti and Halama, 1987).

As mentioned before, the effect of cytostatic or hormonal therapy may be awaited at first. Breast cancer patients, however, in general have already received hormonal or chemotherapy or a combination of these. Radiotherapy of the uveal metastases is then indicated since a protracted secondary remission with second-line systemic treatment is compromised by the earlier hormonal or chemotherapy. If no systemic therapy has been administered in the past, the effect of such therapy on the uveal metastases may be awaited (Wharam and Schachat, 1989). If no effective cytostatic therapy is available, however, or if uveal metastases have developed during chemotherapy, radiotherapy of the uveal metastases should be instituted (Mewis and Young, 1982; Alberti and Halama, 1987; Char, 1989; Wharam and Schachat, 1989).

According to some authors, examination of the orbit and brain is necessary before starting irradiation. A second course of radiation for initially unsuspected orbital or cerebral metastases, causing additional exposure of the eye, can then be avoided (Haik et al., 1983; Char, 1989).

According to several authors, the length of the interval between the initial symptoms and the treatment does not influence the effect of irradiation (Thatcher and Thomas, 1975; Röttinger et al., 1976).

Brachytherapy

For radiotherapy of the eye two methods may be used: irradiation via an external beam or irradiation by means of local application of a radioactive source in a scleral plaque (brachytherapy).

Brachytherapy has been applied sporadically in uveal metastases. In the thirties, this was done for instance with radon seeds with a reasonable effect on prominence and visual acuity (Ask, 1936; Evans, 1937/1938; Cordes, 1944; Hoffman, 1959). This method was abandoned, however, because of the rapid dose reduction and the exposure to radiation of the normal tissues (Alberti and Halama, 1987).

According to some authors, irradiation with a radioactive applicator may be considered in patients with a solitary metastasis (Gerhard et al., 1975; de Bustros et al., 1985). Busse and Muller (1983), for instance, irradiated two uveal metastases with application of Ruthenium-106 with a scleral dose of 400-800 Gy. In one patient the visual acuity improved, in the other it decreased. No scleral necrosis developed. Metastases responded to Rhutenium-106 irradiation far sooner (after 6 to 8 weeks) than uveal

melanomas (12 to 36 months). Haye and Calle (1972) treated three patients with a Cobalt-60 plaque. This method gave poorer results than conventional external irradiation (Haye, 1972). Shields (1983) had better experience with this method. Newell and Harper (1957) treated a patient with local Iodine-131, with good results.

Since metastases often have diffuse or multiple localizations, application of brachytherapy is not indicated (Char, 1989) Also there may be small, as yet imperceptible foci, while the margins of the metastasis often cannot be determined with sufficient exactitude to justify such a taxing treatment (Daicker, 1981). Local application with a radioactive source on the sclera, namely, necessitates surgical interventions to introduce and to remove the plaque (Shields, 1983)

A different form of irradiation, namely by administration of radioactive iodine (I-131), was described by Weisenthal et al (1989) in a patient with an iris metastasis from a thyroid carcinoma. During this treatment the iris tumour and visual acuity remained stable.

External irradiation

In most cases, photons or electrons are used for irradiation of uveal metastases

Photon irradiation can be performed by means of orthovolt or megavolt techniques. The megavolt technique (linear accelerator) gives a sharply defined beam so that good localization of the high-dose area is possible Owing to the minimal lateral scattering, the lateral damage is minimized. In this way, a high depth dose with a low skin dose can be administered with a high dose rate and consequently, a short duration of the irradiation so that the effect of movements of the patient is limited (Orenstein et al , 1972; Shields, 1983) A disadvantage of megavolt photons is that, because of the high penetrating capacity, the normal tissue in front of and behind the target volume receives an undesirably high dose Electrons have the advantage of a high dose reduction in depth. By optimal adjustment of the electron energy the tissue situated behind the target volume can be spared (Chu et al , 1977).

The use of radiation with high ionization density, as that of protons is distinguished from photon and electron radiation by its high biological activity Compared with photons and electrons, this type of radiation offers the advantage of a favourable dose distribution with a well-defined range and little scattering The depth dose of these heavy particles gives a typical dose plateau This renders possible a high tumour dose with low exposure of surrounding structures (Alberti and Halama, 1987)

Gragoudas and Carroll (1979) treated a patient with multiple choroidal metastases from a bronchial carcinoid with proton irradiation combined with laser treatment Char (1989) considered this proton treatment to be of little value since metastases frequently are diffuse or multiple.

Irradiation schemes

In the literature the various authors recommend different schemes (Table 1.6.1.4.3). The total doses in choroidal metastases range from 20 to 56 Gy.

Table 1.6.1.4.3 Recommended total and fraction dose in irradiation of choroidal metastases

Author	Total dose (Gy)	Fraction dose (Gy)	Overall time (weeks)
Haye and Calle, 1972	20-40	-	3
Reddy et al , 1981	21-30	3	1.5-2
Merriam, 1961	24-32	-	2-3
Ferry, 1967	25-30	2.5-3	2
Mewis and Young, 1982	25-30	2.5-3	2
Maor et al., 1977	25-30 *	3-5	1-2
Shields and Augsburger, 1983	25-40	-	-
Dobrowsky et al., 1987	25-50	-	2 5-5
Thatcher and Thomas, 1975	28	2.8	2
Jaeger et al., 1971	30	-	3
Shields, 1983	30	-	3
MacComb and Fletcher, 1967	30	-	2
Orenstein et al., 1972	30	-	2
Letson et al., 1982	30	3	2
Brink et al., 1988	30	3	2
Hoogenhout et al., 1989	30	3	2
Saßmannshausen et al., 1990	30	3.3	3
Röttinger et al., 1976	30-40	2	4-5
Haik et al., 1983	30-40	-	2-4
Chu, 1980	30-40	-	2-3
Stephens and Shields, 1979	30-48	-	-
Alberti and Halama, 1987	30-50	-	3-4
Brady et al , 1982	30-56	-	3-5 5
Char, 1989	35-40	2	3
Lommatzsch, 1989	40	2	5
Chu et al., 1977	40	-	3
Haye, 1986	40	3.3	4
Dobrowsky, 1988	40-50	-	3-5
Zografos and Gailloud, 1983	45	-	-

** doses used most often*

The recommended dose depends on the patient's prognosis quoad vitam. For instance, if metastases refractory to treatment are present outside the eye, 30 Gy suffices. For patients with a reasonable life expectation 50 Gy is advised (Alberti and Halama, 1987). Char

(1989) recommends irradiation of terminal patients with deteriorating eyesight due to uveal metastases with up to about 35 Gy with high fraction doses. This would result in a lower percentage of remissions and more long-term complications, but it may be administered in a shorter time with little risk of side effects during the patient's remaining days. Brady et al. (1982) recommend doses of at least 30 Gy in 3 weeks or 56 Gy in 5.5 weeks. If there is a good chance of survival and metastases are present exclusively in the choroid, it is attempted to prevent complications. Char (1989) for such cases advises a dose of 35 to 40 Gy in fractions of 2 Gy three times per week. More than three sessions per week would be too taxing for the patient (Alberti and Halama, 1987).

Dobrowsky (1988) used electrons (42 MeV betatron) or high-energy photons (Cobalt-60) with a dose of 40 to 50 Gy in three to five weeks. When a lower dose is used the metastases may grow back. MacMichael (1969) treated a number of patients with a single dose of 10 to 15 Gy. Mostly, however, a total dose of 30 Gy is administered (Jaeger et al., 1971; Brasseur et al., 1983). A dose of 30 Gy in 10 fractions in two weeks is the most widely accepted irradiation schedule (MacComb and Fletcher, 1967; Orenstein et al., 1972; Letson et al., 1982; Haik et al., 1983; Brink et al., 1988; Hoogenhout et al., 1989).

In metastases in the iris, also, a dose of 30 Gy is recommended (Stephens and Shields, 1979).

Allegedly, above 30 Gy there is no correlation between the total dose administered and the response to the irradiation (Thompson, 1961; Thatcher and Thomas, 1975; Röttinger, 1976; Brink et al., 1988; Hoogenhout et al., 1989). In Thatcher and Thomas, the total dose in all patients with a complete response to irradiation was minimally 32.5 Gy. If irradiation is administered, they recommended a dose of 28 Gy minimally.

The schemes of 30 Gy in two weeks and of 40 Gy in four weeks have the same effect with respect to improvement of visual acuity or tumour decrease, while the 30 Gy scheme is less of a burden to the patient (Brink et al., 1988; Hoogenhout et al., 1989).

Irradiation technique

In unilateral choroidal metastases a lateral beam will in general be opted for. The anterior delimitation of the irradiation field is situated at the outer bony canthus of the lateral orbital wall so that the anterior chamber can be shielded (Thatcher and Thomas, 1975). If possible, the cornea and lens should not be included in the irradiation volume. However, most patients do not survive long enough for late radiation damage to occur (Daicker, 1981). To protect the lens of the contralateral eye the beam is directed 5 to 10° occipitally or a half field tecnhique is used (Dickson, 1958; Merriam, 1961; Ferry, 1967; MacComb and Fletcher, 1967; Haye, 1968; Haye and Calle, 1972; Orenstein et al., 1972; Thatcher and Thomas, 1975; Röttinger et al., 1976; Chu et al., 1977; Maor et al., 1977; Reddy et al., 1981; Brady et al., 1982; Mewis and Young, 1982; Haik et al., 1983; Shields and Augsburger, 1983; Alberti and Halama, 1987; Hoogenhout et al., 1989; Lommatzsch, 1989; Saßmannshausen et al., 1990). Sometimes an angle of 20° occipitally is applied (Dobrowsky et al., 1987). In case of a lateral beam, when electron irradiation is administered, the dose distribution will be markedly influenced by the bone (MacComb and Fletcher, 1967; Hoogenhout et al., 1989). If no electron beams are available, Cobalt-60

may also be used (Haik et al., 1983; Hoogenhout et al., 1989). Chu et al. (1977) recommend that small temporally situated lesions should be irradiated with 10 MeV electrons, protecting the lens. Owing to a rapid dose reduction the exposure of the surrounding tissue remains limited. In case of a larger tumour volume, the same technique is applied but use is made of a higher electron energy (15 MeV) (Chu et al., 1977).

Sometimes use is made of a ventral beam (Brady et al., 1982) for instance in metastases localized in the lateral or medial part of the choroid; the patient is then asked to look in the contralateral direction to protect the lens (MacComb and Fletcher, 1967). In equatorially situated metastases, the lens and the lacrimal gland can be shielded (Dobrowsky et al., 1987; Hoogenhout et al., 1989). Haye and Calle (1972) recommend a ventral beam in multiple metastases or poor general condition of the patient. It is then not necessary to shield the lens. In lesions situated on the nasal side in the posterior pole, preference is sometimes given to a ventral beam laterally shielded. During the irradiation the patient is made to look away from the radiation beam so that the nasal side of the posterior pole turns forward, toward the beam, and the lens away from the beam (Chu et al., 1977).

The entry field as a rule measured 4x4 sq.cm (Orenstein et al., 1972; Thatcher and Thomas, 1975; Chu et al., 1977; Maor et al., 1977; Hoogenhout et al., 1989). Dickson (1958) used a beam with a diameter of 2.5 cm. The lateral beam was then combined with a medial oblique beam through the bridge of the nose from the other side. This technique made possible an improved depth dose with better protection of the skin. However, there was a higher risk of lens damage. Jaeger et al. (1971) used a circular beam with a diameter of 3 cm, one-half of which was shielded to spare the lens. They combined a lateral beam with the eye looking straight forward with a ventral-medial oblique beam with the eye looking in the lateral direction.

In bilateral metastases, two parallel opposed lateral beams are used (Maor et al., 1977; Alberti and Halama, 1987; Hoogenhout et al., 1989; Saßmannshausen et al., 1990). A ventral and a lateral beam may also be combined to obtain an optimal dose distribution. If a metastases develops in the contralateral eye, the same technique may be applied with minimal overlapping of the area irradiated previously. The anterior radiation field in this case is delimited by the medial canthus; the lateral field of 3x4 sq.cm at the external canthus is directed 70° posteriorly in relation to the anteroposterior radiation beam, without shielding the lens (Chu et al., 1977).

In a very extensive lesion, also, combination of a ventral and a lateral beam may be opted for (Chu et al., 1977; Alberti and Halama, 1987).

In extraocular spread of the choroidal metastasis the field size may be adjusted to the size of the extraocular extension (Alberti and Halama, 1987).

In metastases in the iris, the anterior segment has to be irradiated as well (Shields, 1983). Tumours of the iris may be irradiated with a ventral or a lateral beam. Preference is given to a ventral beam although no protection of the lens is possible (Alberti and Halama, 1987; Lommatzsch, 1989). Char (1989) advises treating iris metastases in the same way as metastases localized in the posterior segment.

Effect of irradiation on visual acuity

The effect of radiotherapy on uveal metastases can be evaluated in various ways. Preservation or, if possible, improvement of the visual acuity is the principal objective. Other important elements are the effect on tumour size and on the secondary retinal detachment, as well as prevention of complications such as secondary glaucoma.

In literature concerning irradiated uveal metastases, authors often omit to mention how they define a positive or negative result after irradiation. Haik et al. (1983) and Abramson (1984) reported that 75% of the irradiated choroidal metastases responded well, without defining this response. Brady et al. (1982) described a positive objective response in nearly 90% of the irradiated eyes, by which they probably meant the effect on tumour size.

A uveal metastasis may go into complete remission due to radiotherapy. The treatment is also successful, however, if regression of the tumour takes place so that a secondary retinal detachment returns to normal and improvement of the visual acuity is accomplished, although the metastasis is still partly present (Ferry, 1967). Stephens and Shields (1979), for instance, described regression of the metastasis after radiotherapy with reduction of the subretinal fluid and improved visual acuity. In small metastases, in particular, complete normalization of visual acuity may be expected (Chu, 1980).

Table 1.6.1.4.4 presents a survey of publications regarding the effect of radiotherapy on the patient's visual acuity A change of the visual acuity is defined as an improvement if an increase of the visual acuity by at least two lines on Snellen's chart was determined occurred or if this change is described as 'distinct' or 'substantial'. Stabilization of the visual acuity is defined as the fact that no effect of the radiotherapy on the visual acuity is observed or that an improvement, if any, amounts to less than two lines on Snellen's chart or is described as 'slight' or as 'some' improvement of the visual acuity. Deterioration of the visual acuity means a decrease of the acuity by at least two lines on Snellen's chart or a description as 'decrease'.

As this table shows, improvement of the visual acuity was reported in proportions ranging from 27 to 90%. The visual acuity of 1.0 before and after radiotherapy should also be regarded as a positive result, however. Considered from this point of view, radiotherapy has been successful in the vast majority of the patients.

The mean visual acuity before irradiation in the 15 patients of Gillet (1971) was 0.64 (20/200-20/20). After irradiation, the mean visual acuity was 0.82 (20/30-20/20). Of the 71 patients of Saßmannshausen et al. (1990) in whom the effect of the irradiation on the visual acuity was known, 61% retained a visual acuity of at least 0 40. After successful irradiation, it took eight months on average (1 to 24 months) before a stable or increased visual acuity was described (Hoogenhout et al., 1989).

Deterioration of the visual acuity is usually the consequence of tumour growth (Saßmannshausen et al., 1990).

MacComb and Fletcher (1967) described preservation of functional visual acuity in eight of the 10 irradiated patients with improvement of the visual acuity for the rest of these patients' lives. Merriam (1961) recorded preservation of adequate visual acuity until death in 14 of the 27 irradiated eyes (duration of survival 1 month to 3 years, median 8.5 months). All the patients of Rottinger et al. (1976) in whom radiotherapy led to improved visual acuity retained this for good (duration of survival 0 to 44 months, median: 8 months).

Author	Number of * patients/eyes	Localization primary tumour	Irradiation scheme			Visual acuity after irradiation **		
			Total dose (Gy)	Fraction dose (Gy)	Overall time (wk)	Increase %	No change %	Decrease %
MacComb and Fletcher, 1967	10 patients	breast	30	3 #	3	90	10	-
Maor et al., 1977	42 patients	breast	25-30	2.5-5	1-2	89	11	-
Letson et al., 1982	8 patients	breast	30-35	3	2	88	12	-
Dobrowsky, 1988	20 eyes	mainly breast	40-50	2-2.5 #	3-5	85	15	-
Röttinger et al., 1976	22 patients	breast	30-40	2	3-4	82	14	5
Haye and Calle, 1972 ∞∞	22 patients	mainly breast	20->25	1.3-2 #	3	59	41	-
Dobrowsky et al., 1987	16 eyes	breast	25-50	2 #	2.5-5	56	44	-
Gillet, 1971	15 eyes	mainly breast		not stated		53	47	-
Merriam, 1961	27 eyes	breast	30-40	2-3 #	2-3	52	48	-
Brink et al., 1988	33 patients	mainly breast ∞	30-40	2-3	2-4	48	36	15
Hoogenhout et al., 1989	45 eyes	mainly breast ∞	30-40	2-3	2-4	38	33	29
Chu et al., 1977	57 eyes	breast	30-40	2 #	3-4	35	65	-
Orenstein et al., 1972	6 patients	breast and lung	25-50	2-3 #	3	33	67	-
Jaeger et al., 1975	21 eyes	mainly breast	30	2 #	3	33	67	-
Thompson et al., 1961	14 eyes	breast	14.6-54	3 #	1-3.5	33	42	25
Saßmannshausen et al., 1990	71 eyes	mainly breast	30	3.3	3	28	55	17
Thatcher and Thomas, 1975	49 eyes	breast	30-50	2	3-5	27	73	-
Mewis and Young, 1982	52 eyes	breast	25-30	2.5-3	2	27	69	4

Metastases from breast cancer in general show a dramatic response to radiotherapy with reduction of tumour size, disappearance of the retinal detachment and improvement of the visual acuity. The response of metastases from other primaries is mostly less dramatic but nevertheless always positive (Shields, 1983).

Effect of irradiation on prominence and secondary retinal detachment

The effect of irradiation on tumour size and retinal detachment is recapitulated in Table 1.6.1.4.5. In 57 to 80% of the irradiated metastases regression of the tumour was observed. Growth of the metastasis after irradiation was described sporadically. Only Saßmannshausen et al. (1990) observed further tumour growth in 11% of the irradiated eyes.

De Bustros et al. (1985) in two out of five successfully irradiated uveal metastases of cutaneous melanomas, nevertheless reported resumed growth later on. Jaeger et al. (1971) in three out of seven patients with preserved visual acuity or tumour regression after irradiation, reported a recurrence within 7 months.

After radiotherapy an increase of pigment clumping in the retina in the tumour region was observed, and ultimately a flat chorioretinal scar with yellowish white mottled pigmentation remained (Jaeger et al., 1971; Pau, 1979; Shields, 1983; Zografos and Gailloud, 1983; Lommatzsch, 1989; Saßmannshausen et al., 1990). Reddy et al. (1981) described the ophthalmoscopical effect as fragmentation of the tumour with necrosis and pigment migration.

According to Chu et al. (1977), the effect of irradiation depends on the size of the intraocular metastatic lesion: metastases which occupy less than half a quadrant of the fundus and are not accompanied by a retinal detachment, they state, always show a positive response. In metastases of larger size and with no or only minimal retinal detachment, this was 77%. If the retinal detachment was larger, the probability of improvement was reduced to only 32%. An early diagnosis is therefore necessary.

Accordingly, if no improvement of the visual acuity is obtained, the most frequent cause of this is a secondary retinal detachment already known prior to treatment (Duke-Elder and Perkins, 1966). Zografos and Gailloud (1983) are of the opinion that if a retinal detachment disappears after irradiation, some loss of visual acuity nevertheless frequently persists. Although a retinal detachment has a poor prognosis, this does not constitute a contraindication to radiotherapy (Chu et al., 1977). Small tumours, namely, sometimes fail to respond to irradiation while irradiation of a large lesion with a retinal detachment may give a good result (Jaeger et al., 1971). A retinal detachment, therefore, may respond well to the treatment (Reddy et al., 1981). According to some authors, presence of a secondary retinal detachment is irrelevant for the prognosis of the visual acuity after irradiation (Merriam, 1961; Thatcher and Thomas, 1975).

When an eye that has been irradiated because of a uveal metastasis is examined histologically, viable neoplastic cells can still be demonstrated in spite of proved symptomatic efficacy (Lemoine and McLeod, 1936; Duke-Elder and Perkins, 1966; Jaeger et al., 1971; Witschel et al., 1975). Necrosis is reported more frequently in irradiated metastases than in irradiated melanomas and retinoblastomas (Goder and Lommatzsch, 1965; Lommatzsch and Goder, 1965).

Table 1.6.1.4.5 Effect of external beam irradiation on tumour prominence and secondary retinal detachment in uveal metastases

Author	Number of * patients/eyes	Localization primary tumour	Irradiation scheme			Prominence after irradiation **		
			Total dose (Gy)	Fraction dose (Gy)	Overall time (wk)	Decrease %	No change %	Increase %
Gillet, 1971	15 eyes	mainly breast		not stated		80	20	-
Saßmannshausen et al., 1990	71 eyes	mainly breast	30	3.3 #	3	80	8	11
Hoogenhout et al., 1989	45 eyes	mainly breast ∞	30-40	2-3	3-4	78	22	-
Brink et al., 1988	35 patients	mainly breast ∞	30-40	2-3	3-4	69	31	-
Chu et al., 1977	57 eyes	breast	30-40	2 #	3-4	63	27	-
Orenstein et al., 1972	7 patients	breast and lung	25-50	2-3 #	3	57	29	14

** number of patients or eyes in which the effect of radiotherapy on prominence was stated; ** in patients or eyes in which the effect of radiotherapy on the tumour prominence and/or retinal detachment was known; # fraction dose, assuming five fractions a week; ∞ one patient acute lymphatic leukaemia; ∞∞ three patients brachytherapy*

By application of radiotherapy the risk of development of a secondary glaucoma caused by the intraocular tumour may be reduced (Ferry, 1967). Even if no improvement of the visual acuity can be achieved, enucleation may be avoided (Thatcher and Thomas, 1975).

According to several authors the duration of the interval between observation of the initial symptoms and the treatment does not influence the effect of the irradiation. In Thatcher and Thomas (1975) this interval ranged from 0.5 to 59 weeks and in Rottinger et al. (1976) from 3 to 26 weeks.

The localization of the metastasis, the distance to the macula (Thatcher and Thomas, 1975), the patient's age and the menopausal state in patients with breast cancer (Merriam, 1961) do not affect the result of irradiation, either.

The earliest effect of irradiation is to be expected two to four weeks after the start of the radiotherapy (Merriam, 1961; Duke-Elder and Perkins, 1966; Thatcher and Thomas, 1975, Brasseur et al., 1983; Haye, 1986) If the effect fails to occur after this length of time, this may be due to exudative macular lesions (Brasseur et al , 1983). The long-term result of irradiation is difficult to assess since most patients are reported to have died within six months after treatment (Haye and Calle, 1972). Most investigators, however, report the mean or median duration of survival after treatment to have been 8 to 20 months (Merriam, 1961; Rottinger et al., 1976; Chu et al., 1977; Maor et al., 1977; Brady et al , 1982; Dobrowsky et al., 1987; Brink et al , 1988; Dobrowsky, 1988).

Interactions of chemotherapy and radiotherapy

Because of possible interactions of cytostatics with radiotherapy, combinations of these according to Alberti and Halama (1987) should only be used on urgent indications and under thorough ophthalmological control The authors regard cytostatic treatment with adriamycin during radiotherapy as contraindicated because a potentiating action on side effects of this drug during irradiation of other tumours is known.

Chan and Shukovsky (1976) described patients who were irradiated for malignant tumours of the nasal cavities or paranasal sinuses with the eye lying in the radiation field. If fluorouracil was administered simultaneously with irradiation, a significant decrease of the visual acuity was observed. Corrected for duration of survival, blindness after three years developed five times as often after use of fluorouracil during irradiation. This was brought about by corneal lesions, phthisis bulbi and optic neuritis. Moreover, cataract was encountered five times as often when fluorouracil was used. Chronic conjunctivitis developed in 75% of the patients (as against 25% of the patients given radiotherapy alone) and in all patients a corneal lesion occurred within two years after treatment (irradiation alone: 15%).

Mostly, however, patients with uveal metastases that were irradiated received chemotherapy at the time of the irradiation (Thatcher and Thomas, 1975; Stephens and Shields, 1979, Dobrowsky, 1988). For instance, Saßmannshausen et al. (1990) described 56 patients, and Thatcher and Thomas (1975) 40 patients who developed uveal metastases in spite of earlier systemic treatment. In addition, many patients had received such treatment prior to the irradiation (Thatcher and Thomas, 1975; Reddy et al., 1981; Letson et al., 1982).

Unfortunately, in radiation therapy the surrounding normal tissue may be damaged during its administration. Both normal and pathological tissues vary greatly in degree of sensitivity to radiation. Fractionation of the irradiation provides a possibility to influence the biological effects of the irradiation on the different tissues (Haik et al., 1983).

Side effects of radiotherapy depend on the total dose, fractionation, overall time and the ophthalmological structures situated in the irradiation volume. Literature data on side effects of radiotherapy on ocular structures are limited. No more than an indication can therefore be given of the total doses that will cause side effects. The side effects can be subdivided into acute and late effects. Different tissues have different sensitivities to radiation (Duke-Elder, 1972; Haik et al., 1983; Alberti and Halama, 1987). Acute side effects of fractionated irradiation are listed in Table 1.6.1.4.6, late side effects in Table 1.6.1.4.7.

Table 1.6.1.4.6 Acute side effects (within six weeks of irradiation) of radiotherapy with a fraction dose of 2 Gy, 5 fractions a week *

Tissue	Side effect	Total dose (Gy)
Skin/eyelids	Erythema	20-30
	Moist desquamation	50-60
	Epilation (temporarily)	30-40
Conjunctiva	Hyperaemia	20-30
	Conjunctivitis	30-40
Cornea	Punctate keratitis	30-50
	Oedema	40-50
Iris	Iritis	60
Retina	Oedema	40-50

* *MacFaul and Bedford, 1970; Duke-Elder, 1972; Merriam et al., 1972; Haik et al., 1983; Alberti and Halama, 1987; Dobrowsky, 1988; Hoogenhout et al., 1989*

Regarding late side effects of radiotherapy, only limited data from a few authors are available in the literature. The doses listed in Table 1.6.1.4.7, therefore, are only an indication of the total dose of which such side effects may be expected.

The ocular structure most sensitive to radiation is the lens. Mitotic lens epithelium is damaged, ultimately leading to cataract (Haik et al., 1983). For irradiation to cause lenticular damage a total dose of only 4 Gy may suffice. With a total dose of over 11.5 Gy cataract develops in all cases. The higher the dose, the sooner it will develop. Thus, the latency time after irradiation with a dose of 4 to 10 Gy will be 6.5 years on average, with 10 to 20 Gy, 5 years and 2 months, with 20 to 40 Gy two years and 8 months and with doses of over 40 Gy 2.5 years on average (Merriam and Focht, 1957).

Radiation optic neuropathy, which may lead to major loss of visual acuity, is characterized by a typical acute swelling of the disk with surrounding exudate, haemorrhages and subretinal fluid and is probably secondary to vascular damage. Such damage may occur after a dose of over 36 Gy and on average manifests itself after 19.3

months (5 to 36 months). Recuperation of visual acuity is possible after a few months (Brown et al., 1982a).

Radiation retinopathy manifests itself ophthalmoscopically with hard exudates, haemorrhages, microaneurysms, cotton-wool spots and teleangiectases. This damage is caused by capillary non-perfusion. Such abnormalities are described after irradiation with a mean dose of 49 Gy (35 to 72 Gy) in fractions of 2 Gy over a period of one to two months. The retinopathy then develops after an average of 18.7 months (7 to 36 months) (Brown et al., 1982b).

Use of orthovolt equipment owing to the unfavourable depth dose distribution and marked scattering of radiation will lead to more cataract, retinopathy, optic nerve damage and neovascularization glaucoma than use of megavolt techniques (Alberti and Halama, 1987).

Table 1.6.1.4.7 Late side effects (more than six months after irradiation) of radiotherapy with a fraction dose of 2 Gy, 5 fractions a week *

Tissue	Side effect	Total dose (Gy) TD 5/5 **
Skin/eyelids	Pigmentation	40-50
	Teleangiectasis	40-50
	Epilation (permanently)	40-50
Lacrimal gland	Atrophy	50-60
Conjunctiva	Teleangiectasis	40-50
Cornea	Atrophy	40-50
	Keratinization	50
	Vascularization	50
	Ulceration/perforation	60
Lens	Cataract	4-6
Uvea	Uveitis	40-50
Retina	Retinopathy	40-50
Optic nerve	Neuropathy	50-60

** MacFaul and Bedford, 1970; Duke-Elder, 1972, Merriam et al., 1972; Brown et al., 1982ab; Haik et al., 1983; Parsons et al., 1983; Alberti and Halama, 1987; Dobrowsky, 1988*

*** Tolerance dose 5/5 is defined as the dose which under standard conditions results in no more than 5% severe side effects within five years after treatment*

Side effects of radiotherapy on the lens and retina in patients with intraocular metastases, who have a relative short duration of survival, have a different meaning than in patients with a primary ocular tumour in whom treatment mostly has a curative intention. Since cataract and radiation retinopathy as a rule only occur after a latency period of one year after radiotherapy, the radiation tolerance of these structures may, if necessary, be exceeded (Alberti and Halama, 1987).

Most authors observed no or no significant side effects of the irradiation (Dickson, 1958; Orenstein et al., 1972; Thatcher and Thomas, 1975; Maor et al., 1977; Stephens and Shields, 1979; Brady et al., 1982; Mewis and Young, 1982) especially when the total

dose did not exceed 30 Gy (Char, 1989). Irradiation cataract is uncommon owing to the frequently brief duration of survival and to shielding of the lens (Merriam, 1961; MacComb and Fletcher, 1967; Jaeger et al., 1971; Thatcher and Thomas, 1975; Röttinger et al., 1976; Brink et al., 1988; Dobrowsky, 1988; Hoogenhout et al., 1989). Chu et al. (1977) described one patient among 57 irradiated eyes with a cataract within one year, Saßmannshausen et al. (1990) one among 152 irradiated eyes, three months after radiotherapy. Letson et al. (1982) in two out of eight irradiated patients subsequently saw deterioration of visual acuity due to development of cataract. If cataract occurs, this is acceptable in relation to the result obtained (Haik et al., 1983).

The most acute side effect is conjunctivitis, which responds well to treatment (Jaeger et al., 1971; Röttinger et al., 1976; Haik et al., 1983; Brink et al, 1988; Dobrowsky, 1988; Hoogenhout et al., 1989). Transient erythema of the skin (grade 1) also occurs frequently, more often with use of orthovolt equipment than with irradiation with high-energy photons or electrons (Jaeger et al., 1971; Röttinger et al., 1976; Chu et al., 1977; Haik et al., 1983; Dobrowsky, 1988). Dobrowsky (1988) in one out of 16 irradiated patients described substantial oedema with erythema of the skin which responded well to oral corticosteroids.

We ourselves after irradiation once observed acute glaucoma due to massive tumour necrosis of a metastasis from a thyroid carcinoma (Brink et al., 1988; Hoogenhout et al., 1989). Pau (1979) also described a patient in whom choroidal and retinal necrosis developed. The lesion was a metastasis from a uterine carcinoma. Saßmannshausen et al. (1990) described two patients with complications of radiotherapy, viz. once a cataract (three months after irradiation) and once, radiation retinopathy (after five months). Three out of 152 irradiated eyes were enucleated because of secondary glaucoma or necrosis which was not definitely attributable to the irradiation.

Brown et al. (1982ab) described a patient with radiation optic neuropathy and two patients with radiation retinopathy.

1.6.1.5 Other methods of treatment

Enucleation of an eye with a uveal metastasis early in this century constituted the usual treatment of this lesion (Giri, 1939). Although according to some authors indications for enucleation in the treatment of uveal metastases still exist at present, most enucleations are performed under the false diagnosis of 'malignant uveal melanoma' (Ferry and Font, 1975; Colombo and Carnevali, 1985).

Enucleation is indicated only if an eye is painful (Allen, 1968; Shields et al., 1983; Char, 1989). Inflammation and glaucoma may render enucleation unavoidable (Leubuscher, 1927; Bonnet and Jambon-Genet, 1948; Ferry, 1967; Offret and Haye, 1971; Haye and Calle, 1972; Ferry and Font, 1975; Stephens and Shields, 1979; Shields, 1983; De Jong et al., 1985; Lommatzsch, 1989; Saßmannshausen et al, 1990). A number of authors in patients with uveal metastases mention as an indication for enucleation, apart from a painful eye due to glaucoma, also blindness of the affected eye (Castro et al., 1982; Shields, 1987). A persistent secondary glaucoma should be treated pharmaceutically as long as possible (Shields, 1987).

In other intractible complaints due to the local tumour an indication for enucleation may also be present (Daicker, 1981). In a metastasis larger than 15 mm in prominence the eye should be enucleated according to Haye (1986). A painful eye in patients in a terminal

phase of the disease may also be treated with retrobulbar injection of alcohol (Ferry, 1967).

Some investigators are of the opinion that in a solitary metastasis in the uvea, e g a metastasis of a carcinoid, enucleation may be useful to prolong the duration of survival (Hart, 1962; Font et al., 1966; Font and Ferry, 1976; Schreck, 1980; Daicker, 1981). However, according to Hemmes (1969), enucleation of eyes with uveal metastases affected the prognosis unfavourably

A number of investigators state that enucleation is sometimes necessary if local symptoms indicate a primary uveal melanoma and no primary tumour is known (Hart, 1962, Daicker, 1981) De Jong et al (1985), however, point out that the localization of a primary tumour can only rarely be identified by histological examination of a uveal metastasis Shields (1983) also regards such a diagnostic enucleation as controversial.

Just as enucleation, ***local excision*** of iris and ciliary body metastases of a carcinoid may sometimes be advisable (Archer and Gardiner, 1982; Shields, 1983; Lommatzsch, 1989) Since these tumours are radioresistant, local excision is justified in case of rapid growth (Rodrigues and Shields, 1978). Malbran et al (1979) point out the possibility of local excision if the primary tumour is unknown.

Photocoagulation or ***laser therapy*** has been applied in a limited number of patients with small uveal metastases (Weve, 1960, Raverdino, 1960, Moura Brazil and Rezende, 1961, Daicker, 1981, Brady et al , 1982) For multiple or diffuse choroidal lesions this treatment is rarely suitable, however (Char, 1989) In the literature, only sporadic reference is made to photocoagulation of multiple small lesions (Eide and Syrdalen, 1990).

Meyer-Schwickerath (1959) reported that in three small peripheral metastases of breast cancer a completely flat scar resulted after one or two photocoagulation sessions A fourth, larger metastasis could not be destroyed and was subsequently treated with irradiation.

François and Weekers (1965) noticed that because of the rapid growth of metastases photocoagulation does not result in destruction of the lesions while meanwhile new metastases develop For these reasons they carried out no more laser treatment of uveal metastases unless the outflow of aqueous humour was blocked and a painful secondary glaucoma developed.

Gragoudas and Carroll (1979) obtained good results with xenon lamp photocoagulation of a tumour rest persisting after proton irradiation of a metastasis of a bronchial carcinoid

Cryocoagulation of uveal metastases is only described exceptionally (Brady et al., 1982)

Daicker and Gysin (1980) described a patient with a thyroid carcinoma in whom two choroidal metastases in the left eye were treated with transscleral cryocoagulation. Three months postoperatively a total retinal detachment developed. Subsequently, several metastases were also discovered in the other eye; these were treated with a combination of cryo- and photocoagulation after which complete scarification of the tumours occurred with preservation of visual acuity until the moment of death. At autopsy, a metastasis in the left eye was found to have broken through the sclera at the site of the cryo-application.

Lincoff et al. (1967) treated four patients with a choroidal metastasis by means of cryocoagulation. However, two patients with a metastasis from lung cancer developed a

retinal detachment. One patient with breast cancer showed few complications but there was rapid regrowth of the choroidal metastasis. In a fourth patient with a metastasis of breast cancer, the treatment was unsuccessful due to exudation, vitreous traction, cystic abnormalities of the macula and progressive tumour growth at the margin of the lesion.

1.6.2 Prognosis

Detection of uveal metastases means a poor prognosis quoad vitam (Cordes, 1944; Jaensch, 1950; Maxwell, 1954; Stevens and Reeh, 1958; Duke-Elder and Perkins, 1966; Ferry, 1967; Gartner, 1985). In Chapter 1.3 (Epidemiology), the connection of uveal metastases with metastases elsewhere in the body is described. At the moment of ophthalmological diagnosis, 60 to 82% of the patients with uveal metastases were already known to have a disseminated malignancy (Timm, 1967; Chu et al., 1977; Saßmannshausen et al., 1990). Most of these patients are described as being in a terminal phase of their disease (Hart, 1962; Gillet, 1971; Röttinger et al., 1979; Daicker, 1981; Castro et al., 1982; Abramson, 1984). Accordingly, uveal metastases are indicative of advanced dissemination of the malignancy (Giri, 1939; Bonnet and Jambon-Genet, 1948; Greear, 1950; Jaensch, 1950; Stevens and Reeh, 1958; Asseman et al., 1964; Casanovas, 1966; Orenstein et al., 1972).

Hemmes (1969) established that patients with a uveal metastasis from breast cancer had a worse prognosis than patients without ocular metastases. He believed that this was due to metastases elsewhere in the body the activity of which was influenced among other things by the presence or absence of uveal metastases. In agreement with Greear (1950) he is therefore of the opinion that a patient with a malignancy should not be subjected to operation of the primary tumour before uveal metastases are excluded.

Of all patients with uveal metastases 43 to 78% die within one year after the ophthalmological diagnosis and 75 to 94% within two years (Table 1.6.2.1). Survival for over two years is exceptional but will become more frequent owing to improved treatment of the primary tumour (Ferry, 1967). Ferry and Font (1974) reported that all patients with metastases in the iris had died within two years after the diagnosis.

Table 1.6.2.1 *Mortality in patients with uveal metastases after ophthalmological diagnosis in terms of percentage*

	Mortality (%)	
Author	after one year	after two years
Ferry and Font, 1974	43	79
Saßmannshausen et al., 1990	50	75
Hemmes, 1969	68	90
Meythaler and Herold, 1979	78	94

The duration of survival after the ophthalmological diagnosis in patients with uveal metastases according to most authors is 7 to 9 months. Some authors report a substantially shorter duration of survival, of 3 months (de Bustros et al., 1985) or a longer survival, of 14 months (Brink et al., 1988) (Table 1.6.2.2).

Table 1.6.2.2 Patient survival after detection of metastases to ocular structures

Author	Number of patients and localization		Survival (months) Mean	Median
de Bustros et al., 1985	9	uvea	3.0	2.4
Ferry and Font, 1975	26	iris en ciliary body	-	5.4
Ferry and Font, 1974	192	eye and orbit	-	7.4
Usher, 1923	90	choroid *	8	-
Meythaler and Herold, 1979	18	choroid	9	-
Orenstein et al., 1972	7	choroid	9.3	9
Brink et al., 1988	49	choroid	14	-

* *survey of the literature*

It is noticeable that in the course of this century the prognosis has failed to improve. The longest duration of survival of a patient with a choroidal metastasis was described by Ferry (1973). It was a male who was originally described by Rosenbluth (1960). In this patient an eye with a metastasis from a carcinoid was enucleated. In spite of metastases elsewhere in the body, the patient was still alive 15 years later. Ferry described another patient, a female, who died 13 years and 2 months after enucleation of an ocular metastasis of breast cancer.

The nature of the primary tumour influences the duration of survival (Table 1.6.2.3). Patients with a metastasis of lung cancer after diagnosis of a uveal metastasis have a mean duration of survival of 5 to 6 months as against 8.5 to as long as 23 months in patients with a metastasis from breast cancer. Stephens and Shields (1979) established that patients with intraocular metastases of a carcinoma of the stomach, pancreas or kidney had a prognosis quoad vitam of 3 to 6 months. The mean duration of survival of patients with a uveal metastasis of a cutaneous melanoma was 2.2 months and that of patients with metastases of an unknown primary tumour 3.7 months. A very poor prognosis was described in patients with a choroidal metastasis of a chorionic epithelioma of the testis. Chitwood (1953) reports a mean duration of survival of these patients of only 5 weeks. Patients with a metastasis from a carcinoid tumour, on the other hand, have a very favourable prognosis (Rodrigues and Shields, 1978). In general, the median duration of survival of patients with uveal metastases is markedly shorter than the mean duration of survival.

Table 1.6.2.3 *Patient survival after detection of metastases to ocular structures of breast or lung cancer*

Author	Number of patients and localization		Survival (months) Mean	Median
Breast cancer:				
Merriam, 1961	20	choroid	8.5	-
Dickson, 1958	7	choroid	10	-
Hart, 1962	25	eye and orbit	10	-
Maor et al., 1977	42	choroid	-	10
Freedman and Folk, 1987	28	choroid	-	10.5
Meur et al., 1974	5	choroid	13	9
Stephens and Shields, 1979	29	uvea	13.4	8
Letson et al., 1982	8	choroid	23	15
Lungcancer:				
Stephens and Shields, 1979	10	uvea	5.2	3.3
Hart, 1962	28	eye and orbit	6	-
Gartner, 1985		not stated	6	-

Freedman and Folk (1987) established in patients with a choroidal metastasis a longer median duration of survival for those with stage I or II breast cancer than for those with stage III or IV breast cancer. Older patients had a better prognosis than younger ones. The median duration of survival of patients with an orbital metastasis was significantly better than with choroidal metastases, independently of the stage of the breast cancer. However, patients with orbital metastases were mostly older. After correction for age, there was no longer a statistical difference in duration of survival between patients with choroidal or with orbital metastases.

Hemmes (1969) was of the opinion that patients with bilateral uveal metastases of breast cancer had a longer duration of survival than patients with unilateral metastases. According to Stevens and Reeh (1958), however, the reverse was true.

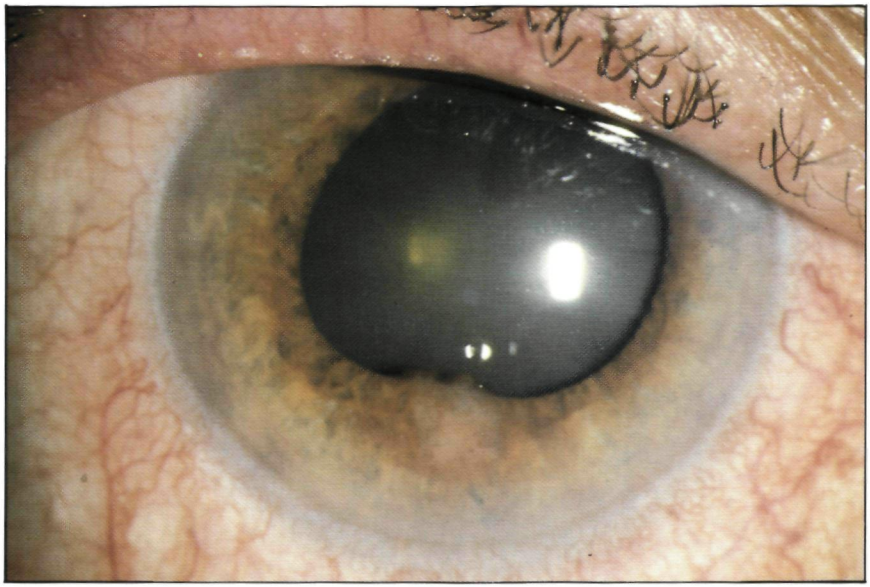
Enucleation of an eye with a uveal metastasis allegedly has an adverse influence on the patient's prognosis quoad vitam (Hemmes, 1969).

The interval between the diagnosis of the primary tumour and the detection of the uveal metastasis does not influence the duration of survival of the patient (Stephens and Shields, 1979).

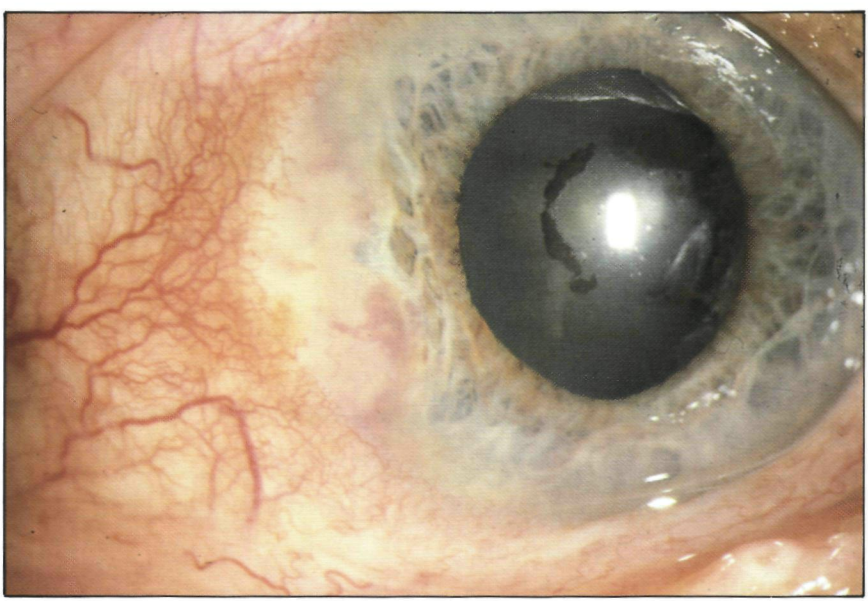
If a patient is irradiated for the intraocular metastasis and is not treated by means of chemotherapy, this allegedly does not influence the duration of survival (Letson et al., 1982).

Possibly, some relationship exists between the duration of survival and the localization of the uveal metastasis. Ferry and Font (1975) in patients with a metastasis in the posterior segment reported a median duration of survival of 7.2 months as against 5.4 months for patients with anterior segment metastases. De Bustros et al. (1985) also report a shorter duration of survival for patients with iris metastases.

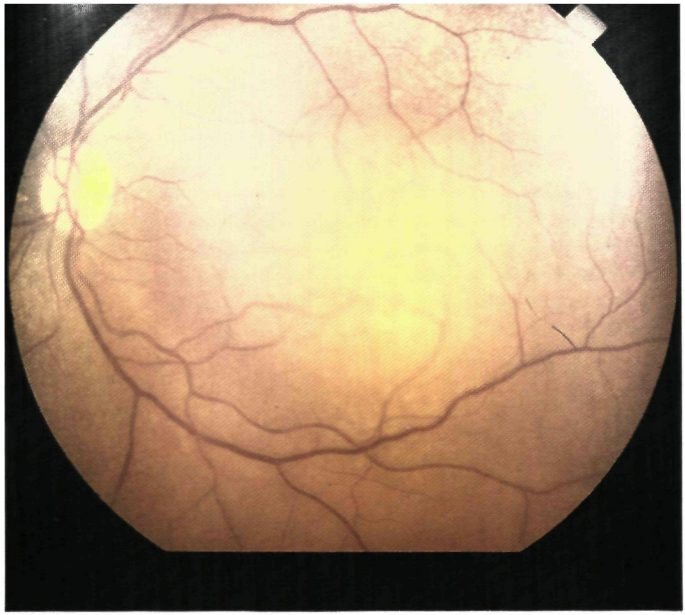
Colour plates



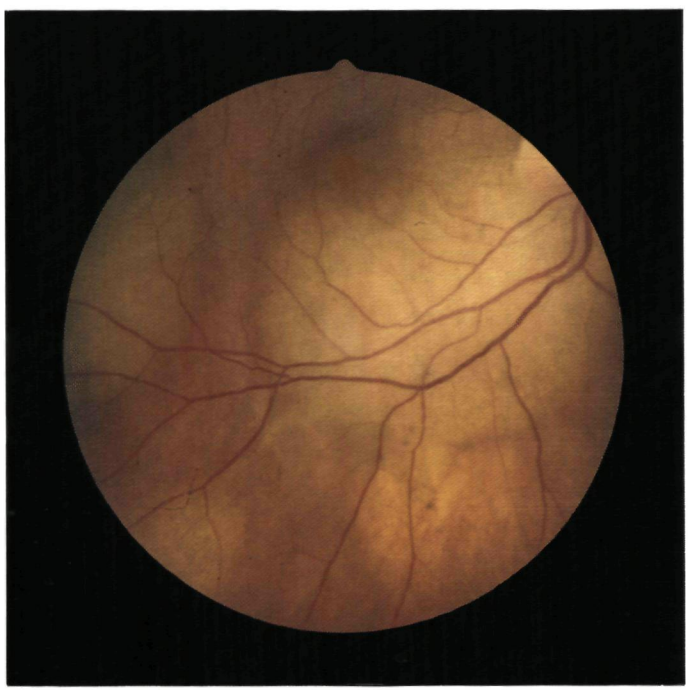
Colour plate 1. External photograph of a grey-coloured slightly elevated iridal metastasis from lung cancer in a painful right eye. Note the hyperaemia of the conjunctiva. At ophthalmoscopy a choroidal metastasis was observed as well.



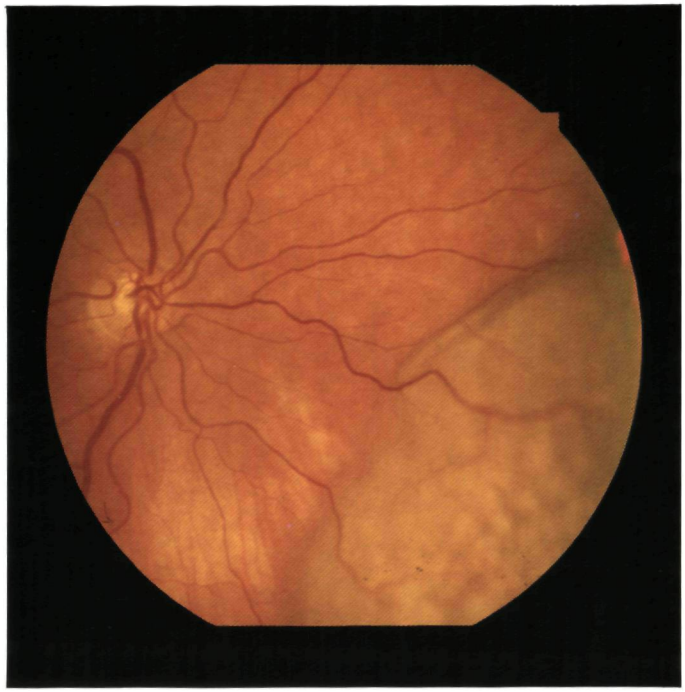
Colour plate 2. External photograph of a ciliary tumour in the right eye which has broken through the iris. One month after diagnosis of an iridocyclitis a glassy white-coloured iridal tumour was observed. Ten days later a pulmonary carcinoma was diagnosed. Note the dilated episcleral vessels and the pigment coating on the lens. Clinical diagnosis: ciliary metastasis.



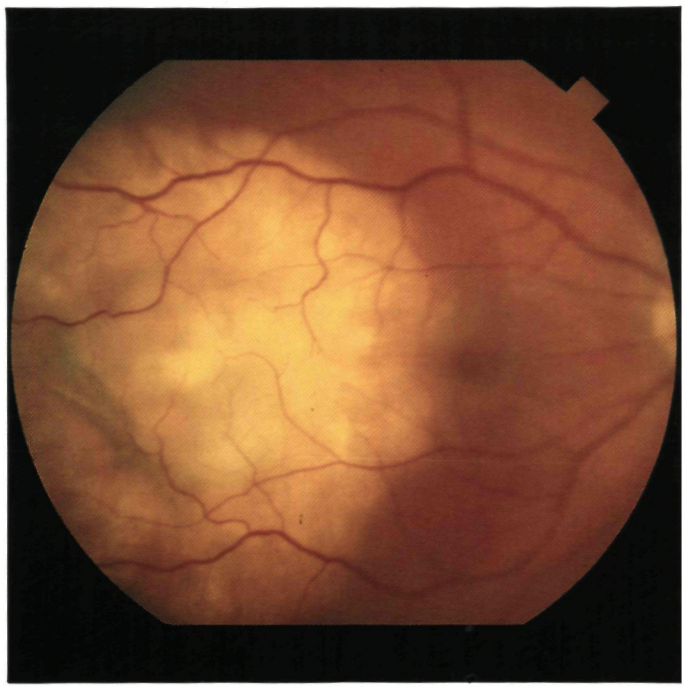
Colour plate 3. Fundus photograph of a yellowish-orange choroidal metastasis in the posterior pole of the left eye in a patient with breast cancer.



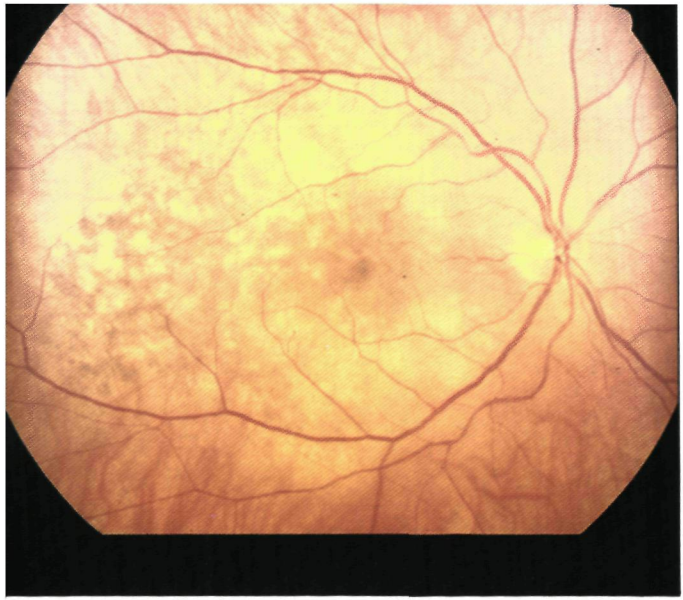
Colour plate 4. Fundus photograph of the right eye of a patient with breast cancer showing three cream-coloured choroidal metastases.



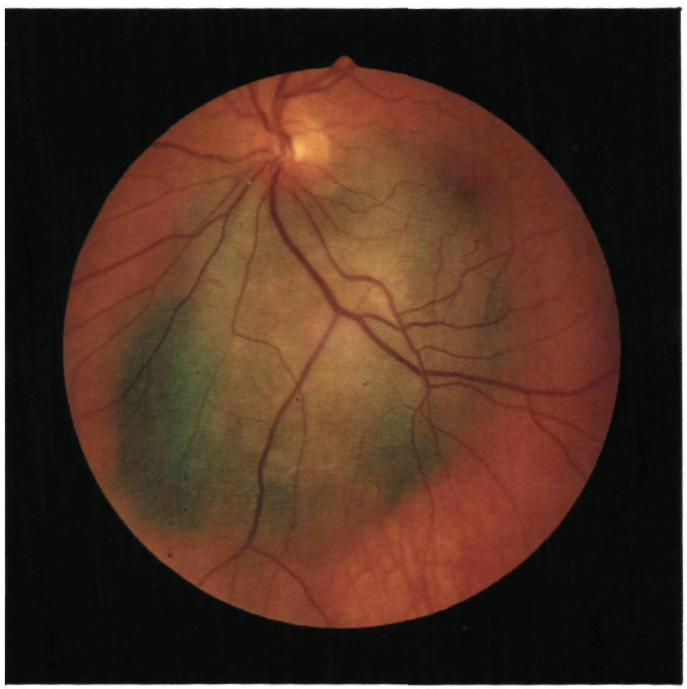
Colour plate 5. Fundus photograph of the left eye showing a yellowish-grey choroidal metastasis with a mottled appearance, originating from breast cancer.



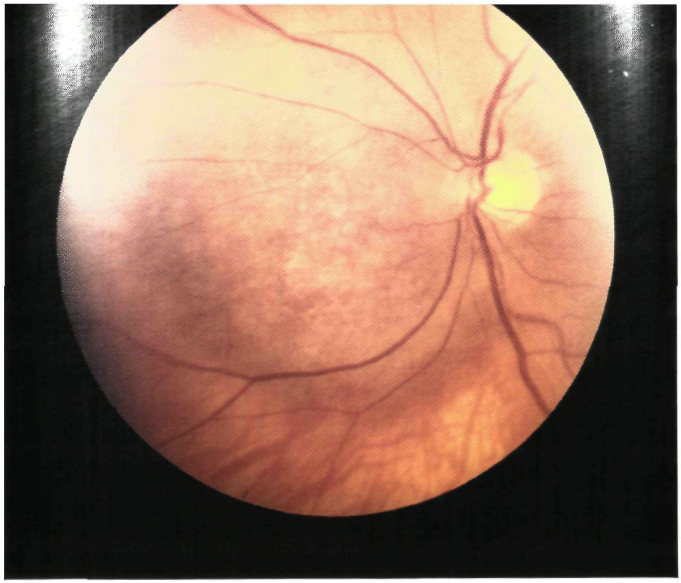
Colour plate 6. Fundus photograph of the right eye showing a yellowish-white choroidal metastasis temporal of the macular area originating from lung cancer.



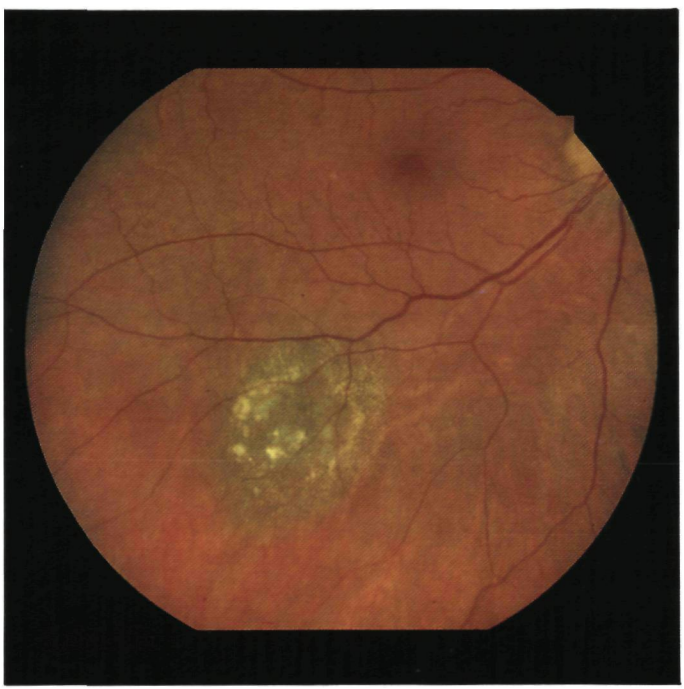
Colour plate 7. Fundus photograph of a yellowish-orange slightly elevated choroidal metastasis with a mottled brownish pigmentation in the right eye in a patient with breast cancer.



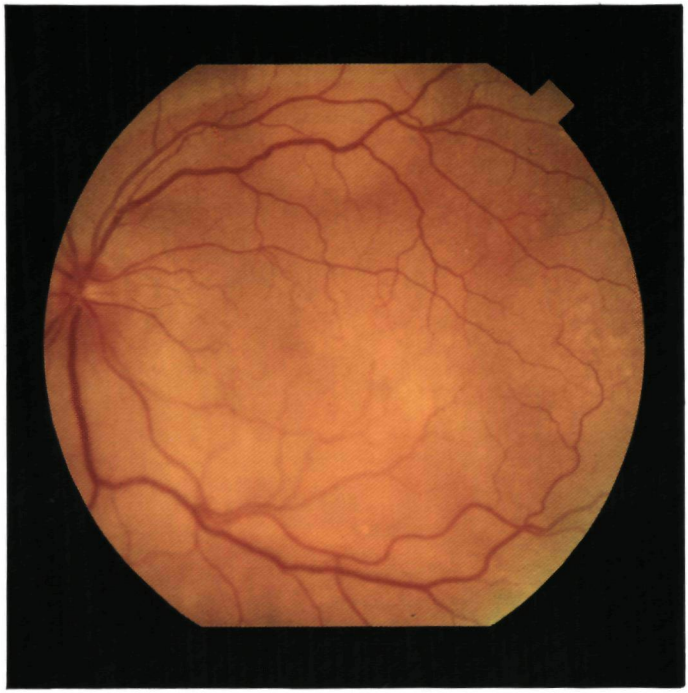
Colour plate 8. Fundus photograph of a predominantly grey-coloured malignant melanoma in the left eye with areas of orange pigment on the tumour surface.



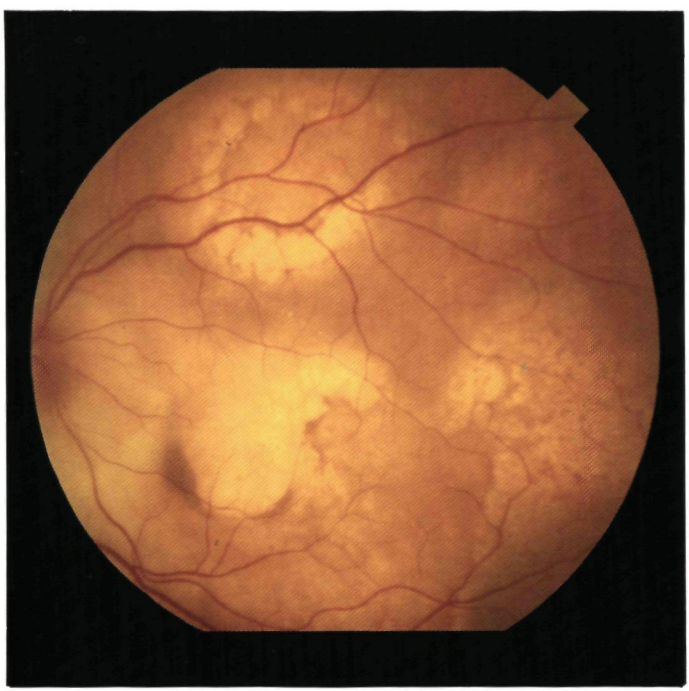
Colour plate 9. Fundus photograph of a salmon-pink choroidal haemangioma located nasally to the optic disk in the left eye.



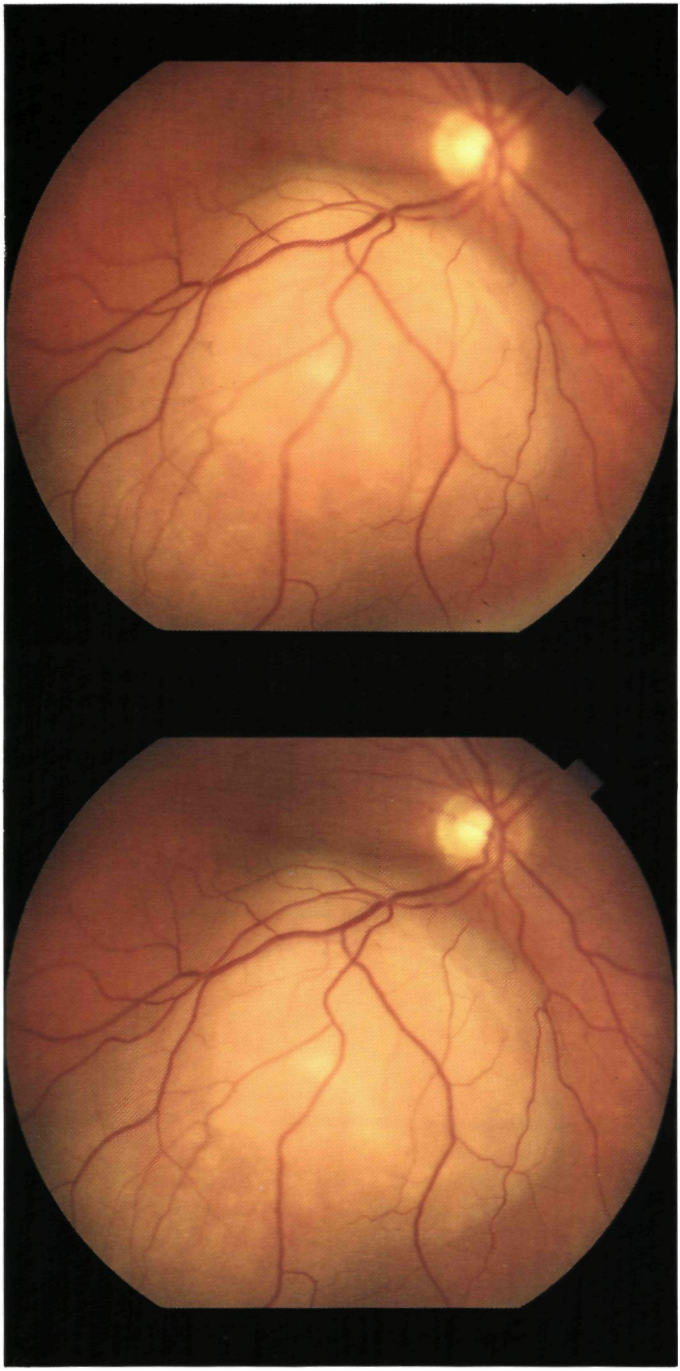
Colour plate 10. Fundus photograph of a grey-coloured choroidal naevus with multiple drusen in the right eye.



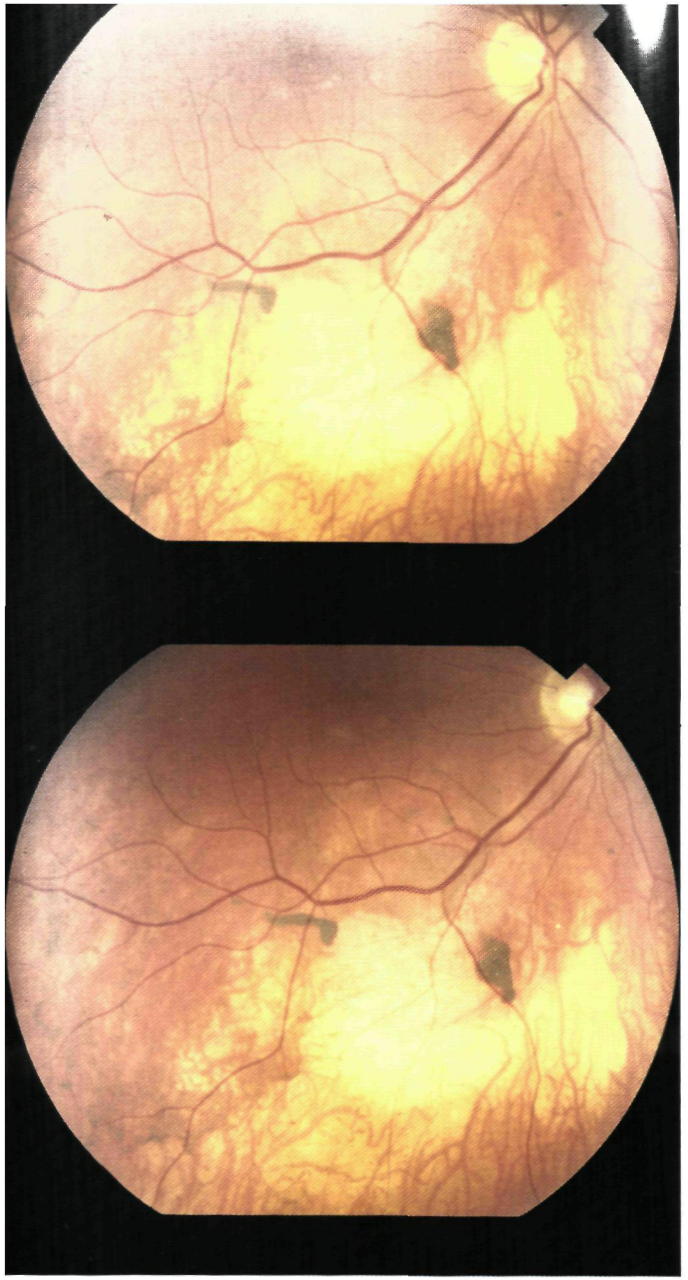
Colour plate 11. Fundus photograph of three yellowish-cream coloured choroidal metastases from breast cancer in the left eye one week before radiotherapy. Visual acuity: 0.4. Visual acuity in the right eye with two choroidal metastases: 1.0.



Colour plate 12. Fundus photograph of the same eye as colour plate 11, four months after start of radiotherapy: in the superiorly and temporally located metastases a positive reaction was observed. However, the inferiorly located metastasis had increased in size round the optic disk and the macula. Visual acuity: 2/60. Visual acuity in the irradiated right eye: 1.0.



Colour plate 13. Stereo fundus photographs of a predominantly cream-coloured choroidal metastasis in the right eye from a seminoma (with elements of teratoma) of the testis, one week before radiotherapy. Visual acuity: 0.8.



Colour plate 14. Stereo fundus photograph of the same eye as colour plate 13, eight weeks after radiotherapy showing disappearance of the tumour resulting in an atrophic, partly pigmented scar. Visual acuity: 0.8.

Part 2
Retrospective study

2.1 Aims of the study and study design

2.1.1 Aims of the study

By collecting and processing all available demographic, anamnestic, diagnostic and therapeutic data on patients with uveal metastases known in the Ophthalmological Clinic of Nijmegen University Hospital, it is attempted to obtain as detailed as possible a clinical picture of this condition. The first objective is to establish in this manner which tumours metastasize to the uvea, and consider what the diagnosis of uveal metastases means for the patient's prognosis quoad vitam.

Differentiation of uveal metastases from other intraocular tumours is highly important. Regularly, in a patient with an intraocular lesion with suspicion of a tumour, no primary tumour elsewhere in the body is known. Conversely, the presence of such a primary malignancy does not exclude the presence of a melanoma or haemangioma in the eye. Furthermore, frequently lesions are encountered in which the various diagnostic techniques give no uniform results. Evaluation of these diagnostic possibilities is therefore important. Differentiation of uveal metastases from other intraocular tumours evidently has considerable consequences. If the tumour is found to be a metastasis of a malignancy already known elsewhere in the body, this indicates dissemination of the tumour which has substantial therapeutic and prognostic consequences. If, on the other hand, no malignancy is known and the ophthalmological findings are nevertheless strongly suspicious of an intraocular metastasis, extensive examination will as a rule be performed in order to discover a primary tumour. Since the various intraocular tumours require also different methods of treatment, an accurate differential diagnosis of these lesions is of major importance.

The last objective of this retrospective study is evaluation of the treatment. Patients with a malignancy carry a heavy burden in any case. The life expectation is limited. Preservation of visual acuity is therefore of great importance for an optimal quality of life.

To sum up, the objectives of this retrospective study are:

- to determine the nature of the primary tumours metastatic to the uvea and the meaning of these metastases for the prognosis;
- to relay a detailed description of the results of the various examination techniques in uveal metastases and their contribution to the diagnostics;
- to define the differential-diagnostic features of uveal metastases;
- to evaluate the methods of treatment applied in uveal metastases.

2.1.2 Study design

The Ophthalmological Clinic of Nijmegen University Hospital is, owing in particular to echographic experience and skill, a regional and extraregional centre to which a relatively large number of patients with suspicion of malignant intraocular tumours are referred.

For about 25 years now the findings in patients with an intraocular tumour have

been recorded photographically. The pictures in question are fundus, slit lamp and external photographs and fluorescence angiograms. The conditions are coded according to the probability diagnosis at initial examination which occasionally is adjusted later.

The patients of this retrospective study were collected through the coding systems of the department of photography, echography and electrophysiology. Also, the protocols of histologically examined eyes were searched for patients with intraocular tumours. The latter yielded no new patients.

In this part we shall constantly speak of *patients* with intraocular tumours rather than of *eyes*. Firstly, because the objective is to examine, and to attempt to treat patients. Also, because it is statistically more correct to consider patients rather than isolated eyes.

Uveal metastases frequently occur bilaterally. In patients with metastases in both eyes, reference will be made to the findings in the eye containing the first-detected metastasis. If metastases were detected in both eyes simultaneously, the reference is to be the right eye since habitually an ophthalmologist examines first the right and then the left eye. Information on the other affected eye of the same patient will be given only if this is essential for the discussion of the results of this retrospective study.

The study covers a period of 20 years, from 14 November 1970 to 14 November 1990, for which period data on 769 patients with suspicion of an intraocular malignancy were retrieved. Of seven patients, only ophthalmoscopical photographs were available, further information being lacking. Three of these patients were coded as choroidal melanoma three as choroidal metastasis and one as choroidal tumour. These seven patients were excluded from the study because of the absence of virtually all relevant data. The study material therefore ultimately consisted of 762 patients. Table 2.1.2.1 lists the percentages of the patients with suspicion of an intraocular tumour who were retrieved from the various archives; some overlapping is possible.

Table 2.1.2.1 *Origin of 762 patients with suspicion of an intraocular tumour according to the different archives* *

Archive	N	%
Photography	377	49
Fluorescein angiography	493	65
Echography	690	91
Electrophysiology	208	27
Histopathology	324	43

** total % exceeds 100 because of overlap of different archives*

On average, 38 new patients with suspicion of an intraocular tumour were examined per year. This number showed a substantial tendency to increase from only a few patients in the first few years of the study to over 70 patients per year from 1987.

In 324 patients (43%) the diagnosis was confirmed histopathologically. On 438 patients (57%) only clinical data were available, however. The diagnosis was then made

on the basis of the case history, the clinical features, the results of the various supplementary examinations and the course of the condition, using the criteria applied in literature and described in the first part of this dissertation.

That the differential diagnosis of intraocular tumours may sometimes be very difficult appears from the fact that in the literature several patients are described in whom an eye was enucleated under the false diagnosis of 'malignant melanoma'. At histopathological examination the eye proved to contain a metastasis (Ferry, 1973; Jarrett, 1976; Ossoinig and Harrie, 1983). Therefore, the clinical diagnosis unfortunately is not correct in all cases. This might be an important item of criticism on this study since in a substantial part of our patients the affected eye was not available for histological examination.

All available data on the 762 patients with suspicion of an intraocular malignancy were collected. When important data, such as the results of histopathological examinations, were lacking, an attempt was made to retrieve them from the family doctor or referring ophthalmologist. A maximum of information was gathered on the follow-up of patients with intraocular tumours in as far as these patients were not followed up in our own clinic. This was done in any case in all patients whose definite diagnoses were not known

On the basis of these data the patients were subdivided into the following seven groups: uveal metastases, malignant uveal melanomas, uveal haemangiomas, uveal naevi, retinoblastomas, miscellaneous intraocular conditions and lesions of unknown nature (Table 2.1.2.2).

Table 2.1.2.2 Diagnosis in 762 patients with suspicion of an intraocular tumour

Diagnosis	N	%
Uveal metastasis	87	11 4
Malignant uveal melanoma	422	55 4
Uveal haemangioma	27	3 5
Uveal naevus	60	7 9
Retinoblastoma	25	3 3
Miscellaneous intraocular tumours *	53	7 0
Lesions of unknown nature	88	11 5

** see Table 2 1 2 3*

The group 'miscellaneous intraocular conditions' includes apart from a number of tumours and lymphoproliferative diseases also benign conditions such as subretinal neovascularizations and haemorrhages, detachments of retina, pigment epithelium and choroid and patients with inflammatory lesions originally believed to be malignant intraocular tumours (Table 2.1.2.3).

Table 2.1.2.3 Diagnosis in 53 patients with 'miscellaneous intraocular disorders'

Diagnosis	N	%
Leukaemia	4	8
Lymphoma	1	2
Leiomyoma	3	6
Adenoma of the non-pigmented ciliary epithelium	1	2
Medulloepithelioma	1	2
Retinal angioma	2	4
Osteoma	1	2
Melanocytoma	1	2
Hamartoma	1	2
Iris cyst	1	2
Choroidal detachment	5	9
Retinal detachment	3	6
Detachment of the retinal pigment epithelium	2	4
Subretinal haemorrhage	9	17
Neovascularization *	8	15
Benign reactive lymphoid hyperplasia	2	4
Juvenile xanthogranuloma	2	4
Posterior scleritis	1	2
Tuberculoma	1	2
Toxocariasis	1	2
Cryptococcosis	1	2
Vortex vein	1	2
Alterations of pigment epithelium after trauma	1	2

* *Kuhnt Junius N=7*

The group of 88 patients with 'lesions of unknown nature' could not be further differentiated for the following reasons:

- 36 patients (41%): examined only once, no follow-up and no characteristic picture;
- 12 patients (14%): with follow-up of 3 months or shorter, without a characteristic picture;
- 8 patients (9%): followed up for 3 to 6 months without characteristic picture;
- 14 patients (16%): flat pigmented lesion without growth which at follow-up did not appear suspicious for a malignancy;
- 5 patients (6%): died before a diagnosis could be made;
- 4 patients (5%): iris lesion without growth at observation;
- 9 patients (10%): diagnosis unknown in spite of follow-up of longer than 6 months without one of the above reasons being involved.

The data on all 762 patients with suspicion of an intraocular tumour were subdivided and coded according to:

- general data (age, sex, etc.)
- signs and symptoms
- ophthalmological examination, including optometry, slit lamp examination and tonometry
- ophthalmoscopy
- echography
- fluorescein angiography
- other examination techniques
- histopathological data
- course and follow-up (including metastasization and mortality)
- treatment.

Using this material, patients with uveal metastases were studied and the data compared with those on the other patients with intraocular tumours.

In the following chapters these data will be described in detail. With a view to the differential diagnostics, the other patient material will also be concisely discussed.

With the aid of these data a survey is presented of the diagnostic and differential-diagnostic features of uveal metastases.

2.2 Epidemiology

2.2.1 Number of new patients

In the Ophthalmological Clinic of Nijmegen University Hospital in the period from 14 November 1970 to 14 November 1990, a total of 87 patients with uveal metastases were examined, an average of 4.4 patients per year. Incidence figures of uveal metastases could not be calculated for lack of a single distinctly defined patient population from whom the patients with uveal metastases examined derived. We can only refer to the frequency of observation of this condition in our clinic.

Table 2.2.1.1 *Number of patients with suspicion of an intraocular tumour in the Ophthalmological Clinic of Nijmegen University Hospital per year*

Year	Uveal metastases	Uveal melanomas	Total number of lesions with suspicion of an intraocular tumour
1970 *	0	4	9
1970 **	0	1	1
1971	0	0	2
1972	0	2	5
1973	1	3	5
1974	2	3	10
1975	4	10	21
1976	4	16	26
1977	2	15	27
1978	4	20	31
1979	6	29	46
1980	5	36	50
1981	6	17	31
1982	7	14	31
1983	2	21	36
1984	7	20	36
1985	2	24	42
1986	6	23	38
1987	6	46	75
1988	11	53	92
1989	5	38	75
1990 ***	7	27	73
Total	87	422	762

** patients with suspicion of tumour before 14 November 1970, but referral after that date; ** from 14 November 1970; *** until 14 November 1990*

Uveal metastases account for 11.4% of all patients examined with suspicion of an intraocular tumour. Malignant melanomas of the uvea were diagnosed five times as often. Table 2.2.1.1 presents a survey of the number of new patients with uveal metastases in the past 20 years. This table also lists the number of patients with uveal melanomas and the total number of patients with suspicion of an intraocular tumour. The number of patients, although subject to fluctuations, has increased during this period (see also Figure 2.2.2.1). It should be mentioned that in March 1989 a prospective search for uveal metastases in patients with breast cancer was started. Where this retrospective study is concerned, this fact may have exerted some negative influence on the number of patients with intraocular metastases examined since March 1989. An occasional patient who otherwise would have been referred by the department of Internal Medicine for suspicion of a metastasis may have been enrolled in the prospective study.

According to the literature (see Chapter 1.3.1), uveal metastases account for 2 to 9% of all intraocular tumours. Compared with this, the proportion of 11.4% reported in this study is large. It should be noted in this connection that the percentages of occurrence mentioned in the literature vary greatly, that the patient populations are frequently described incompletely and that many older publications and histopathological examinations are included. The number of patients with uveal metastases in our study is related to a patient population with suspicion of an intraocular tumour in which naevi, subretinal haemorrhages, neovascularizations, etcetera have also been included, as well as lesions of unknown nature. Had these conditions not been included, the proportion of metastases in relation to all intraocular tumours would have been even higher, namely 15%.

2.2.2 Primary tumours

As was to be expected on the basis of the literature, most uveal metastases in our study originated from breast cancer, viz. in 52 of the 87 patients (60%). The second most frequently diagnosed primary malignancy was lung cancer (20 patients: 23%) (Table 2.2.2.1).

Of the lung tumours, six were defined as small cell anaplastic carcinoma, three as large cell anaplastic carcinoma, four as squamous cell carcinoma and three as adenocarcinoma (four pulmonary tumours classification unknown).

Two patients were observed with a metastasis of a thyroid carcinoma (one follicular and one anaplastic), two of a pancreatic carcinoma, one of a testicular tumour (moderately to poorly differentiated seminoma with areas of teratoma), one of a prostatic carcinoma, one of a transitional cell carcinoma of the bladder, one of a clear-cell carcinoma of the kidney (Grawitz tumour), two of an adenocarcinoma probably originating from the colon and five patients in whom the primary tumour had not been determined. Among the last-mentioned five patients with uveal metastases there were four with an adenocarcinoma of unknown origin, in three of whom histological confirmation of the uveal metastasis was obtained.

Table 2.2.2.1 Localization primary tumour in 87 patients with uveal metastases

Localization	Total		Females		Males	
primary tumour	N	%	N	%	N	%
Breast	52	60	52	80	-	-
Lung	20	23	6	9	14	64
Pancreas	2	2	1	2	1	5
Thyroid	2	2	2	3	-	-
Kidney	1	1	-	-	1	5
Bladder	1	1	-	-	1	5
Prostate	1	1	-	-	1	5
Testis	1	1	-	-	1	5
Probably colon	2	2	1	2	1	5
Unknown	5	6	3	5	2	9
Total	87		65		22	

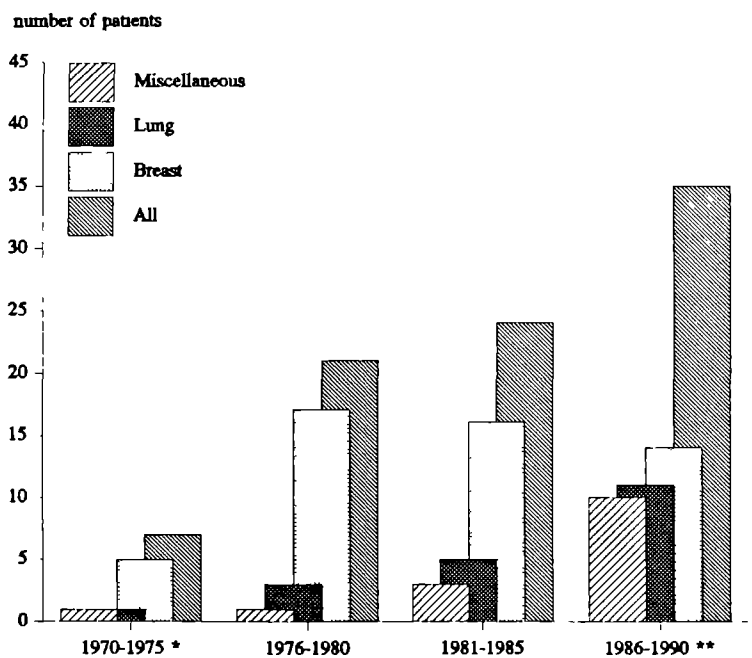


*Figure 2.2.2.1 Number of patients with uveal metastases according to the localization of the primary tumour per year; * from 14 November 1970; ** until 14 November 1990*

According to literature data, uveal metastases detected clinically are secondary to breast cancer in 72% of the cases and to lung cancer in 12% (see Table 1.3.2.4). In our study metastases were found to derive from breast cancer relatively less often than in the literature, and more frequently from lung cancer. However, the present study covers a more recent period than other major survey articles hitherto published. It is known that the incidence of lung cancer has increased markedly whereas that of breast cancer has remained stable (Silverberg et al., 1990). This may have affected the ratio of incidence of uveal metastases originated from these tumours. In our patient material, the number of patients with uveal metastases from lung cancer has indeed increased, as has the number of metastases from the miscellaneous primary tumours. With the exception of the first five-year period, during which only few uveal metastases were diagnosed, the number of metastases from breast cancer has remained at approximately the same level (Figure 2.2.2.1).

In our group of patients, uveal metastases were diagnosed in 66 patients (76%) at a time when a primary malignancy was already known. The mean interval between the primary tumour and the ocular metastasis was 47 months (SD 43; median 32), ranging from 8 days to 14 years (Tables 2.2.2.2 and 2.2.2.3). In patients with a metastasis from breast cancer this interval was 56 months on average (SD 43; median 46 months; range 5 weeks to 14 years), while in patients with lung cancer it was only 14 months (SD 21; median 6 months; range 8 days to 5.3 years).

Table 2.2.2.2 *Relationship between time of diagnosis of primary tumour and time of diagnosis of uveal metastasis*

	Primary tumour detected first		Uveal metastasis detected first	
Localization primary tumour	N	%	N	%
Breast	51	98	1	2
Lung	9	45	* 11	55
Other	6	40	9	60
Thyroid	2		-	
Pancreas	1		1	
Testis	1		-	
Prostate	-		1	
Bladder	1		-	
Kidney	-		1	
Adenocarcinoma, probably colon	1		1	
Unknown	-		5	
Total	66	76	21	24

** in one patient pulmonary tumour and uveal metastasis diagnosed on the same day*

The mean interval between the detection of the primary tumour and the detection of the uveal metastases, as established in the patients of our study, is in accordance with data in the literature in which a mean interval of 42 to 43 months is reported (Schiffer et al.,

1978; Stephens and Shields, 1979).

It was in only 14% of the patients with breast cancer that uveal metastases were diagnosed within one year after the detection of the primary tumour. In five patients (10%) this interval was longer than 10 years with a maximum of 14 years. In patients with lung cancer, on the other hand, the uveal metastasis was discovered within one year after the detection of the primary tumour in 67%.

The mean interval between primary tumour and uveal metastasis was substantially longer in patients with breast cancer than in patients with metastases of lung cancer or of other primary tumours (Table 2.2.2.3).

Table 2.2.2.3 Interval between diagnosis of primary tumour and diagnosis of uveal metastasis

Primary tumour	Number of patients	Interval (months) Mean	SD	Median	Range
Primary tumour diagnosed **before** ***uveal metastasis:***					
Breast	* 49	56	43	45.9	1.2-169.5
Lung	# 9	14	21	5.8	0.3-64.9
Other	6	21	19	18.3	1.5-55.6
Total	* 64	47	43	32.5	0.3-169.5
Primary tumour diagnosed **after** ***uveal metastasis:***					
Breast	1	1	-	-	-
Lung	# 10	1	2	0.6	0.2-8.1
Other	** 3	3	4	1.3	1.0-7.8
Total	** 14	2	3	1.0	0.2-8.1

** of the 51 patients with breast cancer: two patients with unknown interval not included; ** of the nine patients with miscellaneous primary tumours: five patients with unknown primary tumours and one patient with suspicion of a colonic carcinoma after diagnosis of intraocular tumour not included; # in one patient pulmonary tumour and uveal metastasis diagnosed on the same day*

Not in all cases did uveal metastases follow a malignancy that was already known. In seven of the 87 patients (8%) the primary tumour even was not detected at all, in spite of extensive examinations. In two patients, the metastasis probably originated from a colonic carcinoma while metastases elsewhere in the body were known as well. In one of these two patients presence of a colonic carcinoma was already suspected before the intraocular tumour was discovered. In five other patients no primary malignancy could be found. In three of these patients, histological data of the intraocular tumour were obtained. In the first patient an eye was enucleated under the diagnosis of 'malignant choroidal melanoma'. At histopathological examination it proved to be a metastasis of a moderately differentiated adenocarcinoma. In a second patient, enucleation was performed because of total loss of the function of the eye. Histological examination revealed a metastasis of an adenocarcinoma with extrascleral spread. In a third patient, enucleation was decided upon

because the eye was blind and painful. Histological examination revealed a metastasis of an adenocarcinoma. In the two other patients with metastases of unknown localization, metastases elsewhere in the body developed after the ophthalmological diagnosis and the patients' general condition deteriorated very fast.

In 14 patients, no malignancy was known at the time of the diagnosis of the uveal metastasis, but a primary tumour was discovered later, after a mean interval of 8 weeks (median 4; range 6 days to 8 months). The primary tumours were a lung carcinoma in 10 patients, and a breast carcinoma, a pancreatic carcinoma, a prostatic carcinoma and a clear-cell carcinoma of the kidney in one patient each. The length of this interval naturally depends greatly on how, and how quickly, diagnostic examinations for detection of a primary tumour are performed. In none of these cases were metastases elsewhere in the body known at that time.

A uveal metastasis was discovered before a malignancy elsewhere in the body was known in a total of 20 patients (23%) which proportion agrees with literature data.

In one patient, finally, the uveal metastasis was established on the same day that lung cancer was diagnosed.

To be noted is the large proportion (55%) of patients with lung cancer in whom the tumour was diagnosed simultaneously with (one patient) or after the detection (10 patients) of an intraocular tumour. This is known from the literature as well (see Table 1.3.2.9). In the 10 patients in whom the uveal metastasis preceded the pulmonary tumour, lung cancer was detected 6 weeks on average after the finding of the uveal metastasis, ranging from 6 days to 8 months. The median was only 17 days, however. In eight of the ten patients the pulmonary tumour was detected within one month after the uveal metastasis. Besides, in four of nine other patients in whom the diagnosis of the primary tumour preceded the diagnosis of the intraocular metastasis, the pulmonary tumour had been known for less than one month before the ophthalmological diagnosis.

In only one patient with breast cancer was the uveal metastasis detected before the primary tumour.

Over one-half of all patients in whom a uveal metastasis is determined before a primary tumour is known therefore prove to have lung cancer. The probability of breast cancer is very low in such cases.

2.2.3 Connection with metastases elsewhere in the body

If a malignancy is suspected, specific roentgenological examination of the chest is practically always carried out. A search for cerebral metastases, on the other hand, is usually performed only if there are clinical indications of cerebral dissemination. In spite of specific examinations, existing metastases in some cases may fail to be diagnosed, for instance because they are too small for the examination techniques available. The clinical description of metastases elsewhere in the body in patients with uveal metastases is limited to the known diagnosed metastases.

In our study, in 44 patients with uveal metastases (51%) metastases elsewhere in the body were also known at the time of the ophthalmological diagnosis. In 36 patients

(41%), on the other hand, the uveal metastasis was the first sign of dissemination. Of the other seven patients (8%), no data concerning metastasization in the period before the detection of the uveal tumour were available.

In 20 patients with uveal metastases the primary tumour was detected only after the diagnosis of the intraocular tumour. In these patients at that moment no metastases elsewhere in the body were known. In 15 of the 66 patients (23%) with uveal metastases in whom a primary tumour was already known before diagnosis of the ophthalmological lesion, the uveal metastasis was the first sign of dissemination, while in 45 patients (68%) metastases elsewhere were already known [in six patients (9%) no data on metastasization before the ophthalmological diagnosis were available].

Uveal metastases therefore frequently were the first sign of dissemination in contrast to what was reported by, among others, Guthert et al. (1965), Meur et al. (1974) and Nelson et al. (1983). Saßmannshausen et al. (1990) observed metastases elsewhere in the body in 60% and Timm (1967) in 82% of the patients. In our study group, however, this was the case in less than 50% of all patients.

After the detection of the uveal metastasis, metastases elsewhere in the body were established in 61 patients (70%). In three patients (3%) this was not the case [23 patients (26%) unknown].

Pulmonary metastases allegedly precede uveal metastases in nearly all cases, because tumour emboli have to pass through the lungs before they can reach the uvea (Ferry, 1967; Gillet, 1971; François et al., 1976). However, in our study group pulmonary metastases were described in only 27 patients (31%). In 20 patients these were diagnosed before the uveal metastasis (average 9 months; median 1; range 2 days - 50 months). In seven patients, the pulmonary metastases were searched for and detected after the finding of intraocular metastases (on average after 19 months; median 21, range 1-38). If pulmonary metastases were discovered, this occurred in 16 of the 27 patients (59%) within a period of one year before or one year after the detection of the uveal metastases, and in 85% within a period of two years. This means that in only 18% of all patients with uveal metastases pulmonary metastases were known in a period of one year, and in 26% in a period of two years before or after the date of the ophthalmological diagnosis. It appears, therefore, that in the patients of our study there was no connection between pulmonary and uveal metastases. The finding of Mewis and Young (1982) that pulmonary metastases were known in 60% of patients with breast cancer therefore is not in agreement with the proportion of 35% in our study.

Considering the blood supply of the eye and the brain, a relationship between uveal and cerebral metastases might be expected (Allen, 1968; Jensen, 1970; Abramson, 1980).

In our study group, cerebral metastases were known in 15 of the 87 patients with uveal metastases (17%): 12 times before and 3 times after the ophthalmological diagnosis. If cerebral metastases occurred before the uveal metastases, this was on average 6 months earlier (median 4; range 3 days to 18 months). If cerebral metastases were detected only after the diagnosis of the uveal metastases, the average interval was 22 months (median 7; range 3 to 56). Twelve of the 15 cerebral metastases (80%) developed within one year before or one year after detection of the intraocular tumour and 93% within two years. Therefore, a cerebral metastasis was diagnosed in 14% of all patients with uveal metastases within a period of one year, and in 16% within a period of two years before or

after the diagnosis of the uveal metastasis. So, where cerebral metastases are concerned, no distinct relation with uveal metastases existed, either.

Thatcher and Thomas (1975) reported cerebral metastases in 12% of the patients with a uveal metastasis of breast cancer. Mewis and Young (1982) on the other hand, encountered metastases in brain, spinal cord or meninges in 45% of the patients and concluded that metastases in the central nervous system appeared to manifest themselves at the same time as metastases in the uvea. However, cerebral metastases were known in only 13% of our patients with a uveal metastasis of breast cancer.

The occurrence of pulmonary and cerebral metastases in relation to uveal metastases therefore has to be considered in a more general connection: development of uveal metastases is a sign of dissemination of the primary tumour which may give rise to metastases elsewhere in the body, as well, depending on the pattern of metastasization of the malignancy in question. In our patient material, no other clear relationship of the intraocular metastases with metastases in lungs or brain was demonstrable. However, metastatic cells have to break through the blood-brain barrier to reach the brain. For uveal metastases no such barrier exists.

2.2.4 Demography

Of the 87 patients with uveal metastases, 65 (75%) were of the female and 22 (25%) of the male **sex** (Table 2.2.4.1). The fact that breast cancer so often is the primary tumour is an important cause of this sex distribution, which is in accordance with the results of clinical studies of other authors in which 70 to 85% of the patients with uveal metastases are of the female sex (see Table 1.3.3.1).

The mean ***age*** of patients with uveal metastases was 57 years, with a median of 58 years. The youngest patient was a male aged 27 years with a testicular carcinoma, the oldest a male aged 80 years with a clear-cell carcinoma of the kidney (Table 2.2.4.1).

Literature data indicate a mean age of patients with uveal metastases between 50 and 57 years. For patients with breast cancer this mean age is 49 to 61 years and for patients with lung cancer, 51 to 55 years (see Table 1.3.4.2).

The age distribution of patients with uveal metastases in our retrospective study reached a peak in the 7th decade (between 60 and 69 years). Of all patients, 89% were between 40 and 79 years old.

All patients in our study had Dutch nationality and were of the Caucasian ***race***.

Table 2.2.4.1 *Age of patients with uveal metastases from different primary tumours in years*

	Total					Female					Male				
Primary tumour	N	Mean	SD	Median	Range	N	Mean	SD	Median	Range	N	Mean	SD	Median	Range
Total	87	57	13	58	27-80	65	56	12	58	29-79	22	60	13	62	27-80
Breast	52	56	11	56	35-79	52	56	11	56	35-79	-	-	-	-	-
Lung	20	60	12	61	29-76	6	55	16	57	29-72	14	62	10	65	38-76
Other	15	59	16	59	27-80	7	61	17	64	33-77	8	57	16	58	27-80
Pancreas	2	55			42-68	1	42			-	1	68			-
Thyroid	2	72			70-74	2	72			70-74	-	-			-
Kidney	1	80			-	-	-			-	1	80			-
Bladder	1	67			-	-	-			-	1	67			-
Prostate	1	46			-	-	-			-	1	46			-
Testis	1	27			-	-	-			-	1	27			-
Probably colon	2	67			60-74	1	74			-	1	60			-
Unknown	5	55	16	55	33-77	3	56		58	33-77	2	54			52-55

2.2.5 Conclusions

In a period of 20 years, uveal metastases were diagnosed in 87 patients. The primary tumour was breast cancer in 60% and lung cancer in 23%. In one-quarter of the patients detection of the intraocular tumour preceded the diagnosis of the primary malignancy, which was then mostly lung cancer or a tumour of unknown nature.

In 41% of the patients the uveal metastasis was the first sign of dissemination. This is in contrast to the generally held opinion that uveal metastases occur in patients with a widely disseminated malignancy. In our study population, no evident relationship between uveal metastases and metastases elsewhere in the body was found. Uveal metastases, therefore, do not follow lung metastases and do not occur simultaneously with cerebral metastases as is frequently described in literature.

Patients with uveal metastases were three times as often of the female as of the male sex. The mean age at the time of diagnosis was 57 years.

2.3 Diagnostics and differential diagnostics

In the diagnostics of intraocular tumours numerous examination techniques are nowadays available. In the majority of the patients of this retrospective study, not all those examinations have been used. This on the one hand because not all intraocular lesions are accessible to all examination techniques, on the other because certain techniques have only recently been introduced into the diagnostics of tumours. For instance, fluorescein angiography of tumours restricted to the ciliary body is possible only to a limited extent because of the peripheral localization, echography is not carried out in all cases of opthalmoscopically flat lesions and electro-oculography has only recently gained a place in the diagnostics of intraocular tumours. Conversely, certain examinations were carried out several times before a treatment was instituted, for instance if the diagnosis was uncertain or when an expectative policy was decided upon.

In the following chapters, the data referred to are always, unless otherwise stated, those obtained at the first examination at presentation of the patient. Beside the diagnosis, the differential diagnosis of uveal metastases will also be discussed. In this manner it is attempted to give as complete a picture as possible of the modes of presentation of uveal metastases and other intraocular tumours in our clinic.

After a description of the signs and symptoms, we shall successively discuss the findings obtained with the various examination techniques. The following arrangement will be used every time:

- a survey and evaluation of the results of the examination in question in uveal metastases and a comparison of these with the findings of other authors;
- a summary of the findings in uveal metastasis obtained at the examination in question;
- a table listing the principal findings in patients with metastases, melanomas, haemangiomas and naevi of the uvea;
- a short description of the differential-diagnostic aspects;
- conclusions in regard to the value of the technique in question for the differential diagnosis of uveal metastases.

In connection with the differential diagnosis of uveal metastases from other intraocular disorders and phenomena, Table 2.3.1 presents a survey of a number of epidemiological data in patients with metastases, melanomas, haemangiomas and naevi of the uvea from our retrospective study.

As mentioned before, patients with uveal metastases were predominantly of the female ***sex***, which fact is to be ascribed to the frequent occurrence of breast cancer as the primary tumour. In uveal melanomas in our study group, females were concerned with equal frequency as males, whereas in haemangiomas the proportion of males was larger. Of patients with uveal naevi, more were of the female than of the male sex. Sixty percent of patients with a retinoblastoma was of the male, 40% of the female sex.

In miscellaneous disorders, sex distribution was about even. Patients with an intraocular lesion of unknown nature were female in 65% of the cases.

The mean ***ages*** of the patients with metastases, melanomas or naevi varied only

little (57 to 59 years). An exception were patients with haemangiomas, who were markedly younger (average 44 years). These data are in accordance with those in the literature on melanomas (Wilder and Paul, 1951), haemangiomas (Gass, 1974) and naevi (Gass, 1977).

Patients with a choroidal detachment and with age-related macular degeneration were substantially older, 72 years on average. The mean age of the nine patients with a subretinal haemorrhage was 65 years, that of patients with a leiomyoma, 52 years. A distinctly lower mean age was observed in patients with lymphoproliferative diseases, viz. 26 years. In patients with a retinoblastoma, the mean age was 12 months. The oldest patient with a retinoblastoma was 10 years of age. The mean age of patients with lesions of unknown nature was 60 years.

Table 2.3.1 Epidemiological data on patients with metastases, malignant melanomas, haemangiomas and naevi

	Intraocular tumour			
	Metastasis	Melanoma	Haemangioma	Naevus
Number of patients	87	422	27	60
Sex:				
Male	25%	51%	70%	42%
Female	75	49	30	58
Age, mean (SD): yrs	57.2 (12.6)	57.9 (15.1)	44.4 (12.2)	58.6 (16.0)
Malignancy elsewhere in the body *before* diagnosis of intraocular tumour	76%	3%	-	-

In patients with uveal metastases, as mentioned in Chapter 2.2.2, a ***malignancy elsewhere in the body*** was known at the time of the ophthalmological diagnosis in 76% of the cases. This malignancy was mostly breast cancer and less often, lung cancer.

In 14 patients with a uveal melanoma (3.3%) a malignancy elsewhere in the body was known at the time of the first ophthalmological examination. The mean interval between the diagnosis of this malignancy and the detection of the intraocular tumour amounted to 7.5 years, ranging from one day to 33 years. In nine other patients, after diagnosis of the uveal melanoma, a second malignancy was detected (after a mean interval of 45 months). In four other patients a second primary malignancy was described, but the time at which this diagnosis was made was not known.

In all, therefore, in 27 patients with a uveal melanoma (6.4%), a second malignancy elsewhere in the body was known. This is in agreement with the finding of other investigators (Hart, 1962; Jensen, 1963; Char, 1989).

In four patients, the interval between the detection of the uveal melanoma and the finding of a second malignancy was remarkably short. In one patient, a basocellar carcinoma of the skin was diagnosed, after which one day later a choroidal melanoma was discovered. The ocular diagnosis could be confirmed histologically. In another patient four

days before the diagnosis of choroid melanoma, a squamous cell carcinoma of the buccal mucosa was detected. At histological examination of the ocular tumour the diagnosis proved to be correct. In a third patient, the presence of a multiple myeloma had only been known one week when a choroidal melanoma was established. In a last patient, a histologically confirmed choroidal melanoma was diagnosed while a non-Hodgkin lymphoma was detected 1.5 months later. In these patients it is quite well possible that a uveal metastasis will be considered rather than a melanoma.

Table 2.3.2 lists the various disorders that were established as an independent malignancy in patients with a uveal melanoma. In our study group there was no distinct relationship between the occurrence of uveal melanomas and any particular malignancy. In one patient, a carcinoma of the bladder and a lung carcinoma were already established and the patient was also known with chronic lymphatic leukaemia when a choroidal melanoma was diagnosed. In all, therefore, four separate malignancies were involved. In the literature, only one single similar patient, with four malignancies including a malignant uveal melanoma, is described, namely by Pheasant et al. (1979).

Table 2.3.2 Second primary malignancy in 27 patients with malignant uveal melanomas

Second primary malignancy detected **before** ***uveal melanoma (N=14):***

Breast cancer (1); lung cancer (1); probably lung cancer (2); 'tumour' of the testis (1); prostatic cancer (1); basocellular carcinoma of the skin (1); squamous cell carcinoma of the skin (1); squamous cell carcinoma of the nipple (1); buccal squamous cell carcinoma (1); bladder cancer + lung cancer + chronic lymphatic leukaemia (1); non-Hodgkin lymphoma (1); histiocytic lymphoma (1); multiple myeloma (1)

Second primary malignancy detected **after** ***uveal melanoma (N=9):***

Meningeoma (2); astrocytoma (1); osteosarcoma (1); carcinoma of the cervix uteri (1); probably malignancy of the skin (2); probably malignancy of the kidney (1); non-Hodgkin lymphoma (1)

Moment diagnosis second primary malignancy in relation to uveal melanoma unknown (N=4):

Breast cancer (1); lung cancer (1); colonic cancer (1); malignant melanoma skin (1)

The malignancies found in patients with a uveal melanoma in additon to the ocular tumour, therefore, are of an entirely different nature than the primary tumours as described in patients with uveal metastases. While in uveal metastases the primary tumour was breast cancer in 60% of the cases and lung cancer in 23%, in uveal melanomas the nature of the second malignancy was breast cancer in only 7% and lung cancer in 11%. In the other cases the malignancy was of a different nature.

To the individual patient who is known with a malignancy and in whom an intraocular tumour is noticed, these findings are of only limited value, however.

In not one of the patients of our study with a haemangioma, naevus, leukaemia or lymphoma or some other intraocular disorder was a malignant tumour elsewhere in the body known.

In five of the 88 patients with an intraocular lesion of unknown nature (6%) at the time of the first ophthalmological examination, a malignancy elsewhere in the body was

known: once breast cancer, once a clear cell carcinoma of the kidney (Grawitz tumour), once a uterine carcinoma, once breast cancer coexistent with a thyroid carcinoma and once, a malignancy of an unknown nature. These tumours had on average been known for as long as 12 years (range 4 months - 31 years). In three patients, a malignancy elsewhere in the body was discovered after the ocular tumour: once lung cancer, once probable lung cancer and once, a carcinoma of the colon. The mean interval after the ocular tumour was 19 months (range 4-42). In one other patient with a colonic carcinoma, the exact moment of diagnosing in relation to the ocular tumour was not known. In all these patients there were insufficient indications that an intraocular metastasis was concerned.

2.3.1 Signs and symptoms

As already mentioned in Chapter 2.1.2, inter alia for statistical reasons, in the description of data and results of examinations, one affected eye per patients is always postulated, viz. the tumour eye in patients with a unilateral tumour, the eye first diagnosed in patients with bilateral tumours which were detected at different times and the right eye in patients with bilateral tumours in whom tumours were observed in both eyes at the same time. In the description of the signs and symptoms of patients with uveal metastases, therefore, only one single eye is considered.

Ophthalmological complaints were present in our study in 64 of the 87 patients with uveal metastases (74%). Of these 64 patients, 54 (86%) had only one complaint.

The most frequently reported complaint was deterioration of the visual acuity, which was mentioned as the principal symptom by 54% of the patients. Visal field defects and spots before the eyes were the principal complaint in 7% of the patients and was mentioned as one of the symptoms by 18% of the patients. A few patients manifested themselves with photopsia (appearance of sparks or flashes), metamorphopsia, a painful or red eye or diplopia.

Presence of more than one symptom in most cases involved, next to complaints about blurred vision, complaints about visual field defects (Table 2.3.1.1).

In two of the five patients complaining about photopsia, ophthalmoscopy revealed no retinal detachment; in the three others such detachment was present. Complaints about photopsia accordingly were not clearly connected with the presence of a retinal detachment.

In none of the patients complaining about metamorphopsia an Amsler test appeared to have been performed. This test had been executed, on the other hand, in nine patients without complaints about distorted vision. In three of them this test was normal, in six, abnormal. If the Amsler test was normal, the margin of the tumour was found to be 2.3 disk diameters (DD) distant from the fovea. In an abnormal test, this was only 0.4 DD on average. However, this concerned a small number of performed tests of which the pre-test selection was not known.

Uveal metastases may also be asymptomatic. This was the case in 11 patients (13%). In nine of these patients the shortest distance between the margin of the tumour and the fovea was known. It was 2.8 DD on average, ranging from a localization in the

fovea to a distance of 6.0 DD. In one patient, known with amblyopia of the eye in question, the tumour was located in the macular area without having given rise to symptoms.

In five of the 11 patients in whom no symptoms were established in the tumour eye, metatases were present in the other eye which had caused deterioration of the visual acuity and had occasioned the ophthalmological examination. In these patients, therefore, the eye taken into consideration was asymptomatic but there were symptoms in the contralateral eye. Two other patients had been referred to the ophthalmologist by a neurologist and one patient by a surgeon, for evaluation of the disk. One patient was being treated for a pterygium; at control examination two weeks later, the visual acuity had decreased from 5/6 to 5/20 and ophthalmoscopy revealed a uveal tumour. In another patient with age-related macular degeneration, control fluorescein angiography showed a tumour in a temporal superior localization which proved to be a metastasis. Finally, at a control examination of a patient with a macular scar and poor eyesight, retinal detachment was detected which was found to be due to a metastasis.

Of 12 patients with uveal metastases in our study (14%) no data concerning ocular symptoms were known. This concerned inter alia three patients with a tumour arising solely from the iris or the ciliary body.

Table 2.3.1.1 Ophthalmological complaints in 87 patients with uveal metastases

	Number of times noted		Most important complaint	
Complaint	N	* %	N	%
Decreased visual acuity / blurred vision	47	54	47	54
Visual field defect	16	18	6	7
Metamorphopsia	6	7	3	3
Photopsia	5	6	3	3
Ocular pain	4	5	3	3
Headache	3	3	-	-
Diplopia	2	2	1	1
Red eye	2	2	1	1
Asymptomatic	11	13	11	13
Unknown	12	14	12	14

** total % exceeds 100 because some patients had more than one complaint*

In the 84 patients with a tumour originating from the choroid the complaint was related to the shortest distance between the margin of the tumour and the fovea. In 18 patients (21%) this distance was not known, however.

In 21 patients (25%) the metastasis was localized in the macular region. In 67% of these patients this gave rise to deterioration of the visual acuity, 19% complained of visual field defects, 10% about metamorphopsia and 10% about a painful eye. Other symptoms

such as photopsia and diplopia were not encountered in these patients.

In 46 patients (55%) the margin of the tumour was situated at most 1 DD from the fovea. In 63% of these patients this caused complaints about blurred eyesight, in 20% about visual field defects, in 9% metamorphopsia, in 7% ocular pain, in 4% photopsia and in 2%, diplopia.

In patients complaining about loss of visual acuity, the distance to the fovea was 1.5 DD on average while in patients without ocular complaints it was 2.9 DD. This is in accordance with the expectation that tumours situated entirely or partly in the macula will cause complaints about the eyesight more frequently than lesions at a distance from the macula. Standard error was large, however: 1.3 and 1.9 DD, respectively.

However, uveal metastases do not always cause complaints about visual acuity, not even when they are localized in the macular area. Conversely, a metastasis at a large distance from the fovea may lead to complaints about the eyesight such as blurred vision (Table 2.3.1.2).

Table 2.3.1.2 *Primary complaint in 66 patients with choroidal metastases related to the shortest distance between the tumour margin and the fovea* *

Complaint	Number of patients	Distance between tumour margin and fovea (DD)			
		Mean	SD	Minimum	Maximum
Decreased visual acuity	38	1.0	1.3	0	6.0
Visual field defect	4	1.6	2.3	0	5.0
Metamorphopsia	3	1.3	1.5	0	3.0
Photopsia	3	2.7	1.5	1.0	4.0
Ocular pain	2	0.5	0.7	0	1.0
Diplopia	1	1.0	-	1.0	1.0
Asymptomatic	10	2.9	1 9	0	6.0
Unknown	5	0.3	0.5	0	1.0

* *in 18 patients with a choroidal metastasis distance to the fovea unknown; DD: disk diameters*

Seventeen patients at the time of the diagnosis of the uveal metastases in the affected eye also complained about decreased eyesight in the contralateral eye. Thirteen times at that moment metastases were also diagnosed in the contralateral eye. In two instances this diagnosis was made at a later time. One patient suffered from abducens paresis, probably due to a cerebral metastasis. In one patient no ophthalmological abnormalities could be established in the contralateral eye with impaired eyesight.

The ***visual acuity*** with own correction (with own glasses in patients wearing spectacles, without correction in patients without glasses) was known of only 22 patients with uveal metastases and on average amounted to 0.42, ranging from 1/300 to 1.20.

In 70 of the 87 patients the optimal visual acuity could be found out in retrospect. This was the best possible visual acuity that could be achieved after optimal correction of

any refraction abnormalities. This optimal visual acuity was 0.49 on average.

The best visual acuity known was defined as the optimal visual acuity or, if this was not known, the visual acuity with own correction. This was known in 75 patients, amounted to 0.49 on average and ranged from Lp+ to 1.25 (Table 2.3.1.3). In this table the visual acuity of the non-affected eye is also given, depending on whether or not a metastasis was encountered in it, and the difference in visual acuity between the two eyes (if known).

Table 2.3.1.3 Visual acuity in patients with uveal metastases

	N	Visual acuity				
		Mean	SD	Median	Minimum	Maximum
Tumour eye:						
With no correction	20	0.25	0.32	0.12	lp-	1.00
With own correction	22	0.42	0 35	0.35	1/300	1.20
With optimal correction	70	0.49	0.32	0.50	lp+	1.25
With best known correction *	75	0.49	0.32	0.50	lp+	1.25
Contralateral unaffected eye:						
With no correction	10	0.91	0.23	0.90	0.60	1.25
With own correction	15	0.87	0.20	0.80	0.40	1.20
With optimal correction	43	0.89	0.22	1.00	0.05	1.25
With best known correction *	45	0.89	0.22	1.00	0.05	1.25
Contralateral affected eye: **						
With no correction	8	0.47	0.42	0.65	1/60	1.00
With own correction	6	0.61	0.40	0.75	1/300	1.00
With optimal correction	15	0.62	0.40	0.60	lp+	1.00
With best known correction *	17	0.56	0.41	0.60	lp+	1.00
Difference between unaffected contralateral eye and tumour eye:						
With no correction	7	0.68	0.41	0.60	0	1.22
With own correction	10	0.49	0.38	0.50	0	0.98
With optimal correction	43	0.44	0.37	0.40	-0.85	1.13
With best known correction *	45	0.44	0.38	0.40	-0.85	1.13

** visual acuity with optimal correction or in case optimal correction is unknown, with own correction*
*** if at the time of ophthalmological examination a metastasis in the contralateral eye was known*

As Table 2.3.1.3. shows, the visual acuity in the contralateral eye, if no metastasis was known in it, was almost twice as high as in the tumour eye.

In eight patients in whom the distance between the margin of the tumour and the fovea was known, and in whom a visual acuity of less than 3/60 was observed, the tumour in six cases was situated at the site of the macula, once at a distance of 1 DD from the macula and once, at a distance of 3 DD.

In contrast, in six of the 19 patients with a tumour localized at the site of the fovea, a visual acuity of less than 3/60 was established while in only four it equalled or was larger than 0.6.

Figure 2.3.1.1 lists the best visual acuities in the 75 patients with choroidal metastases and known visual acuity in a graph.

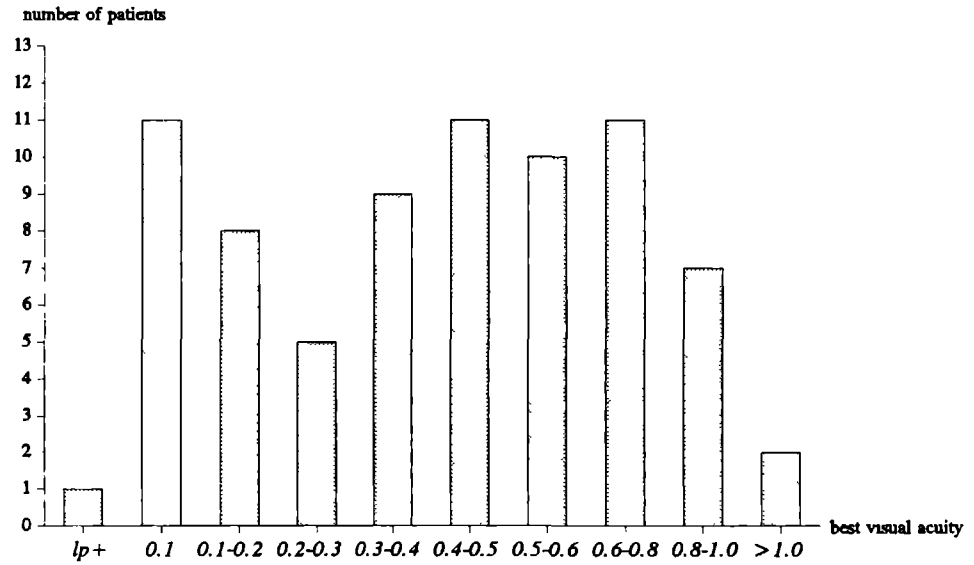


Figure 2.3.1.1 Best visual acuity in 75 patients with choroidal metastases and known visual acuity

There was no distinct correlation between the best possible visual acuity of the tumour eye and the nature of the primary tumour. In patients with breast cancer, the mean visual acuity was 0.51, in lung cancer it was 0.52 and in metastases of one of the other malignancies, it was 0.36 on average.

To detect the development of ***hypermetropia***, if any, the spherical equivalent of the patient's own correction was compared with that of the correction that ensured the best possible visual acuity.

In 27 patients the spherical equivalent of the patient's own correction of both the metastatic eye and the contralateral healthy eye were known. Between the two, no significant difference was observed (mean difference +0.08 diopter for tumour eye minus healthy eye; median 0; range -0.75 to +1.25).

In 34 patients both the spherical equivalent of the patient's own correction and that of the correction to ensure optimal visual acuity were known. With optimal correction this was on average 0.83 diopter higher in the tumour eye which indicates distinct development of hypermetropia. Also, in three other patients, development of hypermetropia was noted without mentioning the patient's corrections.

In the ophthalmological anamnesis of patients with uveal metastases, in nine patients at the time of examination ***other ocular abnormalities*** than the metastases were already known. Three patients were already being followed up with cataract and one, with amblyopia. In addition, in one patient with a visual acuity of 0.80 an abducens paresis and complaints about blurred eyesight, probably due to cerebral metastases, were known. One patient had an anamnesis with a steel splinter in the eye which had caused visual acuity to decrease to 1/60, another patient suffered from an occlusion of the central retinal artery with a visual acuity of 0.40 and one patient was known with diabetic retinopathy and a visual acuity of 0.50. A last patient, with a ptosis and paresis of the oculomotor nerve complained of loss of the field of vision. This was probably brought about by a metastasis in the sphenoid or at the back of the orbit. The visual acuity of this patient was not known.

In 63 patients at the time of examination no other ocular abnormalities were present (15 patients: unknown).

The best visual acuity of the tumour eye in 59 of the 63 patients without known ocular abnormality amounted to 0.53 on average (four patients unknown). In eight patients in whom ocular abnormalities were known, the best visual acuity on average was 0.22 (one patient unknown).

At ***external examination*** of the tumour eye dilated episcleral vessels were observed in two of the 87 patients: once in a patient with a ciliary metastasis of lung cancer and once in a patient with a choroidal metastasis of breast cancer. In one patient with an iridal metastasis of lung cancer scleral hyperaemia was described. In 81 patients (93%) no vascular dilatation or hyperaemia of conjunctiva or sclera was reported (three patients unknown).

Asymmetry of the iris was present in two patients: once in a patient with a ciliary metastasis and once in a patient with metastases in the choroid and iris.

No iridal heterochromia was observed.

Clear ***media*** are required for good assessment of the ocular fundus. However, in 28 patients (32%) opacities of media were present which rendered good ophthalmoscopy difficult. In one patient with bilateral uveal metastases opaque corneas were observed in both eyes, with a hyposphagma in one eye.

Lens opacifications were observed in 25 patients (29%). In 41 patients (47%) the lens was clear [21 patients (24%) unknown]. In 20 patients, increased opacity of the lens was described. A moderate dense cataract was seen three times and a dense cataract, twice. In the five patients with a moderate dense to dense cataract the abnormalities of the lens were symmetrical, as they were in 18 of the 20 patients with mild forms of lenticular opacities.

In one patient the fundus could not be inspected adequately because of a dense vitreous haemorrhage, in two patients visualization was impaired by a slight intravitreous haemorrhage.

Finally, a secondary retinal detachment or a subretinal haemorrhage may impede adequate description and evaluation of the underlying lesion.

Information concerning ***Tyndall or cells in the anterior chamber or vitreous humour*** were lacking in most of the patients in our study (Table 2.3.1.4). In general, such data were recorded only if abnormal results were obtained; this also applied to ***rubeosis*** of the iris.

Table 2.3.1.4 *Occurrence of Tyndall and/or cells in the anterior chamber and/or vitreous in patients with uveal metastases*

	Distinct		Some		Negative		Unknown	
	N	%	N	%	N	%	N	%
Tyndall anterior chamber	2	2	2	2	34	39	49	56
Cells anterior chamber	1	1	3	3	33	38	50	57
Tyndall vitreous	0	-	3	3	12	14	73	83
Cells vitreous	0	-	5	6	15	17	67	77

Table 2.3.1.4 shows that Tyndall in the anterior chamber was described in 4% of the patients with uveal metastases and cells also in 4%. In addition, 3% had Tyndall and 6% cells in the vitreous humour. However, owing to the large number of patients in whom these data were lacking no conclusions can be drawn from these figures.

Rubeosis of the iris was observed in two of the 87 patients: once in a patient with a ciliary metastasis and once in a patient with a choroidal metastasis. Rubeosis was absent in 58 patients (67%) [27 patients (31%) unknown].

In all, 12 patients (14%) showed Tyndall or cells in the anterior chamber or vitreous humour or showed rubeosis. The primary tumours were four times breast cancer, six times lung cancer, once thyroid carcinoma and once, clear cell carcinoma of the kidney. A noticeable aspect is the large number of patients with a pulmonary carcinoma in this group of patients.

The localization of the uveal metastasis was of major importance for these phenomena. In the patient with the iridal metastasis the anterior chamber was initially filled with fibrin. This cleared up after a subconjunctival injection of corticosteroids; only then did the iridal tumour become visible. One of the patients with a ciliary metastasis presented with an iridocyclitis and redness of the eye with normal ocular pressure. There was a pigment coating on the lens and the tumour had broken through the iris. There was substantial vascular injection of the iris, ciliary body and angle of the anterior chamber, and corneal injection with posterior synechiae. In the anterior chamber distinct Tyndall and numerous cells were observed. In the second patient with a metastasis in the ciliary body a secondary glaucoma developed. The patient with a metastasis in the iris as well as in the choroid presented with a red eye and the picture of anterior uveitis with some Tyndall and cells in the anterior chamber.

The occurrence of signs of irritation of the anterior segment of the eye is in accordance with the data of, among others, Ferry and Font (1975). In the four patients in our study with metastases in the anterior segment all four were metastases from lung cancer. Other investigators have also frequently described signs of uveitis in metastases of lung cancer in the iris or the ciliary body (Duke and Kennedy, 1958; Talegaonkar, 1969; Reese, 1976).

Of 62 patients, the ***ocular pressure*** in the tumour eye was reported. It amounted to 14.3 mm Hg on average (SD 3.4), ranging from 8 to 24 mm Hg with a median of 14 mm Hg. A pressure in excess of 20 mm Hg was found only twice, both times 24 mm Hg (once in a patient with a clear cell carcinoma of the kidney and once in a patient with breast cancer). In the contralateral healthy eye of patients with uveal metastases there

were no manifest abnormalities of pressure, the mean pressure being 15.2 mm Hg (SD 3.1).

In one patient with a ciliary metastasis of lung cancer of whom the pressure in the tumour eye was not known, a secondary glaucoma was mentioned. Three other patients developed glaucoma later on: in one patient with a ciliary metastasis of lung cancer the ocular pressure initially was 12 mm Hg but it rose to 36 after one month and to 45 mm Hg after two months; in another patient with a choroidal metastasis of lung cancer, the pressure increased from 16 mm to 32 mm Hg nine months later; in a third patient, with a metastasis of a thyroid carcinoma in whom the ocular pressure at the first examination was not stated, the pressure at a later date was 50 mm Hg.

If glaucoma developed, the lesion in two of the four cases originated from the ciliary body and the primary tumour in three of the four patients was lung cancer.

Summary of the signs and symptoms in patients with uveal metastasis: the most frequent complaint of patients with uveal metastases was decrease of the visual acuity followed by complaints about visual field defects. In patients without ophthalmological complaints the margin of the tumour in general was situated farther from the macula than in patients who did have complaints.

The mean visual acuity of the affected eye, with patient's own correction, amounted to 0.42 and the best possible visual acuity was 0.49 on average. Patients with poor eyesight in general had a macular localization of the tumour. In the tumour eye a distinct hypermetropization had taken place, of 0.83 diopters.

In 32% of the cases there were opaque media, mostly caused by a mild form of a symmetrical cataract. External dilated vessels or hyperaemia of the eye were observed only sporadically, as were signs of Tyndall and cells in the anterior chamber or the vitreous humour or rubeosis of the iris. If these were present, in most cases a metastasis in the anterior segment was concerned, originating from lung cancer.

The mean ocular pressure in the eye with the metastasis was 14.3 mm Hg. A pressure above 20 mm Hg was measured only twice, both times 24 mm Hg. In three patients glaucoma developed later on.

Table 2.3.1.5 presents a review of the signs and symptoms in patients with metastases, melanomas, haemangiomas and naevi of the uvea.

In patients with a ***melanoma*** of the uvea, the pattern of complaints was similar to that of uveal metastases and there was no difference either where visual acuity was concerned. However, the hypermetropization was substantially, although not significantly ($P < 0.10$) less in melanoma than in metastases of the uvea, viz. only 0.18 diopters (SD 1.34) as against 0.83 (SD 1.42) diopters in metastases.

Lens opacities were observed in similar proportions of melanoma patients and patients with metastases. On the other hand, melanoma patients more frequently had dilated vessels or hyperaemia of the eye and signs of inflammation.

The mean intraocular pressure in melanoma amounted to 16.4 mm Hg. Pressures in excess of 20 mm Hg were measured in 10% of the melanoma patients as against 2% in metastases.

Table 2.3.1.5 Signs and symptoms in patients with metastases, malignant melanomas, haemangiomas and naevi

	Intraocular tumour			
	Metastasis	Melanoma	Haemangioma	Naevus
Number of patients	87	422	27	60
Complaints: *				
Decreased visual acuity	54%	53%	52%	18%
Visual field defect	18	18	-	2
Photopsia	6	10	-	-
Metamorphopsia	7	4	-	-
Miscellaneous	13	7	11	12
Asymptomatic	13	9	4	67
Unknown	14	19	37	5
Visual acuity: mean (SD)				
With own correction	0.42 (0.35)	0.40 (0.35)	0.29 (0 34)	0.62 (0.33)
Optimal visual acuity	0.49 (0.32)	0.46 (0.37)	0.39 (0.32)	0.69 (0.45)
Opacifications of the lens:				
none	47%	32%	56%	37%
increased	23	19	7	28
moderately dense	3	9	4	18
dense	2	1	-	2
unknown	24	39	33	15
Dilated episcleral vessels	2%	7%	-%	2%
Scleral/conjunctival hyperaemia	1	3	-	-
Tyndall anterior chamber	4%	7%	-%	-%
Cells anterior chamber	4	7	-	-
Tyndall vitreous	3	3	-	-
Cells vitreous	6	12	4	-
Rubeosis iridis	2	2	-	-
Intraocular pressure (mm Hg):				
Mean (SD)	14.3 (3.4)	16.4 (8.1)	13.9 (4.8)	17.7 (6.1)
Range	8-24	1-80	6-20	9-45

** total % exceeds 100 because some patients had more than one complaint*

In ***haemangioma*** decrease of the visual acuity was the principal complaint of the majority of the patients. There were no reports of complaints about visual field defects, which occurred in 21% of the patients with metastases. The visual acuity in haemangioma was

markedly lower than in metastases and melanomas. This was due to the frequent localization of the lesion in the macular region (see Chapter 2.3.2).

Lens opacities were observed relatively infrequently in haemangioma patients, due in part to the fact that the mean age was lower than in metastases and melanomas of the choroid. Signs of inflammation rarely occurred. In no case were hyperaemia of the eye or dilated vessels observed.

The intraocular pressure was 13.9 mm Hg on average and never exceeded 20.

Naevi in 67% of the cases caused no complaints. If complaints were present, these mostly concerned deterioration of the visual acuity. However, the patients with naevi examined in our study group constituted a selection of patients who had consulted the ophthalmologist because of signs or symptoms.

The mean visual acuity was markedly higher as in patients with a metastasis or a melanoma.

An opaque lens was encountered with a high frequency, namely in one-half of the patients. This also, however, probably was a consequence of the above-named patient selection. In only one patient were dilated vessels encountered. Signs of inflammation were never seen.

The mean intraocular pressure in patients with a naevus was 17.7 mm Hg. In 15% a pressure in excess of 20 mm Hg was measured.

In general, in patients with ***retinoblastoma*** the parents observe that something is wrong with one or both eyes of their child. In 36% a leukokoria was the reason for ophthalmological examination, in 28% strabismus, in 20% absence of eye-contact or decrease in visual acuity.

Complaints of patients with ***intraocular lesions suggestive of a tumour*** other than metastases, melanomas, haemangiomas, naevi or retinoblastomas had a pattern similar to that in uveal metastases. However, choroidal detachments in a large proportion (60%) ran an asymptomatic course. Of patients with other disorders the majority had a decreased visual acuity.

The mean best possible visual acuity in patients with a subretinal haemorrhage was low, viz. 0.19 with a median of 1/300. In patient with aged-related macular degeneration these values were even lower, viz. 0.01 and 1/300, respectively. This made the mean of the best visual acuity far lower than in metastases, melanomas, haemangiomas or naevi of the choroid. Patients with a choroidal detachment had a mean visual acuity of 0.35 (median 0.32), those with a leiomyoma one of 0.50 (median 0.50) and those with a retinal detachment, one of 0.24 (median 1/60). Of only two of the seven patients with a lymphoproliferative disease the visual acuities were known; they were lp+ and and 0.45, respectively.

Opacities of the lens were encountered noticeably often: 22% of the patients with a subretinal haemorrhage had a mild form and 67%, a moderately dense form of cataract. In age-related macular degeneration these proportions were 14% and 43%, respectively. In the other lesions the proportion ranged from 60 to 67%. This could be attributed partly to the more advanced age of many of these patients.

The intraocular pressure was lower than 20 mm Hg in all patients but one. The exception was a patient with an osteoma in whom an intraocular pressure of 26 mm Hg was measured. Thickened episcleral or conjunctival vessels were observed in one patient

with scleritis and in one patient with benign reactive lymphoid hyperplasia.

In one patient with a lymphoproliferative disease, Tyndall and cells in the anterior chamber were seen, and in one patient, Tyndall and cells in the vitreous humour.

Of the patients from the group with ***lesions of unknown origin***, only 28% complained about decrease of the visual acuity. Consequently, the mean of the best known visual acuity was relatively high, viz. 0.65. Some degree of cataract, mostly moderately dense, was present in 40% of the patients. The mean intraocular pressure was 14.8. These data are insuffciently specific to allow a conclusion about the possible nature of these lesions.

Conclusion: the pattern of signs and symptoms in patients with uveal metastases is not characteristic. The same complaints and symptoms may also occur in patients with other intraocular lesions. In patients with miscellaneous intraocular lesions (other than metastases, melanomas, haemangiomas or naevi) a variable picture was observed. It was only in naevi cases that complaints mentioned were clearly less frequent and the mean visual acuity was higher than in patients with metastases. However, where the differential diagnosis of uveal metastases is concerned, these differences are too little specific.

2.3.2 Ophthalmoscopy and slit lamp examination

Adequate evaluation of the fundus of the eye requires clear media. As mentioned before, this condition was not fulfilled in all patients with uveal metastases in our study. In Chapter 2.2.2 it was already mentioned that opacifications of the media were present in 28 patients (32%). A secondary retinal detachment or a subretinal haemorrhage also may impede good observation and evaluation of the underlying lesion.

As regards the ***localization*** of the metastases, in 83 of the 87 patients (95%) the tumour was situated in the choroid. In two patients the tumour was localized primarily in the ciliary body and in one patient, in the iris. In one patient, a metastasis was observed in the choroid as well as in the iris. The percentage of metastases in the anterior segment in our study group was 5%, substantially lower than in the literature where proportions up to 29% are described (Ferry and Font, 1974/1975; Stephens and Shields, 1979; Castro et al., 1982).

In connection with the blood supply of the eye it is to be expected that most uveal metastases will be found in the posterior pole of the eye (see Chapter 1.2.1.4). For the description of the fundus localization of the metastasis in the choroid in the 84 patients in this study, we have based ourselves on the largest tumour in the eye first affected. In 60 patients (71%) the choroidal metastasis was localized temporally of the disk and in 21 patients, nasally (25%) [three patients (4%) unknown] (Colour plates 1-3). This is in accordance with the findings of other investigators (see Chapter 1.6.2).

If the fundus is divided into an superior and an inferior part, the localization of the lesions was superior 44 times (52%) and inferior 37 times (44%) [three patients (4%) unknown]. The slightly higher percentage of metastases in the upper half of the fundus

can be attributed to the importance of the lower half of the visual field Abnormalities in the lower part of the visual field are noticed earlier by the patient than those in the upper part of the visual field, which corresponds with the lower half of the fundus.

If these data are combined, and the fundus divided into eight identical wedge-shaped areas with the optic disk as the centre, an arrangement is obtained as shown in Figure 2.3.2 1 a). Most lesions had a temporal (23%), a temporosuperior (21%) or a temporoinferior (21%) localization

Also, the localization of the choroidal metastasis in relation to the large retinal vessels was recorded For this purpose, a subdivision was made into lesions situated for over 75% of their size within the arcade of the large vessels, for more than 75% outside it and lesions predominantly localized at the site of these vessels. Then, the metastasis was situated within the arcade in 19 patients (23%), outside it in 15 patients (18%) and at the site of the vessels in 44 patients (52%) [six patients (7%) unknown] (Figure 2 3 2 1 b)

If we combine Figure 2 3 2 1 a with the eight sectors of the choroid with Figure 2 3 2 1 b in which the position of the metastases in relation to the large vessels is shown, Figure 2 3 2 1 c is obtained From this figure, the localization of the ocular tumour can be read out accurately

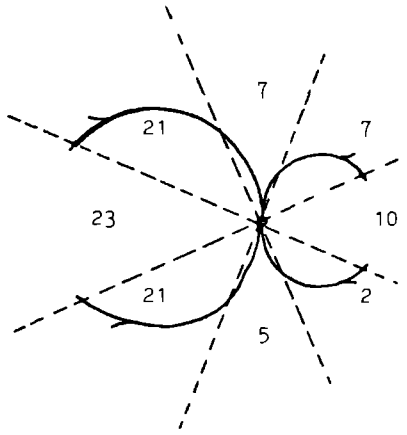
The localizations of most lesions were either temporosuperior at the site of the vascular arcade (19%) or temporal within the arcade (roughly at the site of the macula 17%) or temporoinferior along the vascular arcade (14%). If in patients with choroidal metastases all 142 metastases in both eyes were considered, the localizations were in 20% temporosuperior at the site of the vascular arcade, 13% temporal within the vascular arcade and 13% temporoinferior along the vascular arcade These findings are in agreement with the data that are obtained if only the largest lesion in one eye was considered

In 21 patients with choroidal metastases (25%), the macular area was involved in the process.

In 69 of the 84 choroidal metastases the shortest distance between the margin of the tumour and the fovea was known As mentioned before in Chapter 2 3 1, this distance affects the frequency of the patients' complaints This distance was 1 4 DD on average (SD 1.6; range 0 0-6 0) The distance from the tumour margin to the papilla was known in 68 patients and also amounted to an average of 1 4 DD (SD 1 3, range 0 0-4 0)

Bilateral metastases threaten the sight in both eyes and therefore constitute an even worse impairment of the quality of life. Such bilateral metastases were established in 25 patients (29%) In 18 patients, metastases were observed in both eyes even at the first examination of the patient In seven patients, metastases in the contralateral, initially unaffected eye were only detected at a later time. This occurred after a mean interval of 12 months, with a range from 2 weeks to 4 years (median 3 months) All these metastases were localized in the choroid. Bilateral metastases with one of the lesions situated in the iris or the ciliary body were not encountered in our study group The proportion of bilateral metastases of 29% corresponds to data in the literature (see Table 1 6.9).

Of the bilateral metastases in 25 patients, 21 were observed in patients with breast cancer, two with lung cancer, one with cancer of the pancreas and one, in a patient probably suffering from cancer of the colon Accordingly, the vast majority of the patients with bilateral metastatic lesions have breast cancer as the primary tumour.



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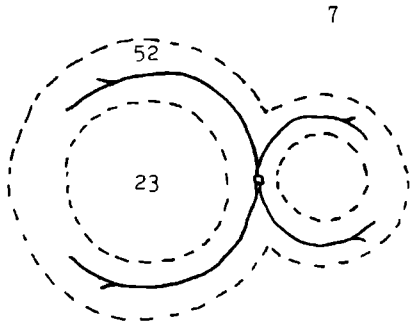

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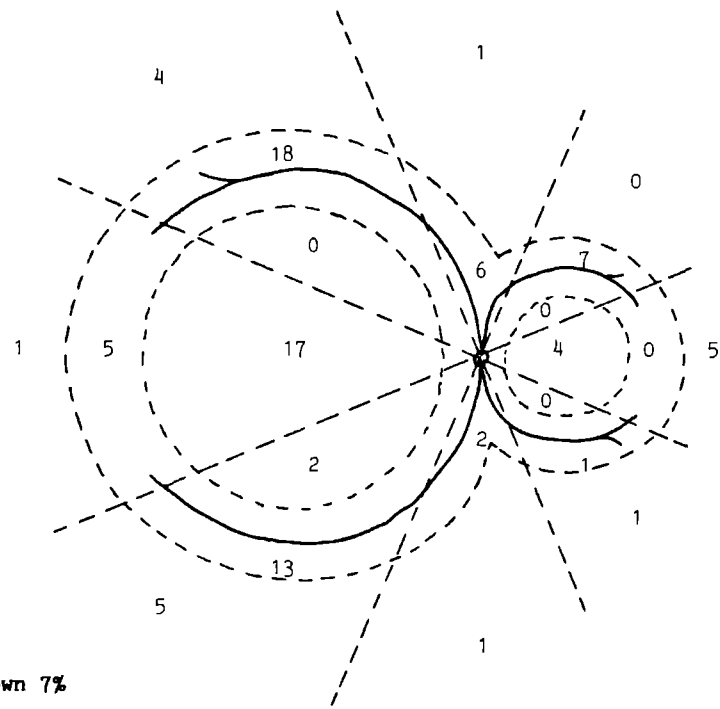


C unknown 7%

Figure 2.3.2.1 Localization choroidal metastasis in terms of percentage.

Correspondingly, bilateral metastases are established in 40% of the patients with breast cancer as against 10% of the patients with lung cancer and 13% of those with another malignancy.

In the 62 patients with a unilateral metastasis, the right eye was affected 36 times (58%) and the left, 26 times (42%). In the whole group of patients, i.e. both those with unilateral and those with bilateral metastases, the right eye was affected 61 times (54%) and the left eye, 51 times (46%). In our study group, therefore, there was no question of a preference of metastases for the left eye as described in the older literature on uveal metastases (Lagrange, 1901; Sattler, 1926).

Among the 87 patients with uveal metastases there were 76 (87%) in whom a solitary metastasis was encountered in the first-affected eye at initial ophthalmological examination In 10 patients (11%) ***multiple metastases*** were found (one patient unknown) (Colour plate 4; Figure 2.3.2.2 a) Five times, two lesions were observed in one eye, four times three lesions and in one patient, seven metastases in one eye. Multiple metastases may fuse to one large tumour through lateral growth of the lesions (Figure 2.3.2 2 b) In patients with multiple metastases, all tumours were localized in the choroid, apart from one patient with a metastasis in the choroid as well as in the iris.

During the entire follow-up period of the patients with uveal metastases, multiple metastases in one or both eyes or bilateral metastases were observed 29 times (33%) In all, there were 146 metastatic uveal lesions in 112 eyes in 87 patients.

Of the bilateral and/or multiple metastases, 83% arose from breast cancer, 10% from lung cancer and 7%, from another malignancy. Of all patients with breast cancer almost half, namely 24 of the 52 patients (46%), had bilateral and/or multiple metastases as against three of the 20 patients with lung cancer (15%) and two of the 15 patients with one of the other malignancies (13%).

Just as no explanation could be found of the fact that breast cancer accounted for such a large percentage of the primary tumours, it is not clear, either, why precisely breast cancer so frequently gives rise to multiple uveal metastases (see Chapter 1 3 2)

In 63 patients with a choroidal localization the largest ***diameter of the metastasis*** was known. It varied from 2 0 to 13 0 DD with a mean of 6 6 DD (SD 4.1) The smallest diameter was known in 64 patients; it amounted to 5.9 DD on average (SD 4.5; range 0 5-13.0). One disk diameter (DD) equals 1.5 mm (Duke-Elder, 1946, Naumann et al , 1966). Consequently, choroidal metastases have a broad base of 9 mm on average.

The ***shape of the metastasis*** is often not mentioned in ophthalmoscopical descriptions of these tumours Most frequently the shape appeared to be flat or dome-shaped and less often lobulated or even mushroom-shaped (Figure 2.3 2 3) Since more data on this aspect are provided by echography, the shape of the tumour will be discussed in more detail under this heading (see Chapter 2.3.4).

The ***colour of the metastasis*** was known in 60 of the 84 patients with a choroidal tumour; it was mostly yellowish-orange or cream and, less frequently, grey (Table 2.3.2.1). Occasionally, a white, reddish-brown or greenish-blue tumour was described. If several metastases in one eye or bilateral metastases were established, these were of the same colour in all cases (Colour plates 4-6)

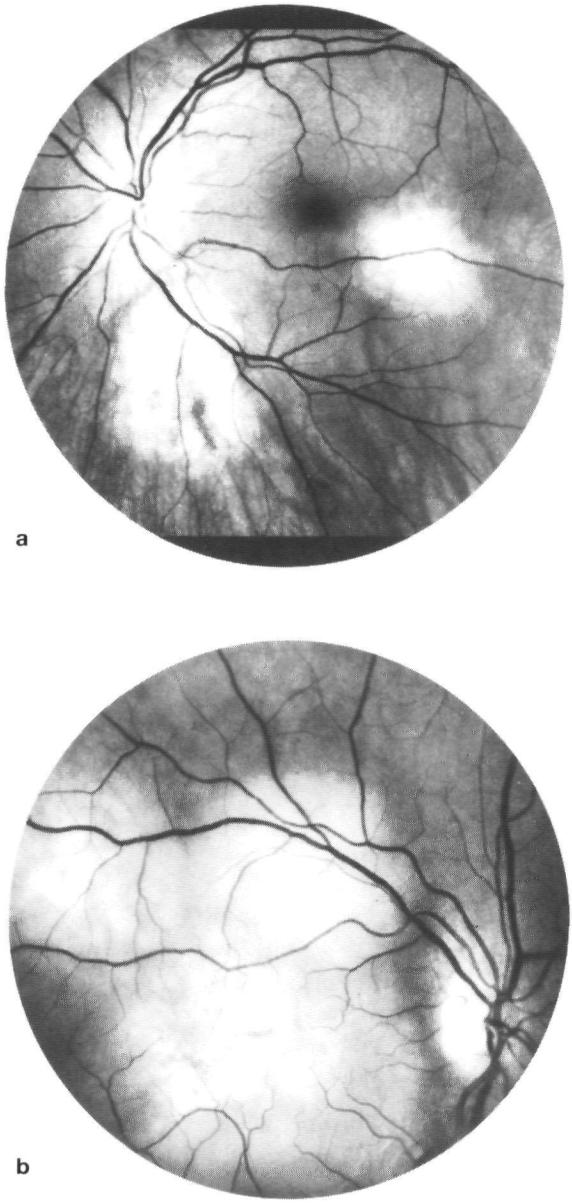


Figure 2.3.2.2 a. Fundus photograph of the left eye showing two separate choroidal metastases from breast cancer.
b. Fundus photograph of the right eye of a different patient showing three choroidal metastases from breast cancer fusing.

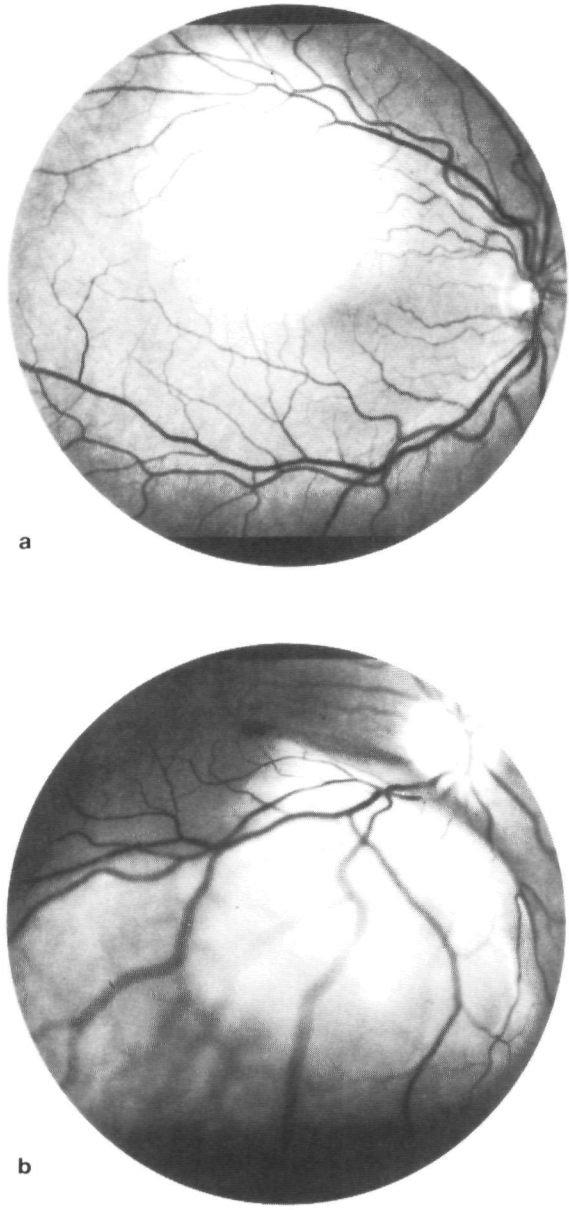


Figure 2.3.2.3 a. Fundus photograph of the right eye showing a slightly elevated choroidal metastasis from breast cancer.
b. Fundus photograph of the right eye showing a prominent lobulated choroidal metastasis from a seminoma (with elements of teratoma) of the testis.

Table 2.3.2.1 *Colours of choroidal metastases according to the nature of the primary tumour*

	All tumours		Breast cancer		Lung cancer		Other	
Colour	N	%	N	%	N	%	N	%
Yellowish-orange or cream	42	50	26	50	8	40	8	67
Grey	11	13	5	10	6	30	-	-
White	4	5	2	4	1	5	1	8
Reddish-brown	2	2	1	2	1	5	-	-
Greenish-blue	1	1	1	2	-	-	-	-
Unknown	24	29	17	33	4	20	3	25

The colour of the metastasis was related to the nature of the primary tumour. A yellowish-orange choroidal metastasis was seen in 50% of the patients with a uveal metastasis of breast cancer and in 40% of patients with a metastasis of lung cancer. In lung cancer, grey metastases are encountered more frequently than in breast cancer, viz. in 30% and 10%, respectively.

Of the 42 yellowish-orange uveal metastases 26 originated from breast cancer (62%) and 8 from lung cancer (19%). Five of the 12 grey lesions (42%) proved to be metastases of breast cancer, 6 of lung cancer (50%). In a yellowish-orange tumour, therefore, the probability of a metastasis of breast cancer is greatest, while a grey lesion may have arisen from lung cancer or from breast cancer with about equal degrees of probability.

In 41 patients with a choroidal metastasis (49%), the pigment was distributed irregularly over the tumour surface, in 12 patients (14%) evenly [31 patients (37%) unknown]. The irregular distribution of the pigment causes the mottled tumour aspect so characteristic of metastases (Colour plate 7) (Reese, 1976; Shields, 1983). No relationship was found between this pigment distribution and the colour of the metastasis.

In contrast to the findings of Shields et al. (1976), that the orange pigment on the tumour surface is observed in virtually all patients with choroidal metastases, such pigment was observed in only one patient with a grey-coloured choroidal metastasis from lung cancer of our study group.

Regarding the presence of ***exudates*** on or round the tumour most of the case histories contained no information. These data could only be retrieved of patients of whom fundus photographs had been made.

Reliable data concerning exudates on the tumour were available concerning 44 of the 84 patients with choroidal metastases. Such exudates were absent in 26 patients (59%) and present in 18 (41%), in six of whom they were described as 'numerous'.

With regard to exudates round the tumour, data were known concerning 43 patients: they were absent 38 (88%) times and present five times (12%), in one instance described as 'numerous'.

Data on exudates were lacking regarding too many patients to allow conclusions to be drawn from the above data.

As known from the literature, a ***retinal detachment*** is a frequent complication in patients with a choroidal metastasis (Figure 2.3.2.4) (Ferry, 1967; Gass, 1972; Shields, 1983). In 38 of the 84 patients with choroidal metastases in our patient group, ophthalmoscopical signs of a retinal detachment were present (45%): 20 times these were described as occupying less than one-quarter of the fundus and 18 times, as more than one-quarter. Total retinal detachment was never observed. No retinal detachment was present in 40 patients (48%) [six patients (7%) unknown].

The frequency of occurrence of a retinal detachment increased with increasing prominence of the tumour. The echographically measured prominence was known in 31 of the 38 patients with a retinal detachment; it amounted to 4.8 mm on average. In 32 of the 40 patients without a retinal detachment this was 2.4 mm on average.

Development of a retinal detachment was also related to the localization of the tumour: a retinal detachment was seen in only four of the 19 patients with a tumour localization within the arcade of the large retinal vessels (21%) as against 22 of the 44 patients with a metastasis along the arcade (50%) and nine of the 15 patients in whom the tumour was situated outside the vascular arcade (60%).

No relationship was found between occurrence of retinal detachments and the nature of the primary tumour.

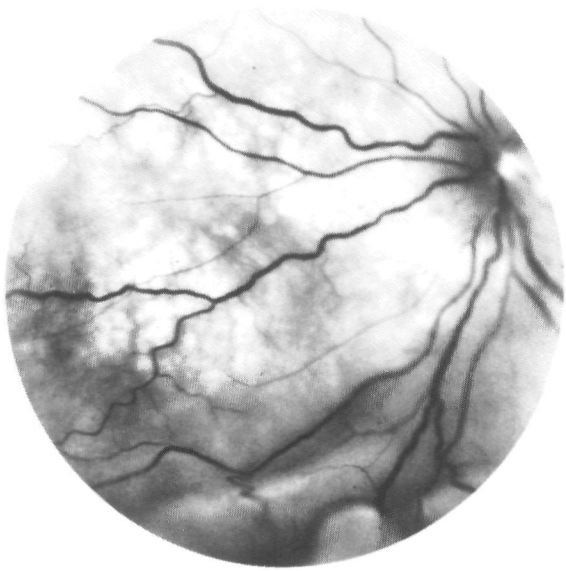


Figure 2.3.2.4 Fundus photograph of the left eye showing a nasally located choroidal metastasis with a secondary retinal detachment inferiorly in a patient with breast cancer.

In 13 patients with uveal metastases (15%) ***blood*** was observed on or round the tumour or in the vitreous (Figure 2.3.2.5).

In 10 patients with a choroidal metastasis, haemorrhages were localized on the tumour surface (12%) while in 53 patients (63%) no such haemorrhages were observed [21 patients (25%) unknown].

Blood round the tumour was seen in only four patients (5%) while this was not the case in 60 other patients (71%) [20 patients (24%) unknown].

In the vitreous a haemorrhage was observed in three patients (4%) which was once very dense and twice, slight. In 68 patients the vitreous was clear of blood (81%), 13 times this was not stated (15%).

Freedman and Folk (1987) at initial ophthalmological examination of 58 patients with an intraocular metastasis, observed a retinal bleeding in one patient and a vitreous haemorrhage in two. In our group of patients with uveal metastases, haemorrhages were encountered much more frequently than is reported in the literature, while in many cases such data were lacking.

Haemorrhages were observed in six of the 52 patients with breast cancer (12%) and in two of the 15 patients with lung cancer (15%). On the other hand, haemorrhages occurred in five of the 15 patients with some other malignancy (33%), namely in one patient with a thyroid carcinoma, one patient with a clear-cell carcinoma of the kidney (Grawitz tumour) and three patients with a tumour of unknown origin.

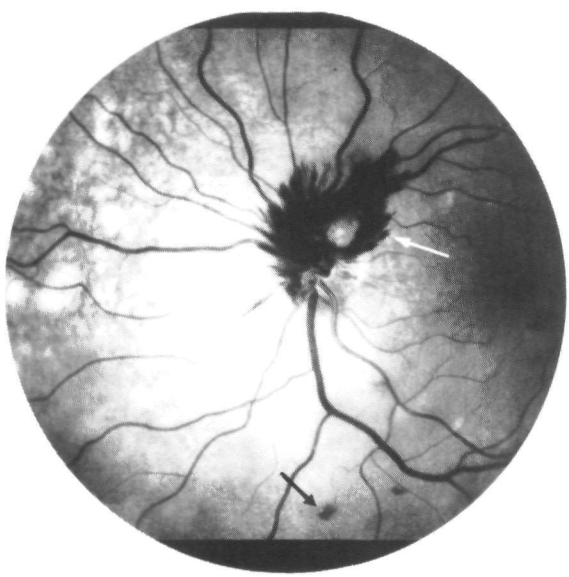


Figure 2.3.2.5 Fundus photograph of the left eye showing a nasally located choroidal metastasis from a pancreatic carcinoma surrounding the optic disk. Haemorrhages into the retinal nerve fibre layer around the disk (white arrow) and in the periphery (black arrow).

A ***metastasis in the anterior segment*** was observed four times.

In the patient with an iridal metastasis originating from lung cancer, after clearing of the abundant fibrin in the anterior chamber after a subconjunctival injection of dexamethasone, a white tumour was observed temporosuperiorly in the iris. Its appearance strongly suggested a metastasis. Opthalmoscopically, no abnormalities were observed.

In one of the two patients with a ciliary metastasis, a swelling existed temporally in the fundus with vascular injection in the angle of the anterior chamber and the ciliary body. On the limbal side the tumour had broken through the iris and caused a hyaline white iridic mass there (Colour plate 2). On and round the tumour a few minor haemorrhages were observed, the vitreous was clear of blood. No retinal detachment was present. The preliminary diagnosis of a 'tumour' was made. Ten days later, lung cancer was diagnosed.

In the other patient with a ciliary metastasis, lung cancer had been diagnosed as long as 1.5 years before the ophthalmological diagnosis. Unfortunately, concerning the ophthalmoscopical image of this tumour, no data are known other than fast growth and break through the iris.

In the last patient with a metastasis in the anterior segment, an adenocarcinoma of the lung had been diagnosed one month previously. Inferiorly on the pupillary margin, a grey iris process was visible (Colour plate 1). At ophthalmoscopy, nasally superior a second choroidal lesion was observed in the periphery without haemorrhages or retinal detachment. Both tumours were described only as 'prominences'.

All these metastases in the anterior segment proved to have originated from lung cancer. Both Barbee et al. (1971) (in iris metastases) and Ferry and Font (1975) (in metastases in the anterior segment) described lung cancer as the primary tumour in 50% of the patients. Although the number of patients with a metastasis in our study group was only small, the fact that the primary tumour was lung cancer in all cases was noticeable. No explanation of this phenomenon can be given.

After irradiation of a bilateral choroidal metastasis, in a fifth patient with breast cancer a metastasis in the ciliary body developed at a later date, with invasion of the angle of the anterior chamber and of the iris.

In 62% of the patients with a metastasis in the uvea the correct ***ophthalmoscopical diagnosis*** was made after only history-taking and standard outpatient examinations such as optometry, tonometry, slit lamp examination and ophthalmoscopy. In 29%, no diagnosis was made and the lesion was described solely as 'tumour' or as 'suspicious lesion' (Table 2.3.2.2). In addition, the diagnosis of malignant melanoma was made four times, a haemangioma once, a naevus once, a retinal detachment once and age-related macular degeneration (Kuhnt Junius), once. In this connection it should be noted that initial examination of a patient with an intraocular lesion suspicious of tumour, this lesion as a rule is not classified further before other examinations such as echography and fluorescein angiography have been performed.

Metastases of breast cancer were mostly diagnosed correctly. Metastases of lung cancer that were regularly mistaken for melanomas, and metastases of one of the other malignancies were frequently not further classified. A number of causes of this fact may be mentioned:

- In 98% of the patients with a uveal metastasis of breast cancer, the primary tumour was already known at the time of diagnosis of the intraocular tumour, as compared with 45% of patients with a metastasis of lung cancer and 40% of patients with metastases of some other malignancy. In patients with breast cancer, therefore, the possibility of an intraocular metastasis will be considered sooner
- Multiple and bilateral metastases were observed most frequently in patients with breast cancer. For this reason, also, in breast cancer patients a metastasis will be considered sooner when an intraocular tumour occurs.
- Metastases of lung cancer ophthalmoscopically show similarities to melanomas This, combined with the fact that the primary malignancy is frequently only diagnosed after the intraocular tumour, and with the predominantly solitary and unilateral presence, explains why in patients with an intraocular metastasis of lung cancer this diagnosis initially will less readily be made

Table 2 3.2.2 *Diagnosis after standard outpatient examinations in 87 patients with uveal metastases according to the nature of the primary tumour* *

	All tumours		Breast cancer		Lung cancer		Other	
Diagnosis	N	%	N	%	N	%	N	%
Metastasis	54	62	44	85	5	25	5	33
Melanoma	4	5	-	-	4	20	-	-
Haemangioma	1	1	-	-	-	-	1	7
Naevus	1	1	1	2	-	-	-	-
Retinal detachment	1	1	1	2	-	-	-	-
Kuhnt Junius	1	1	1	2	-	-	-	-
'Tumour'	25	29	5	10	11	55	9	60

** After only history taking and standard outpatient examinations such as optometry, tonometry, slit lamp examination and ophthalmoscopy*

Summary of ophthalmoscopy in uveal metastases: nearly all uveal metastases were localized in the choroid. In only two of the 87 patients was the metastasis situated in the ciliary body, and in one patient in the iris. One patient presented with a metastasis in the choroid as well as one in the iris. In all these four patients with a metastasis in the anterior segment the primary tumour was lung cancer.

Most metastases were situated in the temporal half of the fundus, especially along or within the vascular arcade Fifty per cent of the metastases were located temporosuperiorly or inferiorly along the vascular arcade or temporally within the arcade of the major vessels. Both the distance between the margin of the tumour and the fovea and that between the margin of the tumour and the disk on average amounted to 1.4 DD

In 33% of the patients up to the moment of treatment, multiple (10 patients) and/or bilateral metastases (25 patients) were observed.

The largest diameter of the tumour was 6.6 DD on average. The colour of the tumour in general was yellowish-orange. However, in metastases of lung cancer grey tumours were frequently observed. The tumour surface mostly showed a mottled appearance and the orange lipofuscin pigment occasionally described in the literature was

observed only once. Exudates on the tumour surface were encountered regularly, round the tumour they were rare.

In almost one-half of the metastases ophthalmoscopy revealed a retinal detachment, dependent on the localization and prominence of the tumour. In 15% of the tumours, blood on or round the tumour or in the vitreous humour was observed.

In the patient with a metastasis of the iris, a white tumour was observed. The colour of the tumours in the patient with a metastasis in the choroid as well as in the iris was grey. A metastasis in the ciliary body, which had broken through the iris, caused a grey iridal mass with some haemorrhages on the tumour surface.

In Table 2.3.2.3 the principal ophthalmoscopical features of patients with uveal metastases are summarized and compared with melanomas, haemangiomas and naevi of the uvea. Subsequently, a short description of these various tumours is given.

Table 2.3.2.3 *Ophthalmoscopical features in patients with metastases, malignant melanomas, haemangiomas and naevi*

	Intraocular tumour			
	Metastasis	Melanoma	Haemangioma	Naevus
Number of patients	87	422	27	60
Localization:				
Choroid	97% *	90%	96%	95%
Ciliary body	2	7	4	-
Iris	2 *	4	-	5
Right eye	54%	50%	30%	60%
Left eye	46	50	70	40
Bilateral	29	0 **	-	7
Multiple ##	33	0 **	-	7
Localization: #				
Temporal	71%	57%	76%	78%
Nasal	25	37	20	20
Unknown	4	5	4	2
Localization: #				
Superior	52%	46%	57%	39%
Inferior	44	49	39	59
Unknown	4	5	4	2

to be continued on next page

Table 2.3.2.3 (continued)

	Intraocular tumour			
	Metastasis	Melanoma	Haemangioma	Naevus
Localization: #				
Inside vascular arcade	23%	16%	41%	23%
Along vascular arcade	52	43	44	42
Outside vascular arcade	18	25	7	30
Unknown	7	17	7	5
Mean tumour distance from: #				
Macula (DD)	1.4	1.4	1.4	2.3
Optic disk (DD)	1.4	1.5	1.4	3.0
Macular involvement #	25%	14%	35%	5%
Mean tumour diameter #∞ (DD)	6.6	9.5	5.7	2.0
Colour: #				
Yellowish-orange/cream	50%	12%	19%	7%
Grey	13	28	15	49
White	5	7	4	-
Reddish-brown	2	4	11	-
Greenish-blue	1	5	-	5
Black	-	2	-	2
Salmon-pink	-	-	26	-
Unknown	29	42	26	37
Mottled aspect #	49%	41%	50%	42%
Orange lipofuscin pigment on tumour surface #	1	13	8	4
Exudates: #				
On tumour surface	21%	18%	4%	20%
Surrounding the tumour	6	3	-	15
Retinal detachment	45%	45%	33%	-%
Blood:				
On tumour surface	12%	13%	-%	-%
Surrounding the tumour	5	6	-	5
In vitreous	4	6	-	-

*DD: disk diameter; * one patient metastasis in the choroid as well as in the iris; ** one patient; # in choroidal tumours; ## bilateral and/or multiple in one eye; ∞ mean of the largest diameter*

Melanomas compared with metastases were situated more frequently in the anterior segment and often nasally in the fundus and outside the arcade of the major retinal vessels. Less frequently the melanoma was encountered at the site of the macular area. A bilateral melanoma was established in only one patient, and a multiple melanoma in one eye in one other patient.

The maximal diameter of the lesion was significantly larger than in metastases. The most frequently observed colour of a melanoma was grey with, almost as often as in metastases, a mottled appearance of the tumour surface. The orange lipofuscin pigment was described in 13% of the patients with a melanoma (Colour plate 8; Figure 2.3.2.6).

With regard to the incidence of exudates, retinal detachment and haemorrhages, no distinct differences existed between metastases and melanomas.

The preliminary diagnosis after history taking and standard examination was melanoma in 44% of the cases and 'tumour' in 47%. In five patients the melanoma was diagnosed as a metastasis, although no other malignancy elsewhere in the body was known. The ophthalmoscopical picture of a choroidal metastasis of lung cancer may show many points of similarity with that of a choroidal melanoma.

Haemangiomas of the iris did not occur in our study group. Once, a haemangioma of the ciliary body was observed, the other haemangiomas were situated in the choroid. Even more frequently than metastases, haemangiomas were localized in the temporal half of the fundus and frequently within the arcade of the major retinal vessels. Of all haemangiomas, 35% were localized in the macular area (Colour plate 9).

The colour was salmon-pink in 26% of the cases. In other tumours than haemangiomas this colour was never observed. In 19% of the haemangiomas the colour was yellowish-orange. The orange lipofuscin pigment was seen only sporadically in haemangiomas. In contrast to melanomas or metastases, exudates on or round the tumour were encountered only rarely. Retinal detachment occurred in 33%, presence of blood was never observed.

The ophthalmoscopical diagnosis was haemangioma in 41%, 'tumour' in 48% of the cases. One single time the diagnosis was metastasis.

Most ***naevi*** that were suspected of being tumours were localized in the choroid, an occasional one in the iris. Of the naevi, 78% were localized temporally. The lesions lay scattered over the entire ocular fundus and were not limited to the area within the vascular arcade. Only 5% were localized in the macular area. Bilateral naevi were established four times. Naevi were substantially smaller than the other intraocular tumours, with a mean maximal diameter of only 2.0 DD.

The colour was mostly grey. Naevi, also, frequently displayed a mottled tumour aspect, and orange pigment was described twice. In naevi, exudates on and round the tumour were observed regularly. Retinal detachments were never observed. Intraocular haemorrhages were extremely rare in naevi (Colour plate 10; Figure 2.3.2.7).

The diagnosis after history taking and standard examination was naevus in 57% and 'tumour' in 40%. One time, the diagnosis of metastasis was made.

In 61% of the 15 patients with ***retinoblastomas*** the tumour was located in the right eye, in 39% in the left eye. In 32% of the patients, bilateral lesions were observed and multiple lesions in one eye in two patients. All retinoblastomas were white in colour and filled the entire ocular cavity in most cases. In 92% of the cases a diagnosis of retinoblastoma was made ophthalmoscopically (Figure 2.3.2.8).

Miscellaneous intraocular lesions. In the patients with a lymphoma or leukaemia the choroid was involved. In four of the five patients, both eyes were affected and multiple lesions were established in all patients. All lesions were situated within the arcade of the major vessels, both temporally and nasally. The colour varied from white to yellowish-orange and grey. Blood on or round the tumour was observed in most cases, and in one patient a vitreous haemorrhage was present. In no case was a retinal detachment observed. In over one-half of the cases the outpatient diagnosis was consistent with a malignant haematological lesion.

Subretinal haemorrhages were present bilaterally in two of the nine patients, but never multiple in one eye. In one patient, a macular degeneration in the contralateral eye was known. All lesions were localized temporally, and only rarely outside the vascular arcade. Three of the nine subretinal haemorrhages were situated at the site of the macular area. The colour was mostly grey, but one black and one white tumour were observed. Retinal detachment was present in two patients. In only one patient was the ophthalmoscopical diagnosis of haemorrhage made. In six patients the lesion was classified as a 'tumour'.

Among the seven patients with age-related macular degeneration one patient with a distinct bilateral tumour was reported. The colour of the macular tumour varied: yellowish-orange, grey or reddish brown. In two patients a retinal detachment was observed, in six patients a vitreous haemorrhage. The diagnosis was twice Kuhnt Junius and four times, 'tumour' (once no diagnosis possible because of vitreal haemorrhage) (Figure 2.3.2.9).

In the five patients with a choroidal detachment, the detachment was situated nasally slightly more frequently than temporally and never within the vascular arcade. The colour was yellowish-orange, grey or reddish brown. Lipofuscin pigment on the surface was observed in one patient. In no case were haemorrhages established. In all cases this diagnosis had been made ophthalmoscopically as well.

All three leiomyomas were localized in the ciliary body. The colour of the tumour was grey or white. Haemorrhage or retinal detachment were never present. Once, the leiomyoma was mistaken for a melanoma and twice it was classified as a 'tumour'.

In all three patients with a retinal detachment which was suspected of being a tumour, a vitreous haemorrhage was present, owing to which in one case the fundus could not be evaluated adequately. In the other two patients the initial diagnosis was melanoma.

In two of the 88 ***tumours of unknown nature***, the ophthalmoscopical diagnosis of metastasis was made without subsequent confirmation. One case concerned a patient who had been known for 8 years with a renal carcinoma and in whom a unilateral yellowish-orange tumour in the choroid was observed without retinal detachment or haemorrhage. In the other patient, with a grey choroidal tumour, no malignancy elsewhere in the body was known.

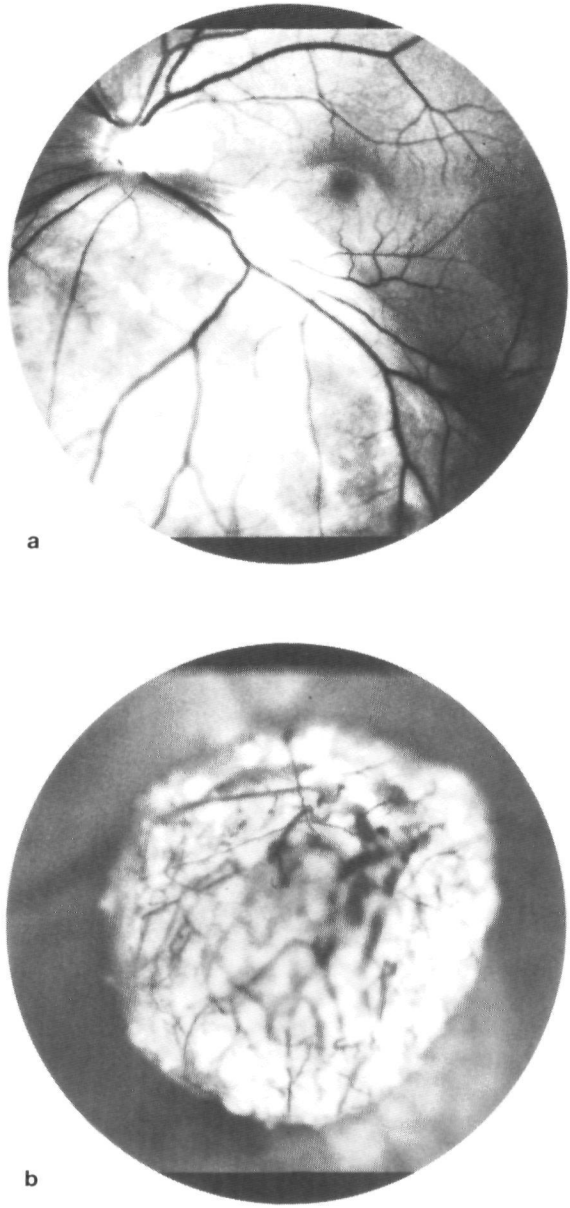


Figure 2.3.2.6 a. Fundus photograph of the left eye showing a prominent pigmented choroidal mass: malignant melanoma of the choroid. b. Fundus photograph of the right eye of a different patient showing a mushroom-shaped amelanotic malignant melanoma of the choroid just inferiorly and obstructing the view of the optic disk.

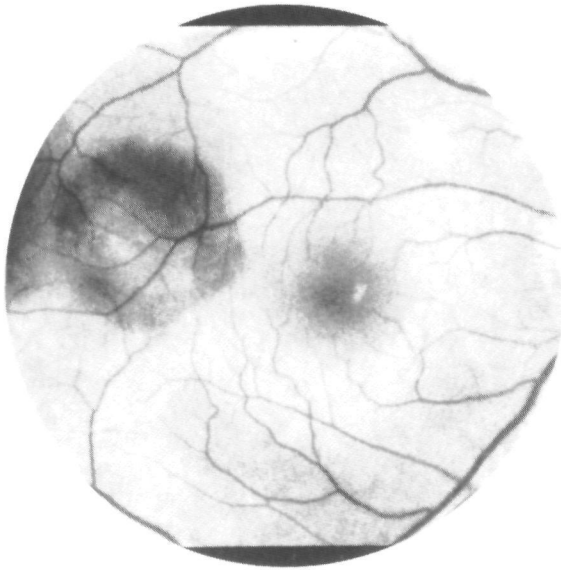


Figure 2.3.2.7 Fundus photograph of a grey-coloured slightly elevated choroidal lesion located temporally of the macula in the right eye: naevus of the choroid.

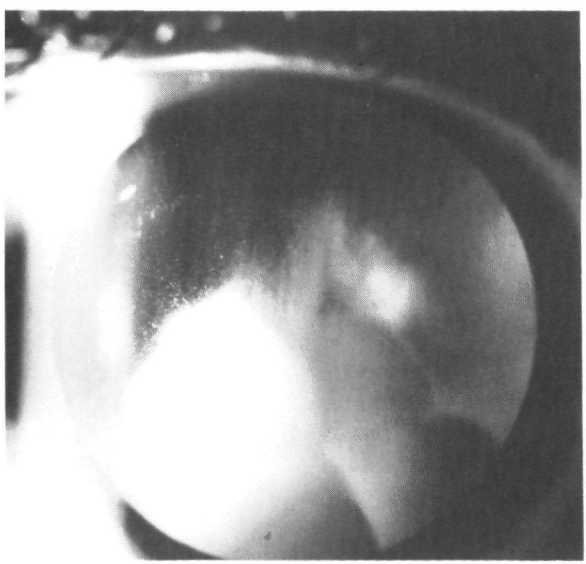


Figure 2.3.2.8 External photograph of the right eye showing a retinoblastoma.

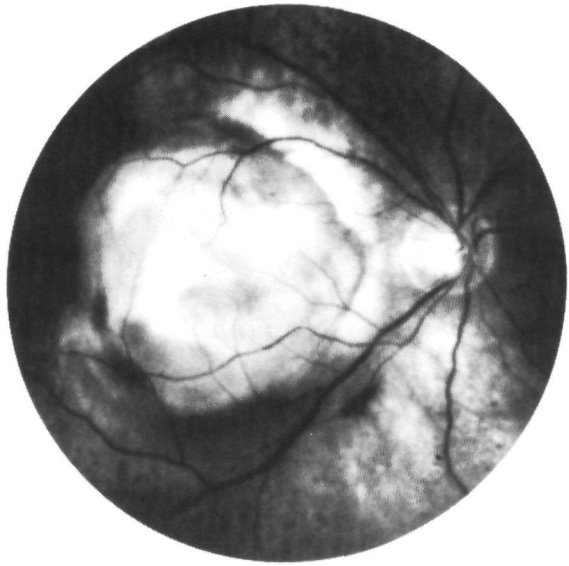


Figure 2.3.2.9 Fundus photograph of the right eye showing a prominent subretinal tumour in the macular area: age-related macular degeneration (Kuhnt Junius).

Conclusion: ophthalmoscopy makes an essential contribution to the differential diagnostics of intraocular tumours, although no ophthalmoscopic picture pathognomonic of uveal metastases exists. Great importance attaches to the bilateral and/or multiple presence of the lesions, as frequently observed in metastases in contrast to the findings in melanomas and haemangiomas of the uvea. In retinoblastoma, bilateral lesions are observed in a high percentage, also. Multiple lesions are also encountered in naevi, retinoblastomas, lymphoproliferative diseases, subretinal haemorrhages and macular degenerations.

Melanomas of the uvea mostly have a grey colour, unlike the yellowish-orange lesions in metastases. The orange lipofuscin pigment that may be present in melanomas is only rarely observed in metastases.

Haemangiomas may be typically salmon-pink in colour. In many respects the ophthalmoscopical picture may resemble that of metastases. However, intraocular haemorrhages in haemangiomas were not described in our study group.

Naevi are relatively small lesions, nearly always with a grey colour and without secondary retinal detachment or haemorrhages. Consequently, differentiation from metastases in most cases is quite well possible.

Retinoblastomas are white, highly prominent lesions and have ophthalmoscopically distinct features from other intraocular tumours.

2.3.3 Fluorescein angiography

In our study group, fluorescein angiographic data were available of 49 of the 84 patients with choroidal metastases.

In 35 patients (71%) sufficient details could be observed for adequate evaluation of the fluorescein angiogram. Figure 2.3.3.1 shows an example of fluorescein angiography in a patient with multiple choroidal metastases from breast cancer. In 14 patients (29%), only poor evaluation was possible, either due to opaque media (nine patients) or in connection with technical problems such as a peripheral localization of the tumour (five patients).

Thus, of many patients no or only limited fluorescein angiographic data were available. Partly this was due to the large number of patients who were examined in the outpatient department only once or were referred specifically for one particular examination, e.g. echography. Consequently, the data given below concern only patients of whom at the time of the retrospective study photographs or an extensive report of the fluorescein angiographic examination were available.

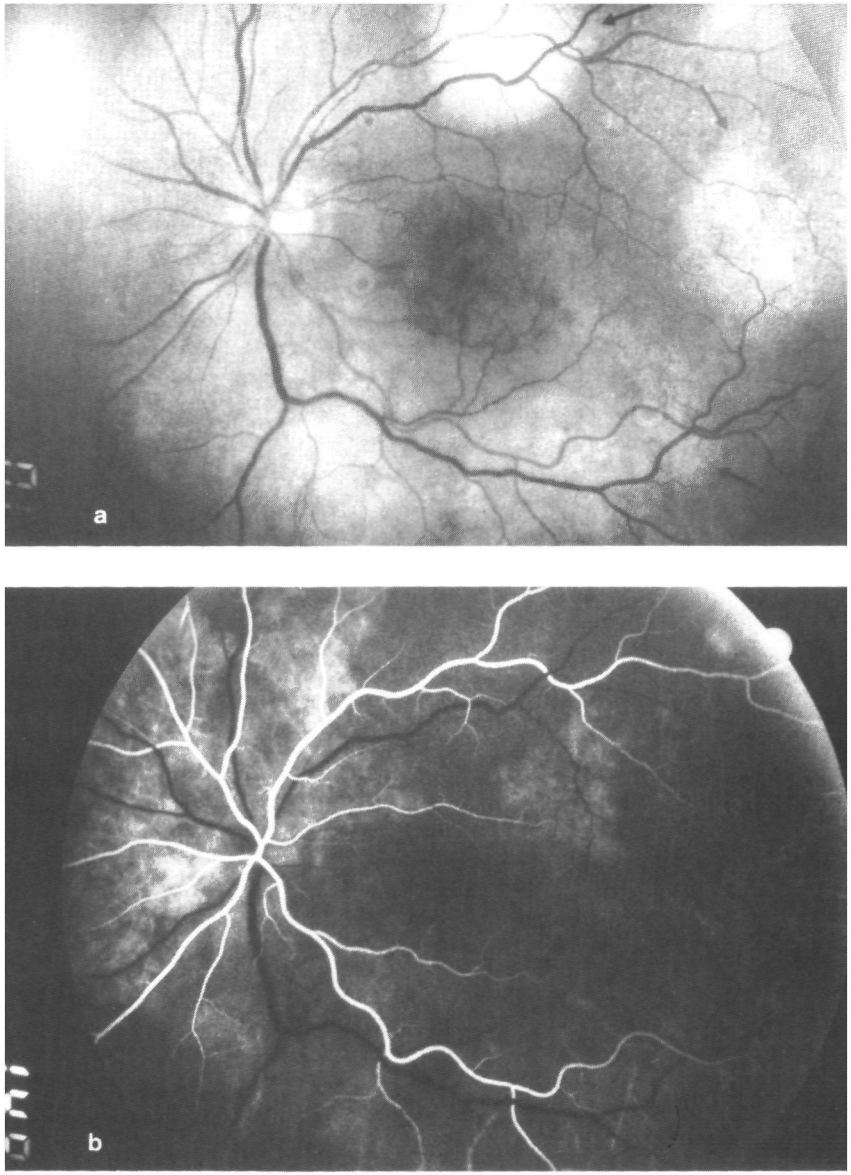
Fluorescein angiography was performed in one patient with a ciliary metastasis and break through the iris. This patient will be described separately.

As regards the ***moment of staining***, in the 49 patients with choroidal metastases staining of the choroid occurred after an average of 13 seconds and filling of the retinal arteries after 12 seconds (Table 2.3.3.1). The retinal veins filled with fluorescence 15 seconds on average after the injection of the dye, 3 seconds later than the arteries. A first fluorescence of the tumour was observed after 21 seconds.

Table 2.3.3.1 *Moment of staining of various intraocular structures after injection of fluorescein in patients with choroidal metastases*

		Moment of staining (sec)		
	N	Mean	SD	Range
Choroid	35	13	6	3-29
Retinal arteries	33	12	5	3-25
Retinal veins	35	15	6	4-32
Tumour	35	21	29	4-142

In the patients of whom both the moment of staining of the tumour and of the surrounding choroid were known, the tumour on average stained 5 seconds after the choroid. In case of known moment of staining of the tumour and of filling of the retinal arteries, the tumour stained 2 seconds after the retinal arteries and, in case of known moment of staining of the tumour and of filling of the veins, 3 seconds after the retinal veins. This interval was not connected with the colour of the metastases but clearly related to the nature of the primary tumour. In relation to the retinal arteries, the metastases of the different primary tumours stained simultaneously. However, metastases of breast cancer or of one of the other malignancies started to fluoresce in a period from 0 to 1 second *before* the retinal veins, while in metastases of lung cancer fluorescence on average only took



gure 2.3.3.1 a. Fundus photograph of three choroidal metastases from breast cancer in the e (arrows) b-f. Fluorescein angiography of the same lesions: b. Arterial phase with diffi pofluorescence at the site of the metastatic lesions.

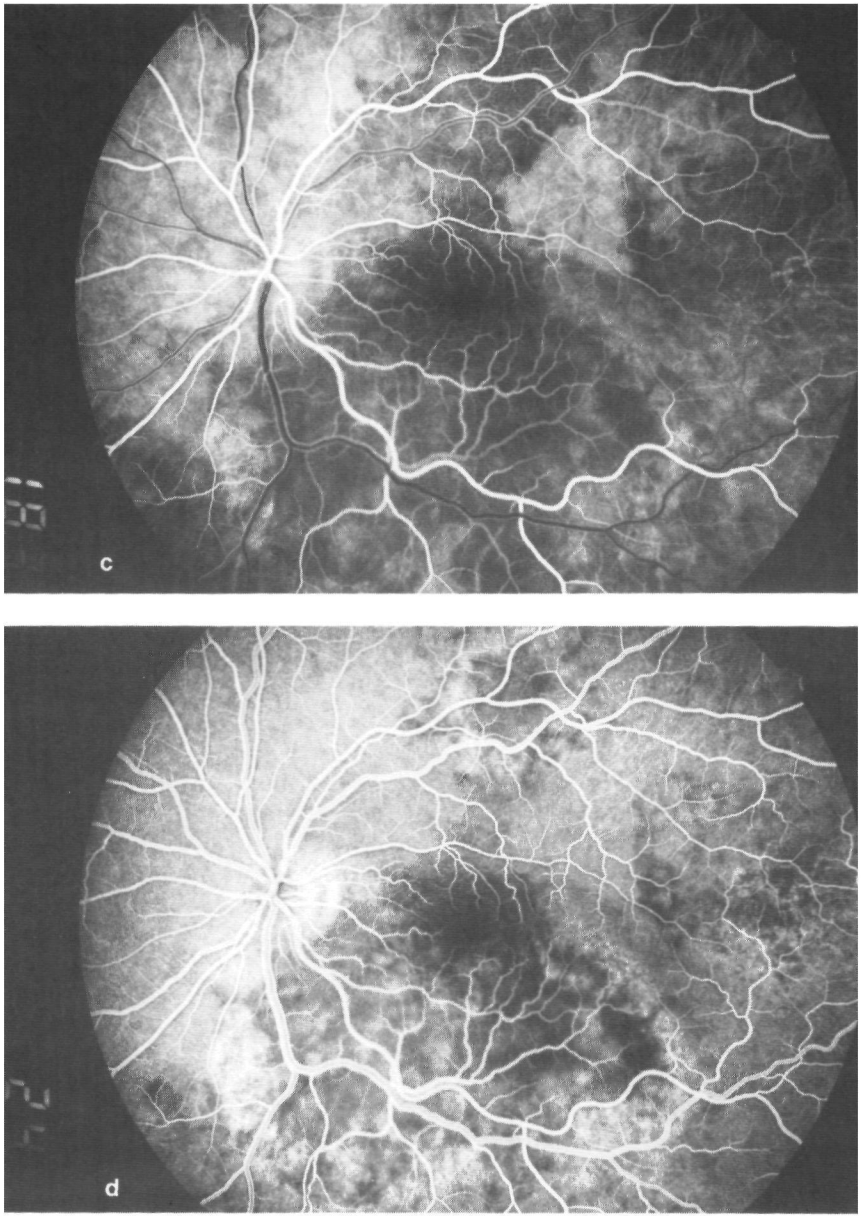
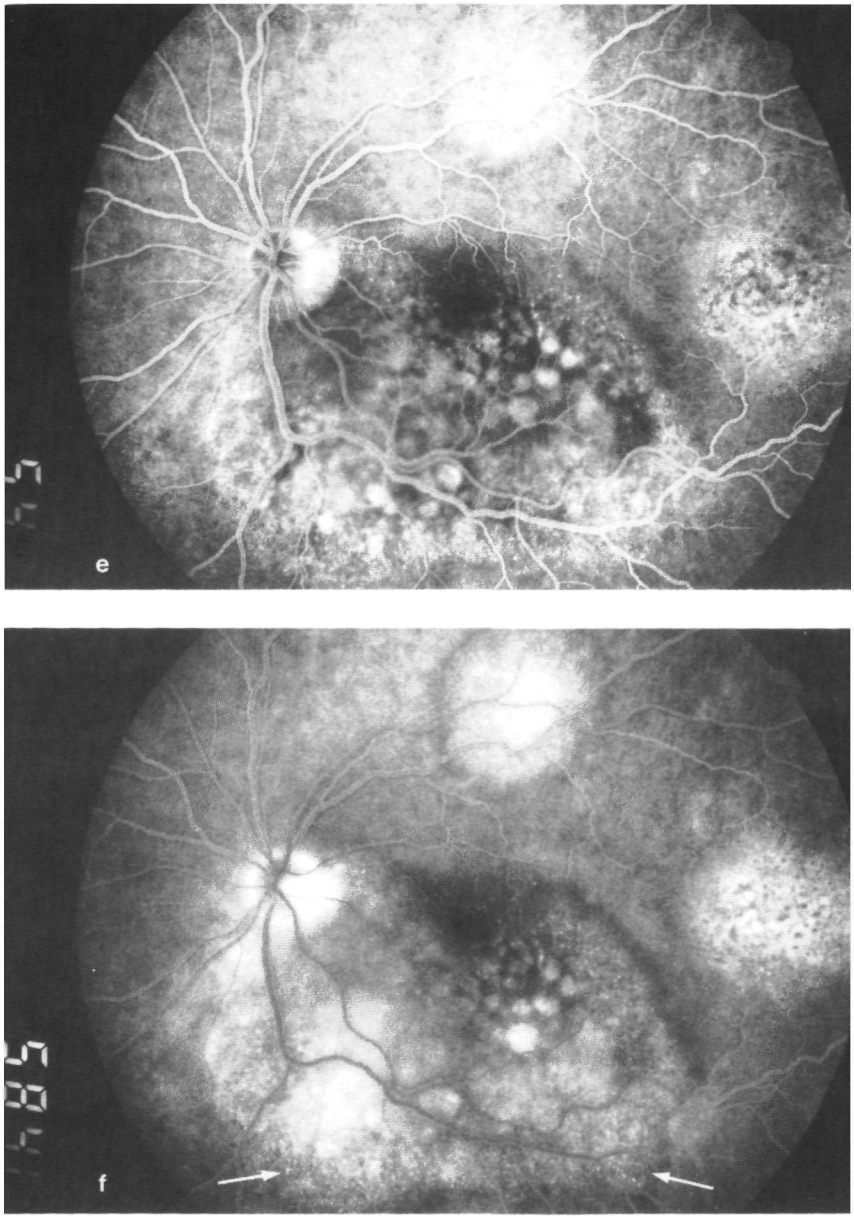


Figure 2.3.3.1 (continued) c. Early venous phase: the lesions remain relatively hypofluoresc
d. Venous phase: hypofluorescence of the lesions with grossly mottled hyperfluorescence.



igure 2.3.3.1 (continued) e. and f. Late venous and late phases with hyperfluorescence of etastases showing some hyperfluorescent spots on the tumour margin (arrows).

place 22 seconds *after* the veins. In relation to the surrounding choroid, metastases of breast cancer on average stained 2 seconds later, metastases of one of the other tumours 1 second later and metastases of lung cancer as long as 25 seconds later. Between the various primary tumours there existed no distinct differences with regard to the interval of staining between veins and arteries on the one hand and the surrounding choroid and arteries on the other.

It appears, therefore, that metastases of lung cancer at fluorescein angiography stain relatively late compared with metastases of other malignancies.

Of more importance than the timing is the ***pattern of staining***. For instance, a tumour may show some fluorescence even in an early phase, but subsequently lag behind in relation to the staining of the surrounding choroid so that the tumour is classified as relatively hypofluorescent.

Staining of the tumour occurred usually simultaneously with, and less frequently after staining of the surrounding choroid. In relation to the retinal arteries, staining was observed as often simultaneously with as after these vessels, in relation to the retinal veins as often before as simultaneous and less often, later (Table 2.3.3.2).

Table 2.3.3.2 *Moment of staining of choroidal metastases in relation to the moment of staining of the surrounding choroid, the retinal arteries and the retinal veins*

	Staining choroidal metastasis							
	Before		Simultaneous		After		Unknown	
	N	%	N	%	N	%	N	%
Choroid	1	2	21	43	12	24	15	31
Retinal arteries	1	2	16	33	15	31	17	35
Retinal veins	13	27	12	24	8	16	16	33

In our study, the fluorescence of the tumour was classified in three categories:

1. predominantly hypofluorescent;
2. predominantly hyperfluorescent;
3. fluorescence of the same intensity as that of the surrounding choroid.

The moments at which the pattern was determined were (Table 2.3.3.3):

a. early arterial phase: the moment of the first filling of the retinal arteries with fluorescein;
b. arterial phase: the moment halfway between the staining of the arteries and that of the veins;
c. early venous phase: the moment of initial staining of the retinal veins;
d. late venous phase: the late phases after the fluorescein had passed from the retinal veins.

Table 2.3.3.3 *Fluorescein angiographic patterns in various phases in relation to the surrounding choroid in patients with choroidal metastases*

	Early arterial phase		Arterial phase		Venous phase		Late venous phase	
	N	%	N	%	N	%	N	%
Hypofluorescence	31	63	25	51	9	18	1	2
Isofluorescence	7	14	13	27	31	63	39	80
Hyperfluorescence	2	4	2	4	5	10	8	16
Unknown	9	18	9	18	4	8	1	2

In the two arterial phases, metastases were predominantly hypofluorescent. Early hyperfluorescence was rare. At the moment of staining of the retinal veins, however, a change in the staining of the choroidal metastases had occurred, from predominantly hypo- to isofluorescent. Only 18% of the metastases still showed hypofluorescence in the early venous phase while 63% showed a fluorescence of the same intensity as the surrounding choroid. In the late venous phase, a hypofluorescent tumour was observed in only one patient (Figure 2.3.3.2).

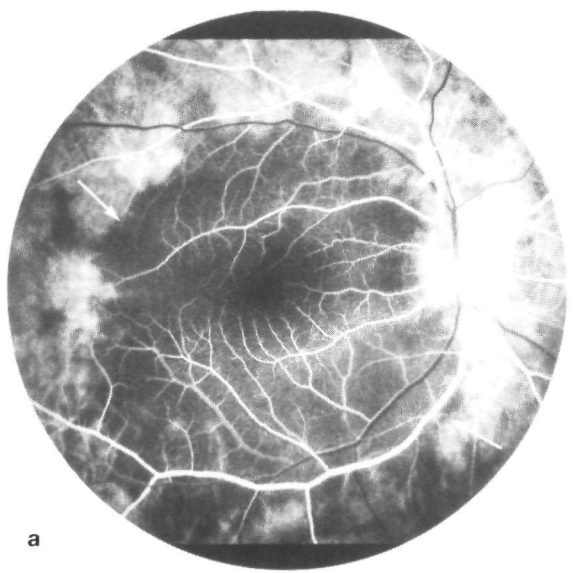
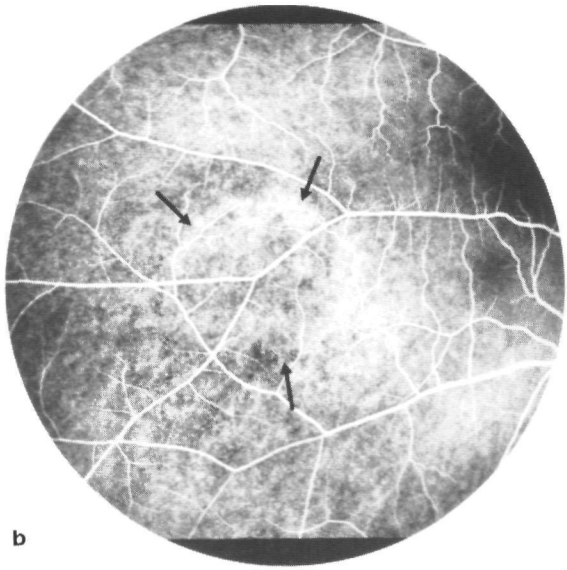


Figure 2.3.3.2 *a. Fluorescein angiogram of a choroidal metastasis in the right eye in a patient with presumed colonic carcinoma. Early venous phase with hypofluorescence of the tumour (arrows).*



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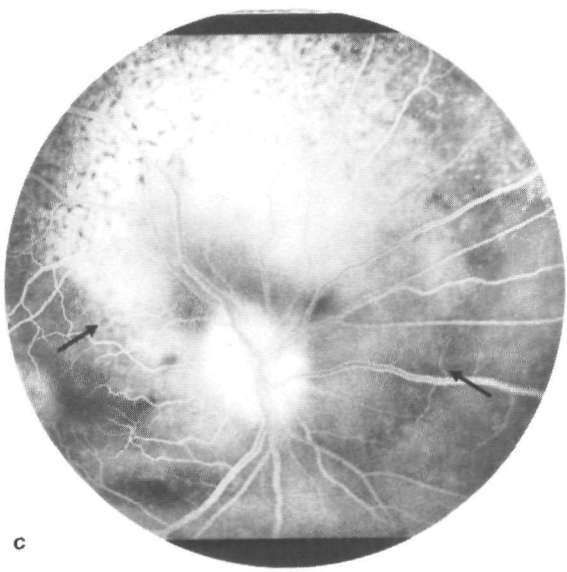


c

Figure 2.3.3.2 (continued) b. Fluorescein angiogram of a choroidal metastasis temperoinferior in the right eye in a patient with breast cancer. Venous phase with a fluorescence of the tumour (arrows) of almost the same intensity as the surrounding choroid. c. Fluorescein angiogram of a choroidal lesion in the right eye in a patient with pancreatic carcinoma superior to and surrounding the optic disk, compatible with choroidal metastasis (arrows). Late venous phase with hyperfluorescence of the tumour.

The nature of the primary tumour had no appreciable influence on this fluorescence. The only noticeable element was that metastases of tumours other than breast or lung cancer in the late venous phase were never isofluorescent but half were hypo- and half hyperfluorescent. However, a highly varied patient population was concerned here.

The large proportion of hypofluorescent tumours in patients with uveal metastases is in agreement with the findings of Norton et al. (1964) and Gass (1972). In general, staining of the tumour started only in the venous phases, as also described by Offret and Haye (1971), Orsoni (1968) and Bonnin (1986).

This division into hypo-, iso- and hyperfluorescence is fairly rough, however. Therefore, hypofluorescence of the metastases was specified further as a diffuse hypofluorescence of the tumour, without staining of clearly distinguishable fluorescent areas, a predominant hypofluorescence of the tumour with areas of finely mottled hyperfluorescence and a hypofluorescent lesion with grossly mottled hyperfluorescence. If the intensity of the staining of the larger part of the tumour was the same as that of the surrounding choroid, a subdivision was made into diffuse isofluorescent tumours and isofluorescence with either finely mottled or grossly mottled hypo- or hyperfluorescence. The hyperfluorescent metastases, finally, were subdivided into diffuse hyperfluorescent tumours, hyperfluorescence with finely mottled hypofluorescence and hyperfluorescence with grossly mottled hypofluorescence (Table 2.3.3.4).

In the majority of the patients, the hypofluorescence of the tumour in the early arterial phase was diffuse without clearly staining areas (see Table 2.3.3.2). In the arterial phase, however, in most patients with a hypofluorescent tumour a grossly mottled hyperfluorescence was also observed. The fluorescence of the tumour, which in the early and late venous phases showed the same intensity as the surrounding choroid, in the vast majority of the patients was accompanied by either a finely mottled or a grossly mottled hyperfluorescence (Figure 2.3.3.3).

To summarize the principal fluorescence patterns in choroidal metastases in the various phases, in the early arterial phase 43% of the tumours showed diffuse hypofluorescence, in the arterial phase 29% a hypofluorescence with grossly mottled hyperfluorescence. In the early venous phase, 33% of the metastases showed the same fluorescence as the environment with a grossly mottled hyperfluorescence and 22% with a finely mottled hyperfluorescence. In the late venous phase, 47% showed isofluorescence with grossly mottled hyperfluorescence and 33%, isofluorescence with a finely mottled hyperfluorescence.

Table 2.3.3.4 *Fluorescein angiographic patterns in various phases in relation to the surrounding choroid in patients with choroidal metastases*

	Early arterial phase		Arterial phase		Venous phase		Late venous phase	
	N	%	N	%	N	%	N	%
Hypofluorescence:								
diffuse	21	43	7	14	-	-	-	-
+ finely mottled hyperfluorescence	4	8	4	8	4	8	1	2
+ grossly mottled hyperfluorescence	6	12	14	29	5	10	-	-
Isofluorescence:								
diffuse	4	8	3	6	3	6	-	-
+ finely mottled hypofluorescence	-	-	-	-	-	-	-	-
+ grossly mottled hypofluorescence	-	-	2	4	1	2	-	-
+ finely mottled hyperfluorescence	2	4	5	10	11	22	16	33
+ grossly mottled hyperfluorescence	1	2	3	6	16	33	23	47
Hyperfluorescence:								
diffuse	2	4	-	-	1	2	4	8
+ finely mottled hypofluorescence	-	-	-	-	2	4	2	4
+ grossly mottled hypofluorescence	-	-	2	4	2	4	2	4
Unknown	9	18	9	18	4	8	1	2

As regards the ***course of the fluorescein angiography***, it was only in 39 of the 49 patients that data of all phases of the fluorescein angiography were available. The vast majority of these patients (67%) showed increasing fluorescence from the early arterial to the late venous phase (Figure 2.3.3.4). In 15% of the patients, the fluorescence of the tumour remained constant throughout all phases, and in 10% the staining initially increased and subsequently decreased again. In two patients, the fluorescence first decreased and subsequently increased again, and in one patient the fluorescence decreased from the first phase of the examination (Table 2.3.3.5).

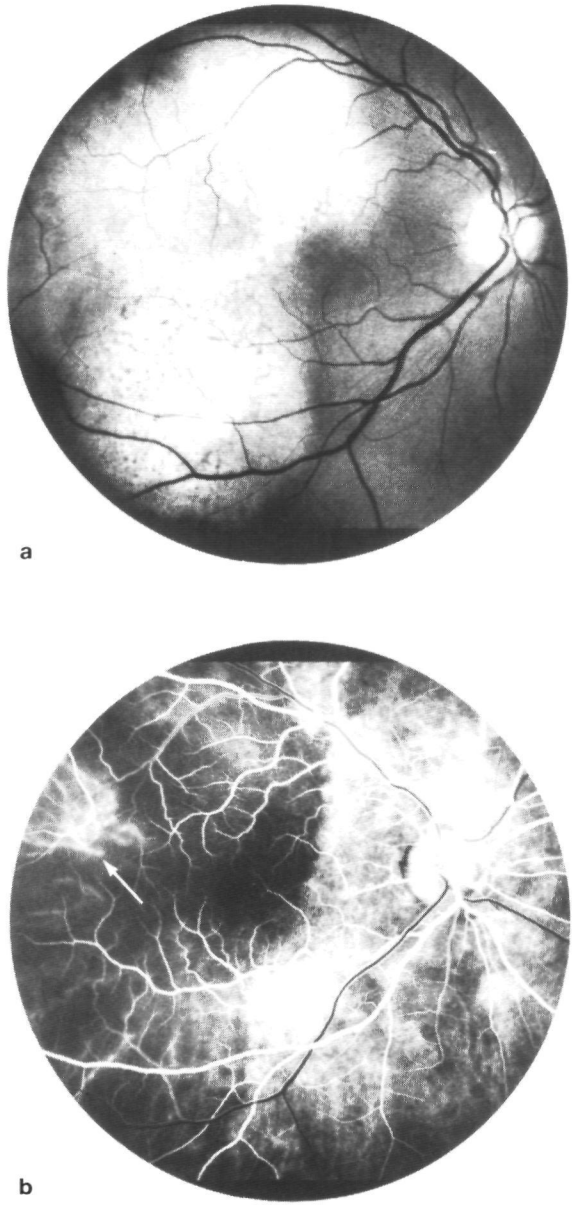
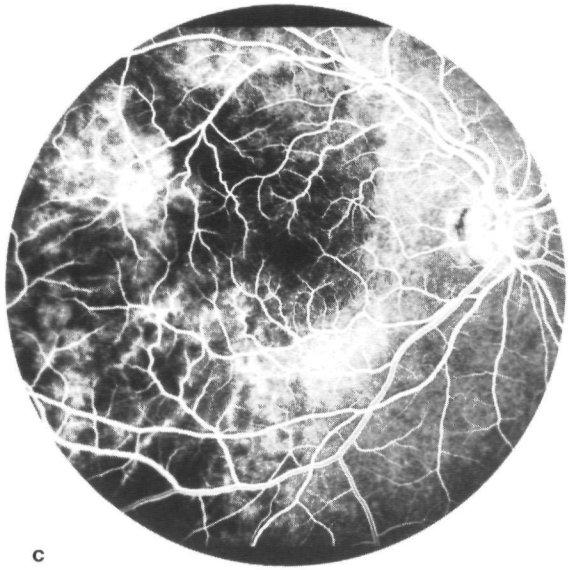


Figure 2.3.3.3 a. Fundus photograph of the right eye in a patient with breast cancer showing three fused choroidal metastases with pigment clumping on the tumour surface.
b-d. Fluorescein angiogram of the same lesions: b. Arterial phase with diffuse hypofluorescence of the lesions and with tumour vessels (arrow).



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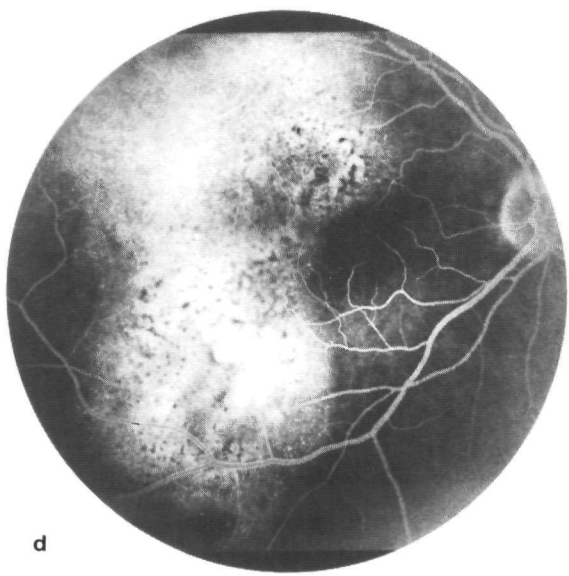
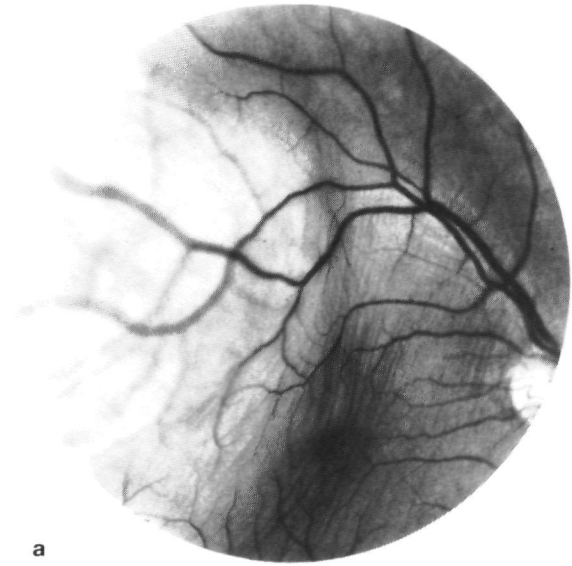


d

Figure 2.3.3.3 (continued) c. Early venous phase. Hypofluorescence of the tumours with grossly mottled hyperfluorescence. d. Late venous phase with staining of the lesions and hypofluorescent spots at the site of the pigment clumps on the tumour surface.



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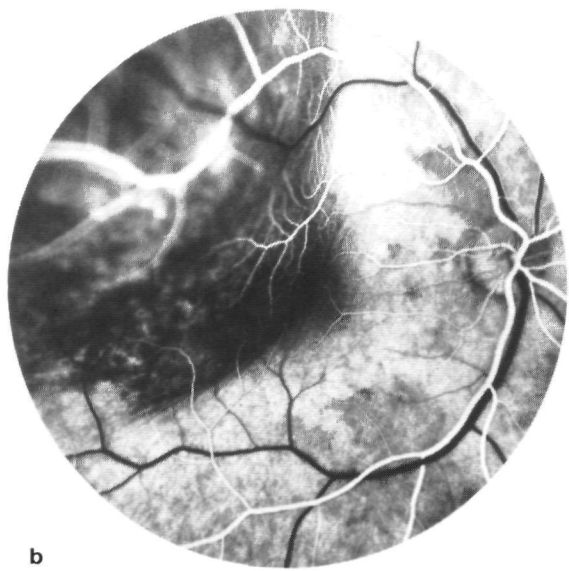
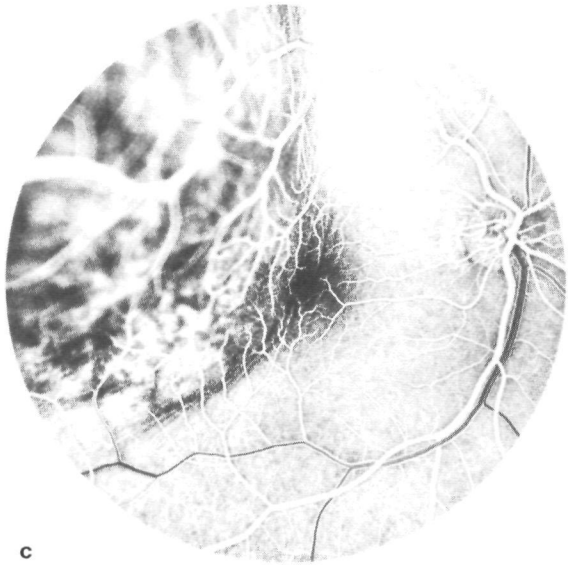


b

Figure 2.3.3.4 a. Fundus photograph of the right eye with a yellowish-orange choroidal tumour in a presumably healthy patient. b-d. Fluorescein angiogram of the same lesion: b. Arterial phase with hypofluorescence of the lesion.



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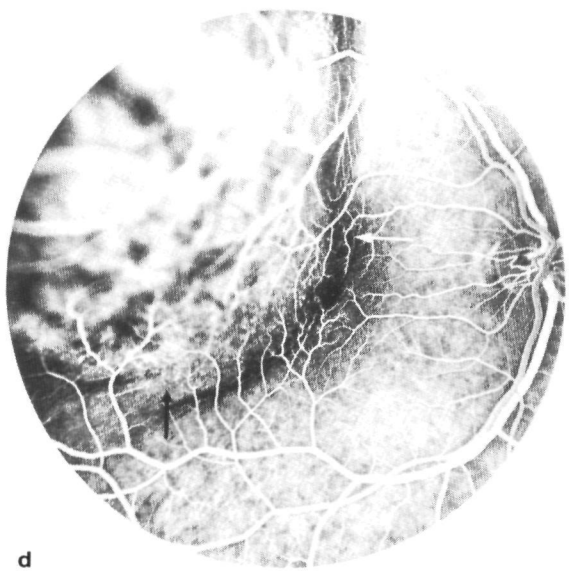


d

Figure 2.3.3.4 (continued) c. Early venous phase with hypofluorescence of the lesion and grossly mottled hyperfluorescence on the tumour surface. d. In the late venous phase the tumour fluoresces with almost the same intensity as the surrounding choroid. Note the hypofluorescent margin (white arrow) and some hyperfluorescent spots at the tumour margin (black arrow). Choroidal metastasis from lung cancer.

Table 2.3.3.5 *Course of the fluorescein angiographic pattern in 39 patients with choroidal metastases*

Fluorescein angiographic pattern								N	%
Early arterial phase		Arterial phase		Venous phase		Late venous phase			
hypo	-	hypo	-	hypo	-	iso		6	15
hypo	-	hypo	-	iso	-	iso		12	31
hypo	-	hypo	-	iso	-	hyper		2	5
hypo	-	hypo	-	hyper	-	iso		1	3
hypo	-	hypo	-	hyper	-	hyper		2	5
hypo	-	iso	-	hypo	-	iso		2	5
hypo	-	iso	-	iso	-	iso		2	5
hypo	-	iso	-	hyper	-	hyper		1	3
hypo	-	hyper	-	iso	-	iso		1	3
hypo	-	hyper	-	hyper	-	hyper		1	3
iso	-	hypo	-	iso	-	iso		1	3
iso	-	iso	-	iso	-	iso		6	15
hyper	-	iso	-	iso	-	iso		1	3
hyper	-	iso	-	iso	-	hyper		1	3

hypo: hypofluorescence; iso: isofluorescence; hyper: hyperfluorescence

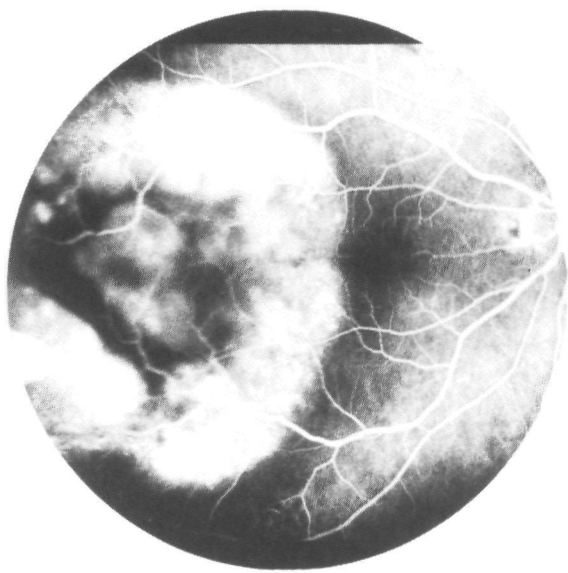


Figure 2.3.3.5 *Fluorescein angiogram showing a choroidal metastasis from lung cancer in the right eye with hypo- and hyperfluorescent areas.*

The most frequently observed course in fluorescein angiography of choroidal metastases was a pattern of hypofluorescence in the two arterial phases and a fluorescence similar to that of the environment in the two venous phases (31%). In 15% of the tumours, hypofluorescence was observed up to and including the early venous phase, with isofluorescence in the late venous phase. In 15% of the patients the fluorescence remained constant in all phases, with the same intensity as that of the surrounding choroid. Other patterns of fluorescence were seen only exceptionally. No different patterns for different primary tumours could be distinguished. Even when the course of the fluorescence was specified further into the patterns as listed in Table 2.3.3.4, no specific pattern for choroidal metastases could be discerned and many different patterns were described. There was no question, therefore, of a characteristic fluorescein angiographic image in choroidal metastases (see also literature: Chapter 1.4.3).

In 14 patients (29%), clearly distinguishable large ***hypofluorescent areas*** in the metastases were described. ***Hyperfluorescent areas*** were observed in three patients (6%) (Figure 2.3.3.5). No relationship existed between the occurrence of these hypo- or hyperfluorescent areas and the nature of the primary tumour.

In 30 patients, the pigment distribution on the tumour surface could be compared with the fluorescence pattern of the metastasis. Eighteen times, areas of ophthalmoscopical hyperpigmentation corresponded to hypofluorescence and once, in a patient with lung cancer, to hyperfluorescence. In 11 patients, this pigmentation showed no clear correlation with hypo- or hyperfluorescent areas in the tumour. Intraocular blood stays hypofluorescent (Figure 2.3.3.6).

The maximal ***diameter*** of the tumour in the fluorescein angiogram was 8.1 disk diameters (DD) on average (SD 4.3; range 1.5-14.0), the minimal diameter was 7.1 DD (SD 5.2; range 1.0-13.0).

Of 38 patients, both fundus photographs and fluorescein angiograms were available so that the tumour sizes measured could be compared. This revealed that the maximal diameter of the metastasis at fluorescein angiography on average was 1.4 times (SD 0.8) that measured at ophthalmoscopy. Five times, a smaller tumour was measured at fluorescein angiography, 18 times a tumour of exactly the same size and 15 times, a larger tumour. This indicates that at fluorescein angiography, metastases apparently in 39% of the cases extend farther into the choroid than could be observed ophthalmoscopically.

In 36 patients (73%), a ***hypofluorescent margin*** round the tumour was seen, which margin was absent in 10 patients (20%) [three patients (6%) unknown]. No distinct relationship with the nature of the primary tumour existed.

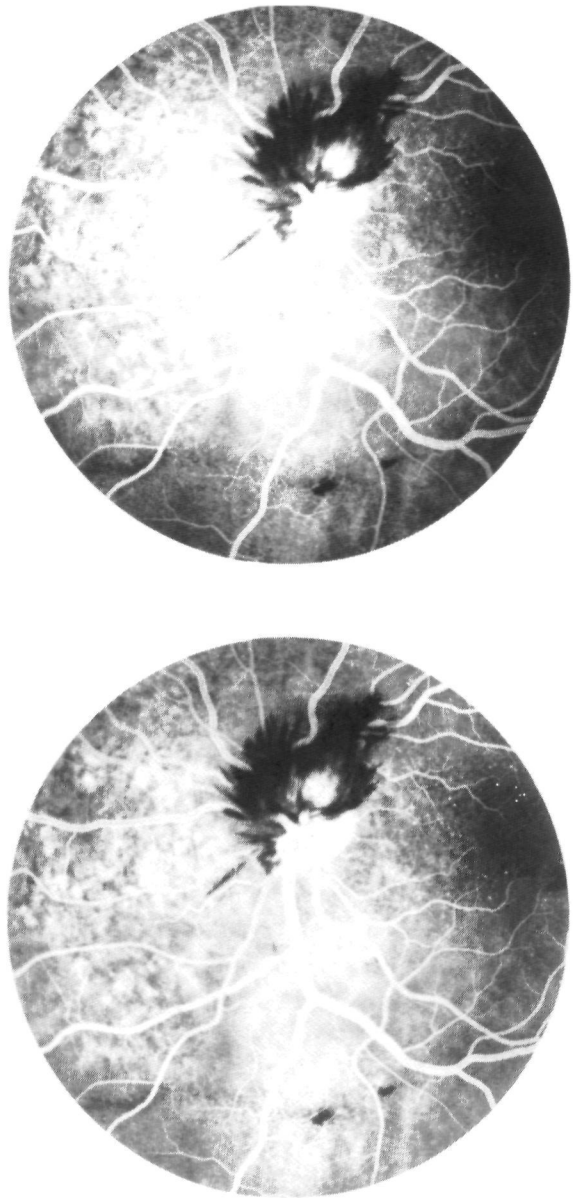


Figure 2.3.3.6 Stereo fluorescein angiogram showing intraretinal haemorrhages on different levels of the retina in the left eye of a patient with pancreatic carcinoma. (Same patient as in Figure 2.3.2.5).

In five patients (10%), fluorescein angiography revealed ***tumour vessels*** (double circulation): three times in a patient with breast cancer, once in a patient with lung cancer and once in a patient with a thyroid carcinoma (Figure 2.3.3.7 and Figure 2.3.3.8). The presence of such vessels was doubtful in seven other patients (14%): three patients with breast cancer, one patient with a testicular tumour, one with a probable carcinoma of the colon and two with unknown primary tumours. In 37 patients (76%), no tumour vessels could be demonstrated.

Therefore, just as in the studies of Gass (1974) and Wessing (1977), in our study tumour vessels were observed in patients with metastases, in contrast to the findings of Davis and Robertson (1971), Hayreh (1974) and Danis (1979).

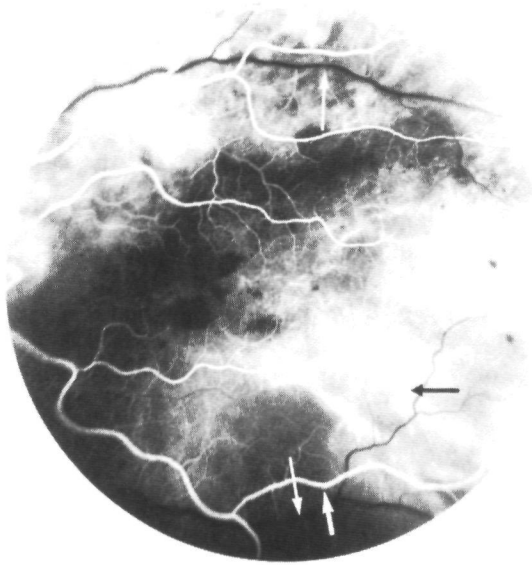


Figure 2.3.3.7 Fluorescein angiogram of a choroidal lesion in the left eye in a presumably healthy patient. Early arterial phase with double circulation: retinal arteries (thick white arrows); retinal veins (thin white arrows); tumour vessels (black arrow). Histopathology of the enucleated eye: metastasis of an adenocarcinoma of unknown localization.

In 31 patients with choroidal metastases (63%) ***hyperfluorescent spots*** were distinguishable, namely 21 times at the margin of the tumour and 10 times scattered over the entire tumour surface (Figure 2.3.3.9). In 18 patients (37%) such spots were absent.

The moment of staining of these spots was 61 seconds on average after the staining of the retinal arteries (SD 72; median 23; range 2-225). This is in accordance with the findings of Farnarier et al., (1973) and Shields (1983).

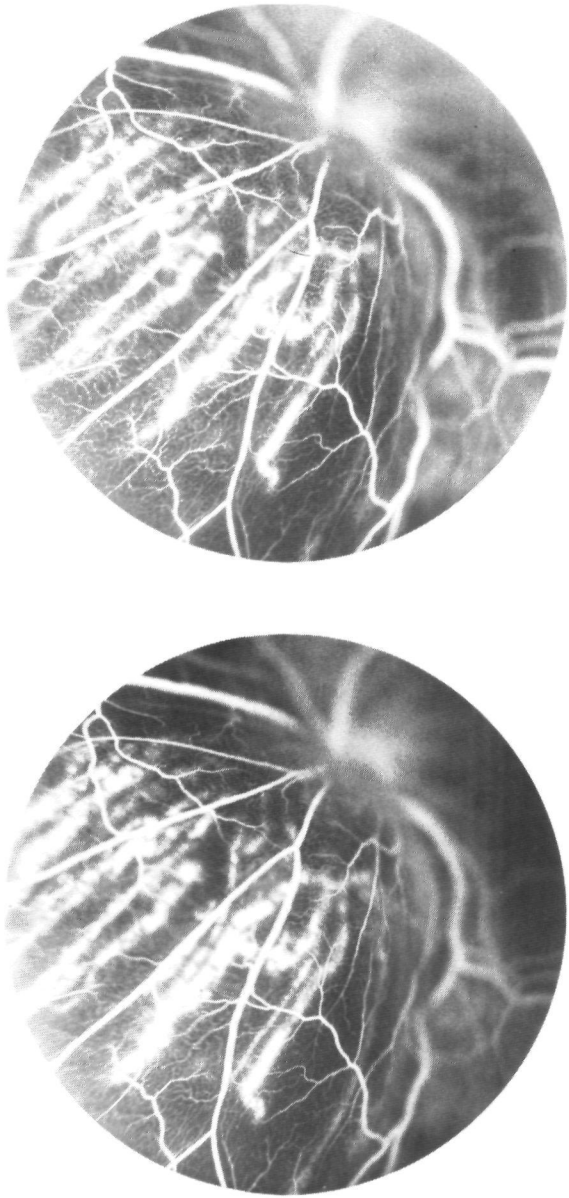


Figure 2.3.3.8 Stereo fluorescein angiogram in the venous phase showing a prominent choroidal metastasis from lung cancer. Note the retinal and choroidal vessels. These choroidal vessels should not be confused with tumour vessels.

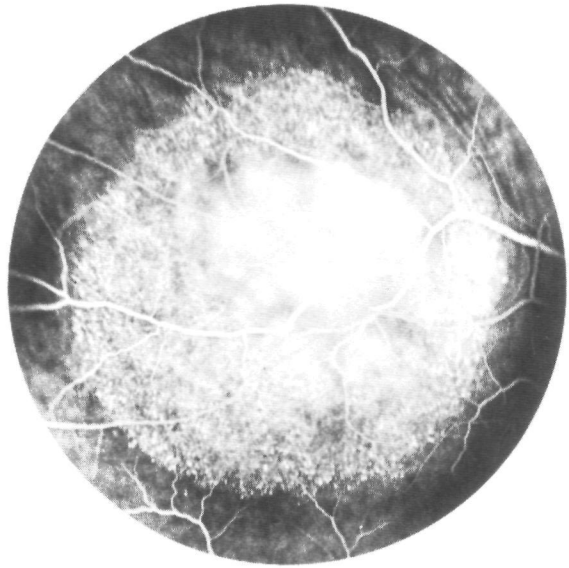


Figure 2.3.3.9 Fluorescein angiography of the right eye showing a choroidal metastasis from breast cancer. Late venous phase with multiple hyperfluorescent spots on the tumour surface.

Fluorescein angiographic signs of a ***retinal detachment*** were present in 24 patients (49%) and absent in 21 (43%), while in four patients (8%) this was unknown. A retinal detachment was observed ophthalmoscopically in 45% and echographically in 52% of the patients.

The ***fluorescein angiographic diagnosis*** 31 times was metastasis (63%), 5 times melanoma (10%) and 13 times, 'tumour' (27%). This diagnosis was connected with the nature of the primary tumour. For instance, 84% of the metastases of breast cancer were designated at fluorescein angiography as metastasis, as against only 38% of the metastases of lung cancer and 20% of the metastases of one of the other malignancies. On the other hand, metastases of lung cancer or of another malignancy were classified as melanoma in 25 and in 30% of the cases, respectively, as against in only one patient with a metastasis of breast cancer. Finally, 13% of the metastases of breast cancer were classified as 'tumour', as were 38% of the metastases of lung cancer and 60% of the metastases of one of the other malignancies.

At fluorescein angiography just as at ophthalmoscopy, metastases of breast cancer were classified correctly more often than metastases of lung cancer or of one of the other malignant tumours, while the fluorescein patterns of these tumours were not clearly different from one another. The examiner's awareness of the presence of a primary tumour and of multiple and bilateral lesions, as is often the case in patients with uveal metastases of breast cancer, will doubtless have played a part in this connection.

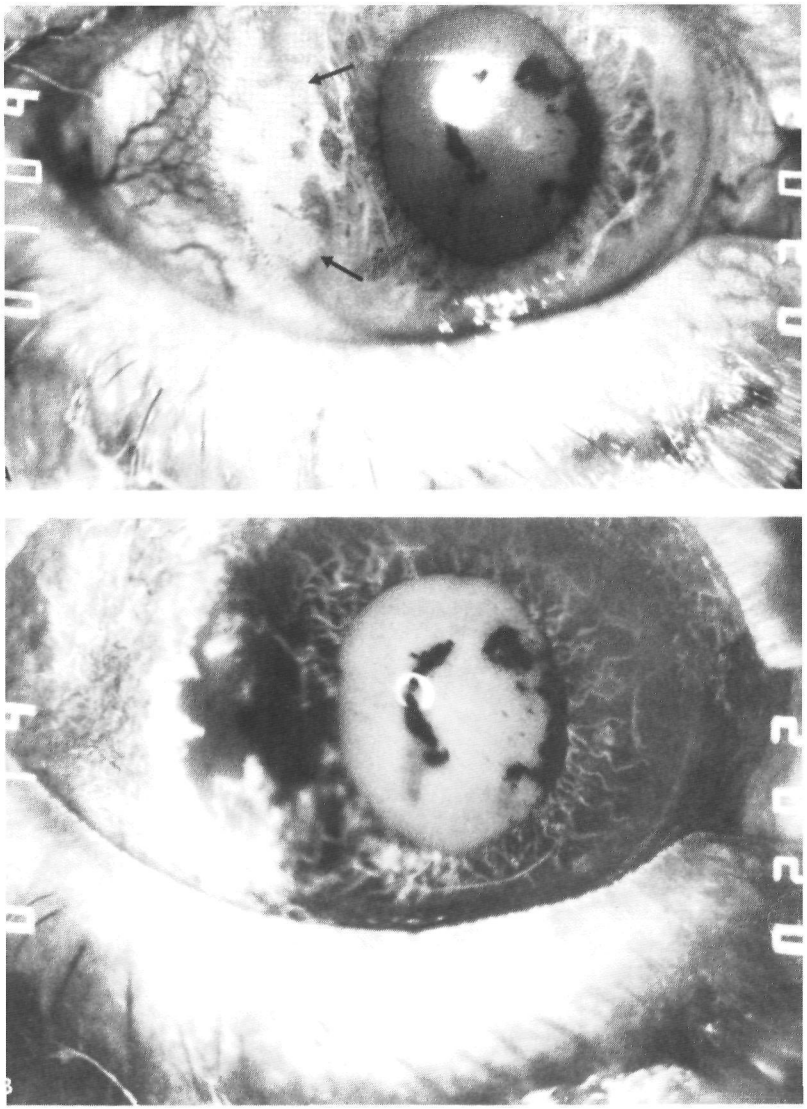
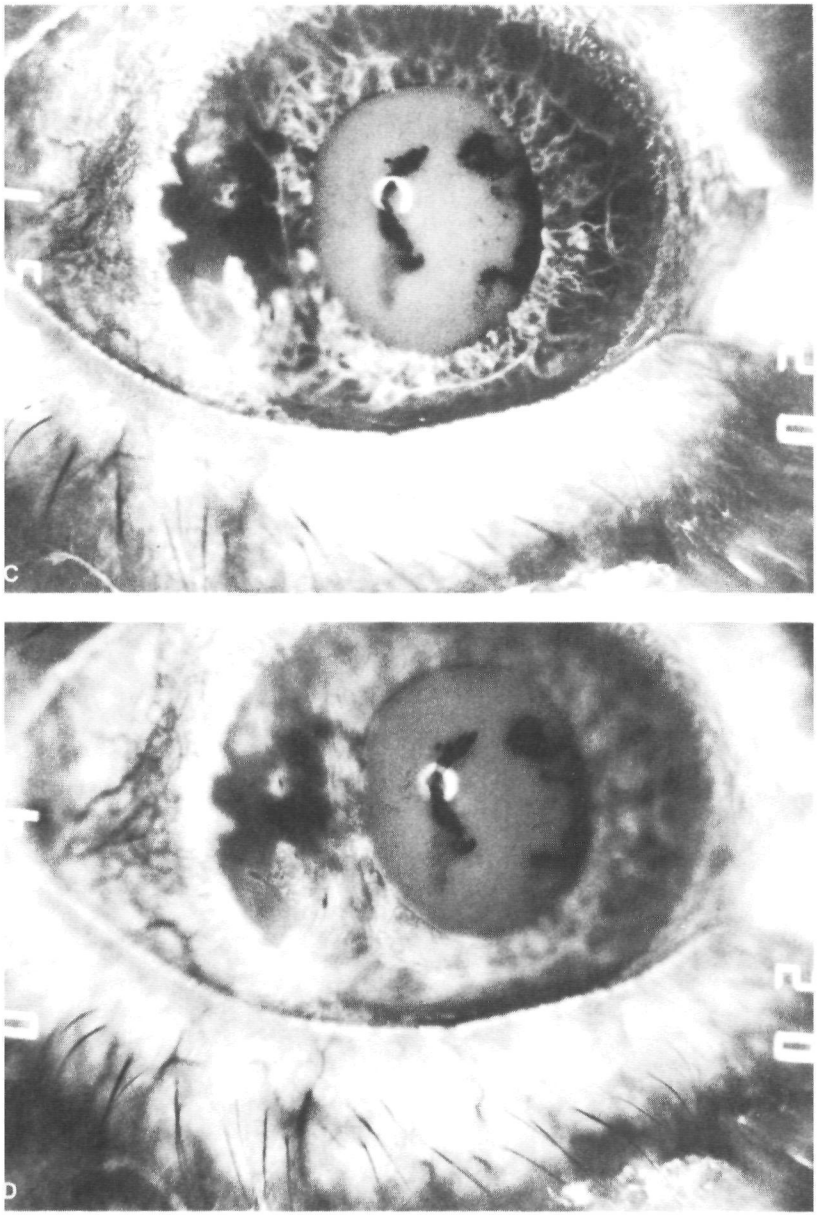


Figure 2.3.3.10 a. External photograph of the iridal part of a ciliary tumour in the right eye which has broken through the temporal part of the iris (arrows) (see also Colour Plate 2). b-d. Fluorescein angiography of the iris: b. Tortuous iridal vessels at the tumour margin in the early phase.



'igure 2.3.3.10 (continued) c-d. Relative hypofluorescence of the tumour in all phases. 'ote pigment coating on the lens. Metastasis from lung cancer in the ciliary body with xtension through the iris.

In one patient with a ***ciliary metastasis*** with break through the iris, fluorescein angiography was performed. Photographs were made only of the iridic portion of the tumour. At the margin of this lesion, from the early phase dilated tortuous iris vessels were visible which were connected with vessels in the superficial layers of the tumour. The tumour itself stained slightly, with a relative hypofluorescence in the late phases Figure 2.3.3.10).

Summary of fluorescein angiography in uveal metastasis: choroidal metastases on average stained 21 seconds after the injection of the dye, which is 5 seconds after the staining of the choroid and 2 seconds after the retinal arteries. Fluorescence of the tumour was observed before staining of the retinal arteries in one case, at the same time in 16 and later, in 15 cases (17 unknown). Metastases of lung cancer showed a relatively late staining.

In the arterial phase, most metastases were hypofluorescent which hypofluorescence in the early arterial phase was mostly uniform, but subsequently in part grossly mottled. Starting from the venous phases, in an increasing proportion a fluorescence was observed of the same intensity as the surrounding choroid, with an overlying finely or grossly mottled hyperfluorescence. Hyperfluorescent tumours were observed only rarely. The most frequent pattern was a hypofluorescent tumour in the early arterial phases with isofluorescence from the early venous phase, which was described in 31% of the patients. In addition, in 15% of the patients a hypofluorescence was observed until in the early venous phase, following which isofluorescence developed, while 15% of the patients had isofluorescence in all phases. The nature of the primary tumour proved not to influence the fluorescein angiographic pattern in choroidal metastases. A fluorescein angiographic pattern clearly recognizable as a metastasis proved not to be demonstrable.

In 29% of the patients circumscribed large hypofluorescent areas were observed. Hyperfluorescent areas were present in 6% of the patients.

A hypofluorescent margin round the tumour was described in 73% of the metastases. In 63%, hyperfluorescent spots on the tumour surface were observed, mostly only at the margin of the lesion. Distinct vessels in the tumour were described in 10%, doubtfully present vessels in 14%.

The ratio of the tumour bases measured at fluorescein angiography and at ophthalmoscopy amounted to 1.4. Metastases therefore extend farther into the choroid than can be observed ophthalmoscopically.

The fluorescein angiographic diagnosis in 49 patients with choroidal metastases was metastasis in 63%, melanoma in 10% and 'tumour' in 27%. This was dependent on the nature of the primary tumour: metastases of breast cancer in general were classified correctly, while metastases of lung cancer and of other malignancies as a rule were designated as melanoma or as 'tumour'. This was not based, however, on separate fluorescein angiographic patterns.

In a patient with a ciliary metastasis with break through the iris, tortuous iris vessels were observed at the tumour margin. The tumour itself remained relatively hypofluorescent.

Table 2.3.3.6 presents a survey of the principal fluorescein angiographic features for the differential diagnosis of choroidal metastases.

Table 2.3.3.6 *Fluorescein angiographic features in patients with metastases, malignant melanomas, haemangiomas and naevi of the choroid*

	Intraocular tumour			
	Metastasis	Melanoma	Haemangioma	Naevus
Number of patients	49	291	13	35
Moment of staining tumour: mean (SD): sec.	21 (29)	17 (38)	12 (5)	16 (10)
Interval between staining retinal arteries and tumour: sec.	2	1	-1	2
Staining tumour:				
Before retinal arteries	2%	6%	23%	-%
At the same time as retinal arteries	33	26	31	57
After retinal arteries	31	11	8	31
Unknown	35	57	38	11
Tumour fluorescence:				
Early arterial phase:				
Hypofluorescence	63%	42%	15%	71%
Isofluorescence	14	14	62	26
Hyperfluorescence	4	1	-	-
Unknown	18	43	23	3
Arterial phase:				
Hypofluorescence	51%	39%	23%	66%
Isofluorescence	27	18	54	34
Hyperfluorescence	4	1	-	-
Unknown	18	42	23	-
Early venous phase:				
Hypofluorescence	18%	22%	-%	46%
Isofluorescence	63	36	-	54
Hyperfluorescence	10	4	100	-
Unknown	2	38	-	-
Late venous phase:				
Hypofluorescence	2%	11%	-%	49%
Isofluorescence	80	45	-	51
Hyperfluorescence	16	6	100	-
Unknown	2	37	-	-
Hypofluorescent margin	73%	54%	62%	40%

to be continued on the next page

Table 2.3.3.6 (continued)

	Intraocular tumour			
	Metastasis	Melanoma	Haemangioma	Naevus
Hyperfluorescent spots:				
At tumour margin	43%	30%	15%	6%
On whole tumour surface	20	11	-	23
None	37	21	85	71
Unknown	-	38	-	-
Tumour vessels:				
Positive	10%	32%	15%	-%
Doubtful	14	9	15	-
Negative	76	20	46	97
Unknown	-	39	-	-
Retinal detachment	49%	33%	15%	-%
Ratio tumour base fluorescein angiography and ophthalmoscopy	1.4	0.9	1.0	0.9

Of one-third of the patients with a ***melanoma*** of the choroid, no fluorescein angiograms were available and in the other cases their descriptions were often incomplete. Therefore, the fluorescein angiographic differential diagnosis of melanoma from metastases of the choroid can only be discussed in general terms.

Choroidal melanomas stained somewhat earlier than metastases. It was rare for staining to occur only after filling of the retinal arteries.

In melanomas, just as in metastases, in both arterial phases the fluorescence of the lesion mostly lagged behind that of the surrounding choroid. In the venous phases, hypofluorescence of the tumour was described more frequently. The fluorescein angiographic pattern of choroidal melanomas did not differ greatly from that of metastases. However, a diffuse hypofluorescence of the tumour was described in 15% of the melanoma cases and never in metastases.

A hypofluorescent margin round the tumour and hyperfluorescent spots on the tumour surface could be observed with relatively equal frequency in melanomas and in metastases. Tumour vessels, however, were observed far more frequently in melanomas than in metastases (Figure 2.3.3.11 and Figure 2.3.3.12).

The ratio of the tumour bases measured at fluorescein angiography and at ophthalmoscopy was smaller in melanomas than in metastases. Apparently, therefore, angiographically melanomas in general do not extend farther than can be observed ophthalmoscopically. This in contrast to choroidal metastases.

No convincing fluorescein angiographic distinction between metastases and melanomas could be made in our study group.

The fluorescein angiographic diagnosis in patients with a choroidal melanoma was in general correct: the diagnosis of melanoma was made in 82%, in 13% 'tumour'. In only three patients was the melanoma erroneously diagnosed as a metastasis.

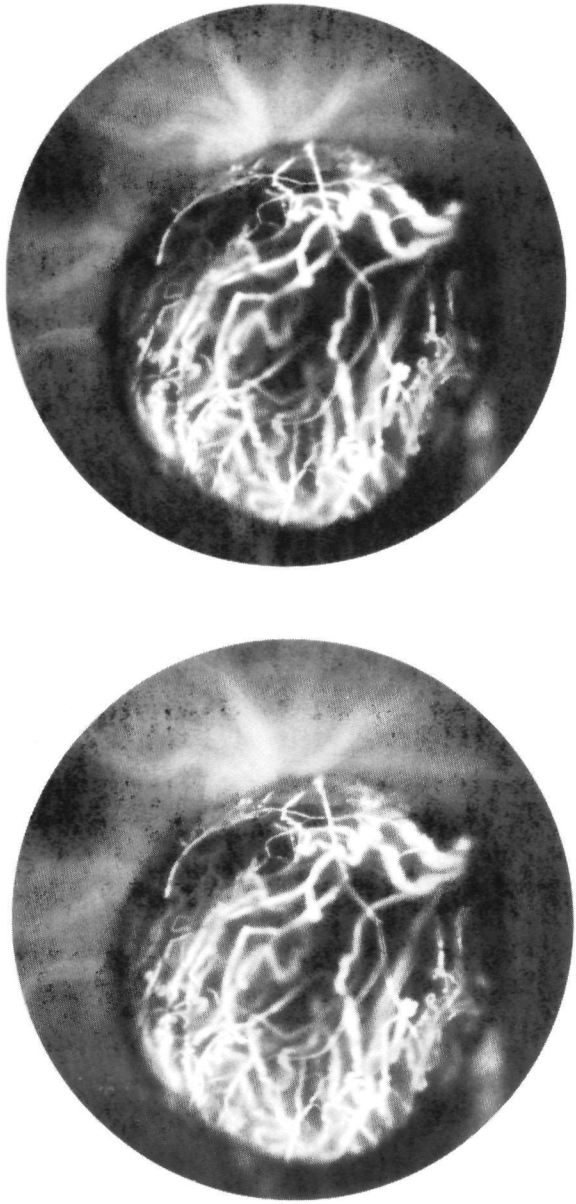
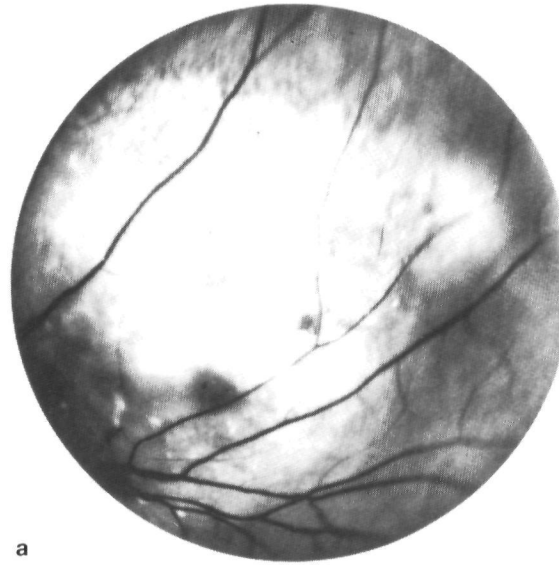


Figure 2.3.3.11 Stereo fluorescein angiogram in the venous phase of a mushroom-shaped malignant melanoma of the choroid in the left eye with very distinct tumour vessels.



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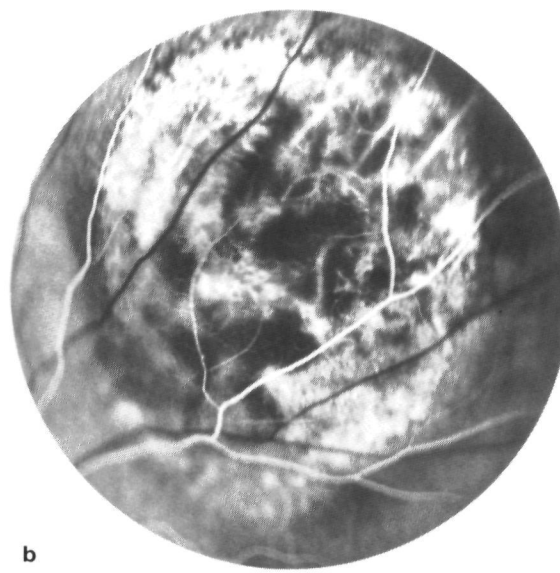
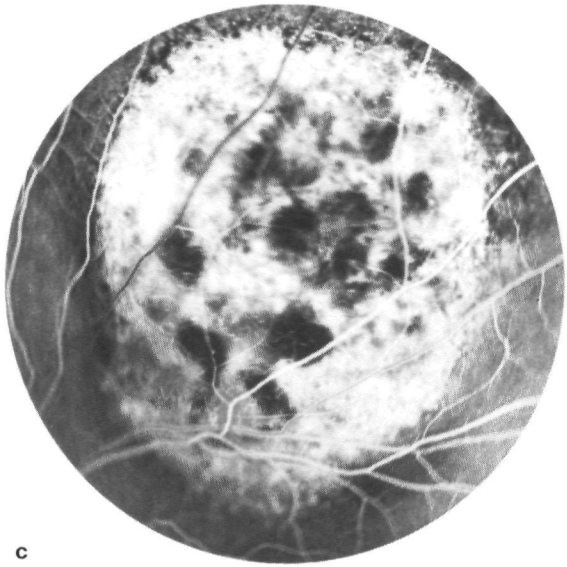


b

Figure 2.3.3.12 a. Fundus photograph of a choroidal amelanotic malignant melanoma in the left eye.
b-d. Fluorescein angiogram of the same lesion: b. Arterial phase showing double circulation and progressive staining of the tumour.



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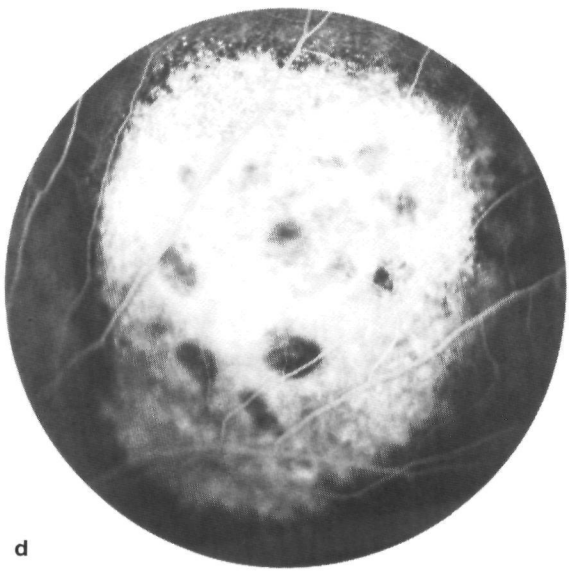
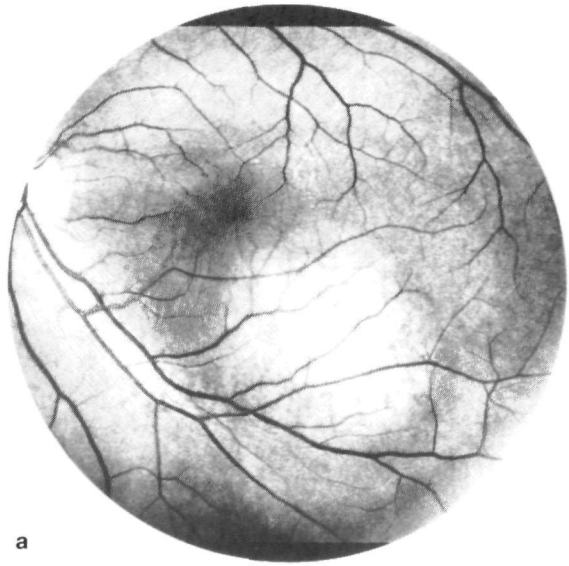


d

Figure 2.3.3.12 (continued) c-d. Early venous and venous phases with mottled hyperfluorescence of the tumour, areas of hypofluorescence and some hyperfluorescent spots at the tumour margin.



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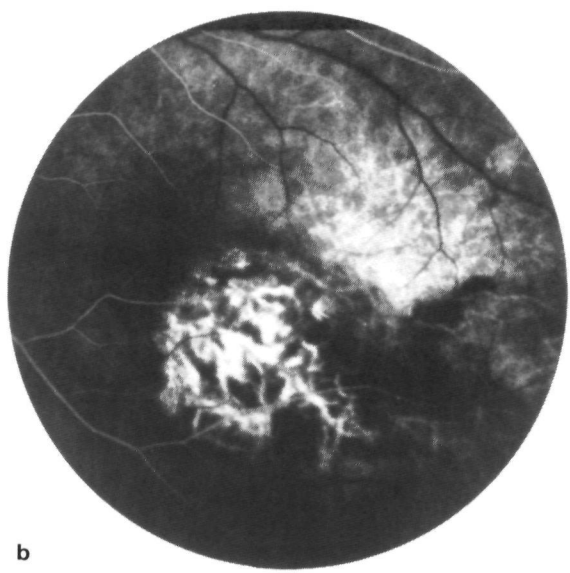
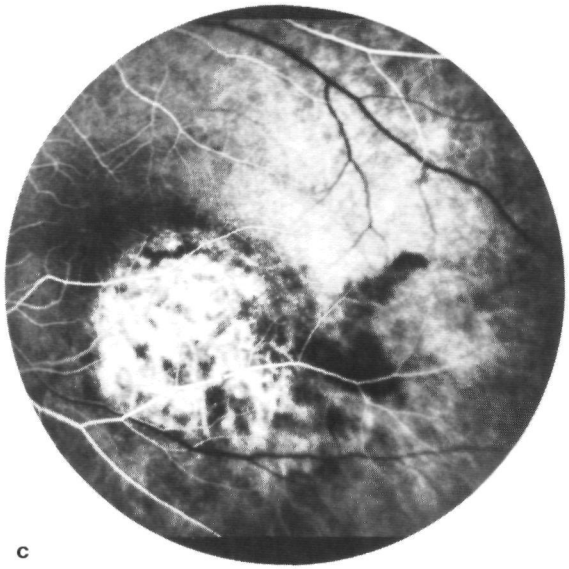


b

Figure 2.3.3.13 a. Fundus photograph of a choroidal haemangioma in the left eye. b-d. Fluorescein angiogram showing the same lesion: b. Early arterial phase with characteristic sponge-like configuration of tumour vessels.



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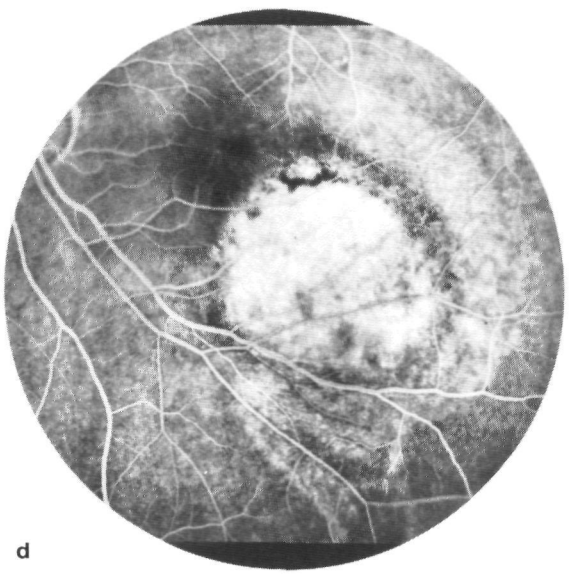
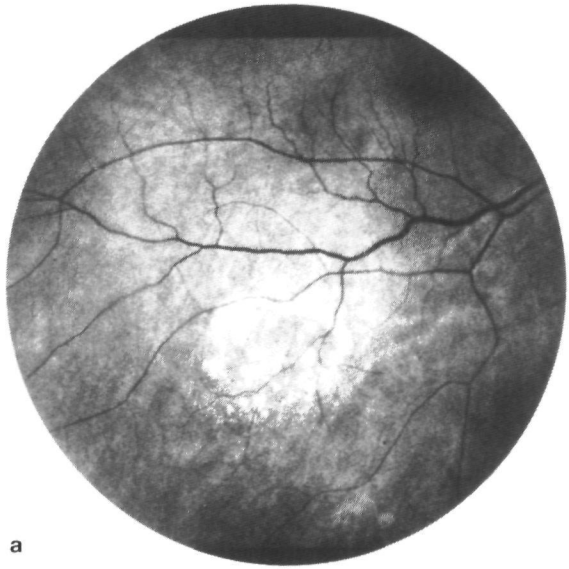


d

Figure 2.3.3.13 (continued) c. Early venous phase with progressive staining of the lesion. d. Venous phase with hyperfluorescence of the tumour and a hypofluorescent margin surrounded by a ring of hyperfluorescence caused by secondary changes in the pigment epithelium.



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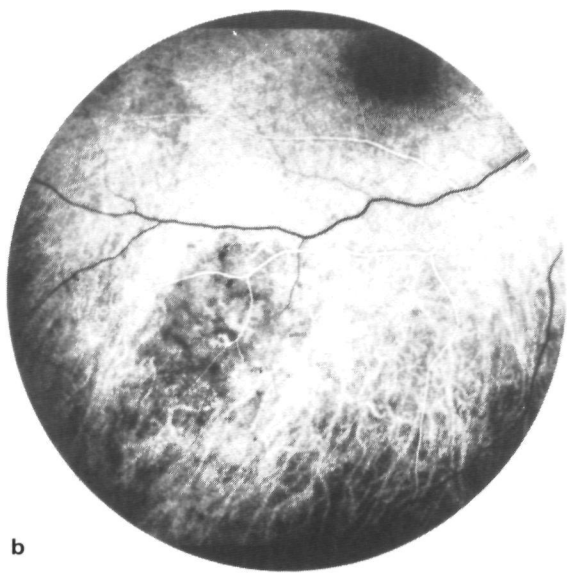
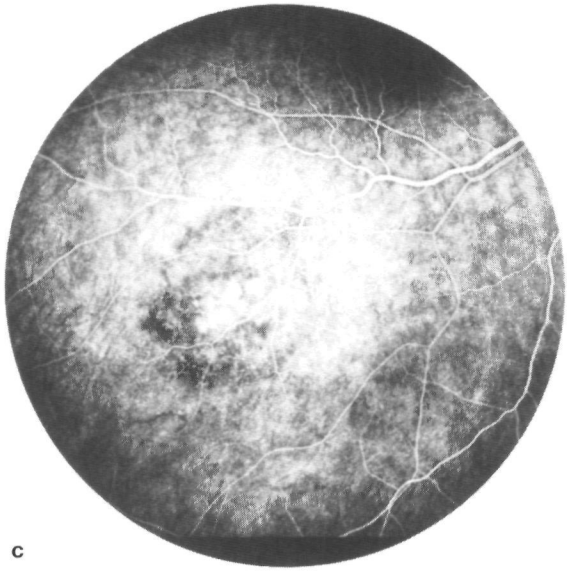


b

Figure 2.3.3.14 a. Fundus photograph of a choroidal naevus in the right eye with multiple drusen on the tumour surface. b-d. Fluorescein angiography of the same lesion: b. Arterial phase with blocking of the background fluorescence.



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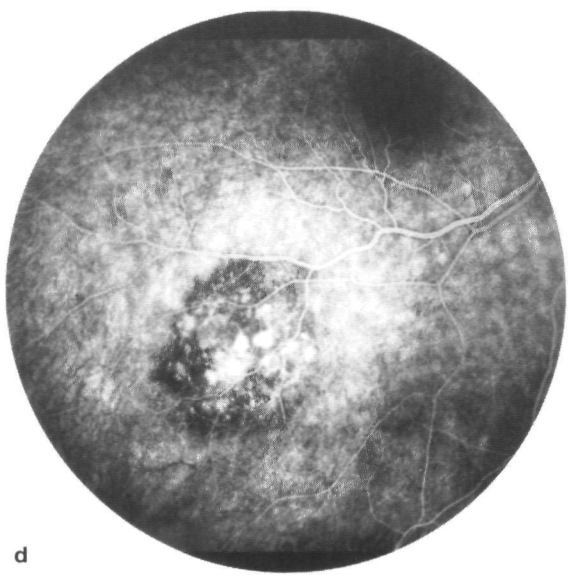

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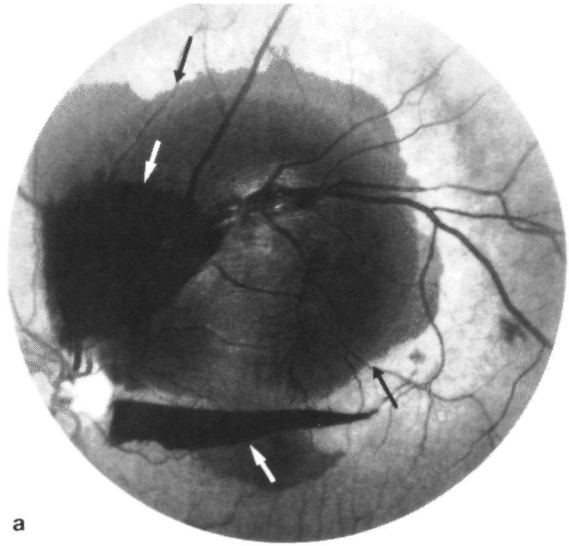
Figure 2.3.3.14 (continued) c-d. Venous phases with staining of the drusen. The lesion itself stays hypofluorescent.



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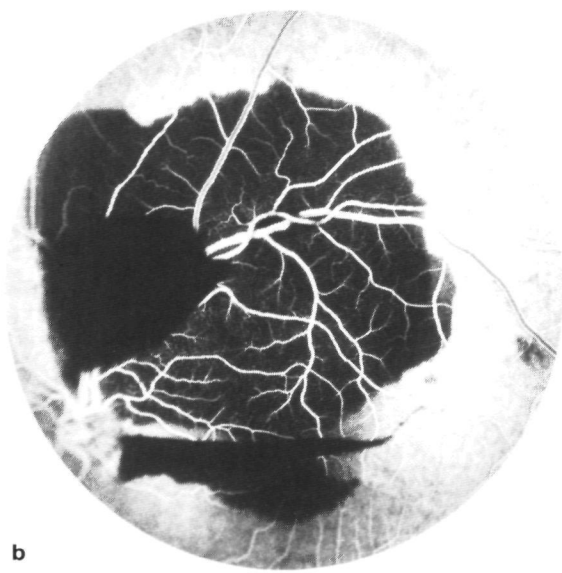


b

Figure 2.3.3.15 a. Fundus photograph of the left eye with preretinal (white arrows) and subretinal (black arrows) haemorrhages. b. Fluorescein angiogram of the same lesion in the early venous phase: complete block of the choroidal fluorescence by the subretinal and of the retinal vessels by the preretinal haemorrhage.

Haemangiomas of the choroid stained substantially earlier than metastases or melanomas, frequently even before the retinal arteries filled with fluorescein. Accordingly, from the early arterial phase, haemangiomas showed a fluorescence of an intensity comparable to that of the surrounding choroid with hyperfluorescence in late phases. Virtually always this staining was mottled, independently of the stage of the fluorescein angiography. Arterially, its pattern was grossly mottled or finely mottled with equal frequency. In later stages, a grossly mottled staining was observed practically exclusively. In nine patients (33%) a characteristic fluorescein angiographic pattern was observed as a sponge-like configuration (Figure 2.3.3.13).

In 70% of the haemangiomas, the fluorescence of the tumour remained stable during all phases, in contrast to metastases and melanomas of the choroid. Tumours with a hypofluorescent rim were seen in a similar proportion of the cases. Hyperfluorescent spots on the tumour surface, however, occurred only sporadically in haemangiomas. Just as in melanomas, tumour vessels were described relatively often.

The ratio of the tumour bases measured at fluorescein angiography and at ophthalmoscopy was the same as that in melanoma and therefore lower than in metastases.

In 57% of the cases the fluorescein angiographic diagnosis was haemangioma, in 29% it was 'tumour'. In one patient, a haemangioma was mistaken for a metastasis.

Naevi of the choroid stained at the same moment as metastases and melanomas. In the arterial phases, the lesion in general was hypofluorescent compared with the environment. From the early venous phase, isofluorescence was also regularly observed. Hyperfluorescence was never described. The most frequent observation was hypofluorescence of the lesion in all phases of the fluorescein angiogram (Figure 2.3.3.14).

The pattern of fluorescence in the early arterial stage was usually diffusely hypofluorescent, and subsequently hypofluorescent with finely mottled hyperfluorescence. In the venous phases, either hypo- or isofluorescence of the tumour was mostly seen, both combined with a finely mottled hyperfluorescence.

A hypofluorescent margin and hyperfluorescent spots were described regularly, although less frequently than in metastases and melanomas. Hyperfluorescent spots, if present, were rarely limited to the margin of the lesion.

The diagnosis at fluorescein angiography was naevus in 75% of the cases and 'tumour' in 25%. The diagnosis metastasis was never made.

In no patient with a ***retinoblastoma*** was fluorescein angiography performed. In these children ophthalmological examination was limited as much as possible.

Of ***miscellaneous lesions*** no or only a few fluorescein angiograms were available. It was only of five patients with a ***subretinal haemorrhage*** that data were present. Any staining of the lesion occurred an average of 3 seconds after the retinal arteries. In general, diffuse hypofluorescence of the lesion was observed, which in later phases might display some hyperfluorescent spots. One patient had an isofluorescent lesion with grossly mottled hyperfluorescence from the earliest phases, in another patient in later stages a fluorescence was observed that had the same intensity as the surrounding choroid. No hyperfluorescent lesions were described (Figure 2.3.3.15).

Three of the five haemorrhages showed a hypofluorescent margin Hyperfluorescent spots or indications of vessels in the lesion were never observed In the fluorescein angiograms, the haemorrhages were of the same size as observed ophthalmoscopically

The diagnoses were twice subretinal haemorrhage, three times 'tumour'

Conclusion: at fluorescein angiography, no characteristic pattern of metastases is demonstrable nor are any other specific features visible

The pattern of staining and the presence of a hypofluorescent margin and of hyperfluorescent spots in melanomas is similar to that in metastases Although tumour vessels are observed more frequently in melanomas than in metastases, they are not specific For the differentiation of metastases from melanomas, fluorescein angiography is of only limited value

Haemangiomas compared with metastases show a more typical picture In general they cause earlier and more pronounced fluorescence with in one-third of the cases a typical sponge-like configuration with less frequent hyperfluorescent spots and more frequent tumour vessels than metastases

Naevi and subretinal haemorrhages can be reasonably well distinguished from metastases by means of fluorescein angiography

Therefore, fluorescein angiography makes a certain contribution to the differential diagnosis of metastases from haemangiomas, naevi and subretinal haemorrhages For the differentiation from melanomas, on the other hand, this technique is less suitable

2.3.4 Echography

For ophthalmological echography (ultrasonography, USG), use is made of the unidimensional A-scan and the bidimensional B-scan, the results of which have to be combined for adequate interpretation of the total echo image The various echographical criteria are described in detail in Chapter 1 4 4

During the study period three instruments were used As A-scan the Kretz scan Technik 7200 MA was used, as B-scans the Bronson Turner B-scan of Grumman Health Systems and the Ophthascan S of Biophysic Médical

Figure 2 3 4 1 shows an A- and B-mode echogram of a normal eye

Echographic examinations were carried out in 72 of the 87 patients with uveal metastases of this retrospective study In two patients no adequate echography proved to be possible because of the peripheral localization of the tumour The results mentioned below concern 69 patients with choroidal and ciliary metastases (further termed uveal metastases) and one patient with a metastasis in the iris who will be discussed separately. If echography had been performed several times, the reference concerns the first examination (Figure 2.3.4 2)

According to Coleman (1973) and Guthoff (1988), characteristic of the echographic image of uveal metastases is a flat lesion with a relatively broad base In our study, the mean ***prominence*** of the metastasis was 3 6 mm, ranging from a choroidal infiltration

(prominence 0 mm) to a pronounced prominence of 15.0 mm [in a metastasis of a clear cell carcinoma of the kidney (Grawitz tumour)] (Table 2.3.4.1).

The mean ***tumour base*** was known of only 53 patients; in 14 patients the base could not be measured since no B-scan was available (early phase of the study), in two patients the infiltration of the choroid was so diffuse that the tumour base could not be distinguished from the surrounding choroid. In the remaining 53 patients, the mean base of the metastasis amounted to 11.7 mm, ranging from 5.0 to 23.0 mm.

In patients of whom both the prominence of the lesion and the tumour base were known, the ratio between prominence and base was determined. In metastases this was 0.32 on average and it ranged from 0.06 to 1.40. This ratio provides some information on the shape of the tumour.

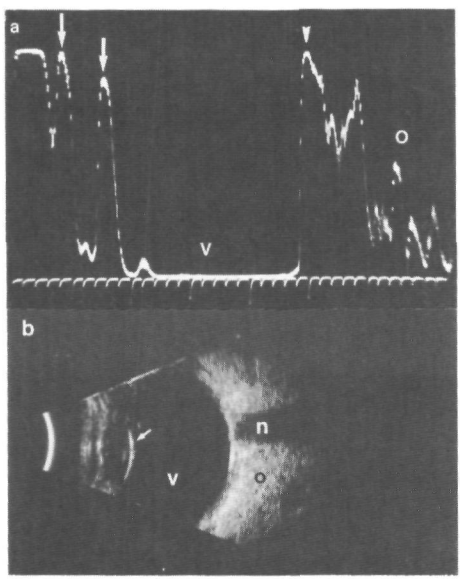


Figure 2.3.4.1 A- and B-mode contact echogram of a normal eye. a. A-mode: white arrows: anterior and posterior surface of the lens; white arrowhead: retina/sclera; O: orbital fat; V: vitreous. b. B-mode: white arrow: lens; n: optic nerve; o: orbital fat; v: vitreous

In Table 2.3.4.1 the prominence, base and ratio are subdivided according to the nature of the primary tumour. It shows that the mean prominence and ratio of metastases of breast cancer were substantially smaller than those of metastases of other malignancies. The mean base of the lesion was similar in the different malignancies, however.

Uveal metastases are described as having a predominantly flat ***shape***. In addition, dome-shaped, lobulated and even a few mushroom-shaped tumours are described (Coleman et al., 1974; Shields and Tasman, 1977; Kerman and Fishman, 1987; Guthoff, 1988).

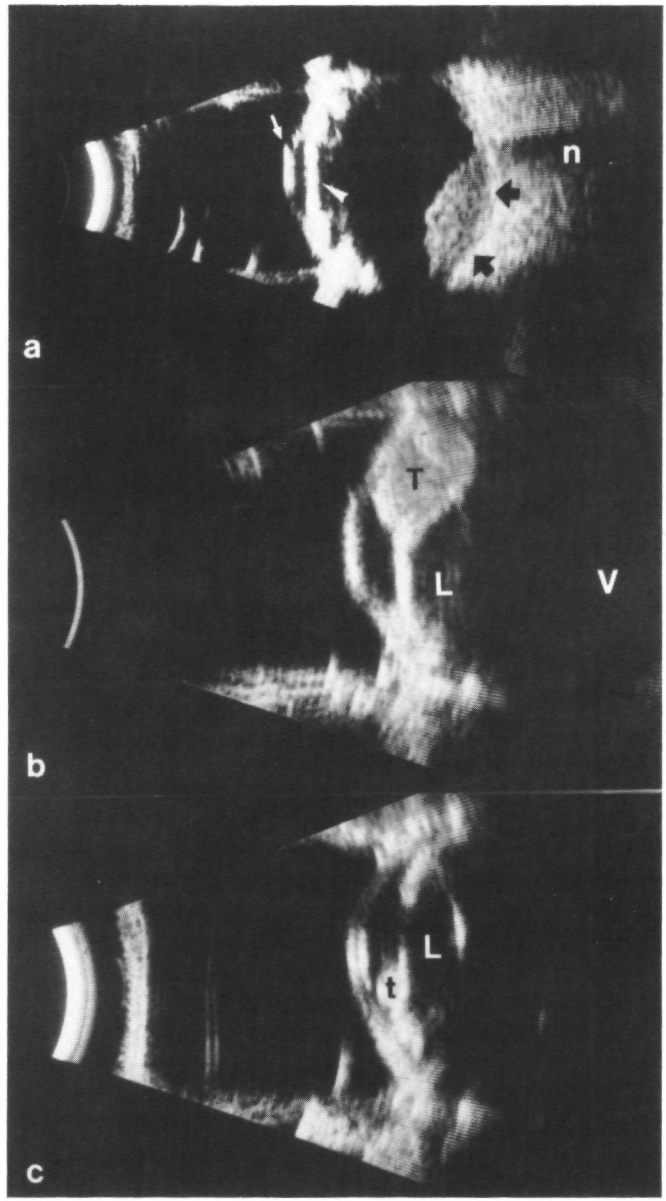


Figure 2.3.4.2 Immersion B-mode echogram (with the aid of a perspex cylinder filled with methylcellulose 2%) of three different uveal metastases: a. Choroidal metastasis (white arrow: cornea; white arrowhead: lens; black arrows: choroidal metastasis; n: optic nerve). b. Ciliary metastasis which has broken through the iris (L: lens; T: tumour; V: vitreous). c. Iridal metastasis (L: lens; t: tumour).

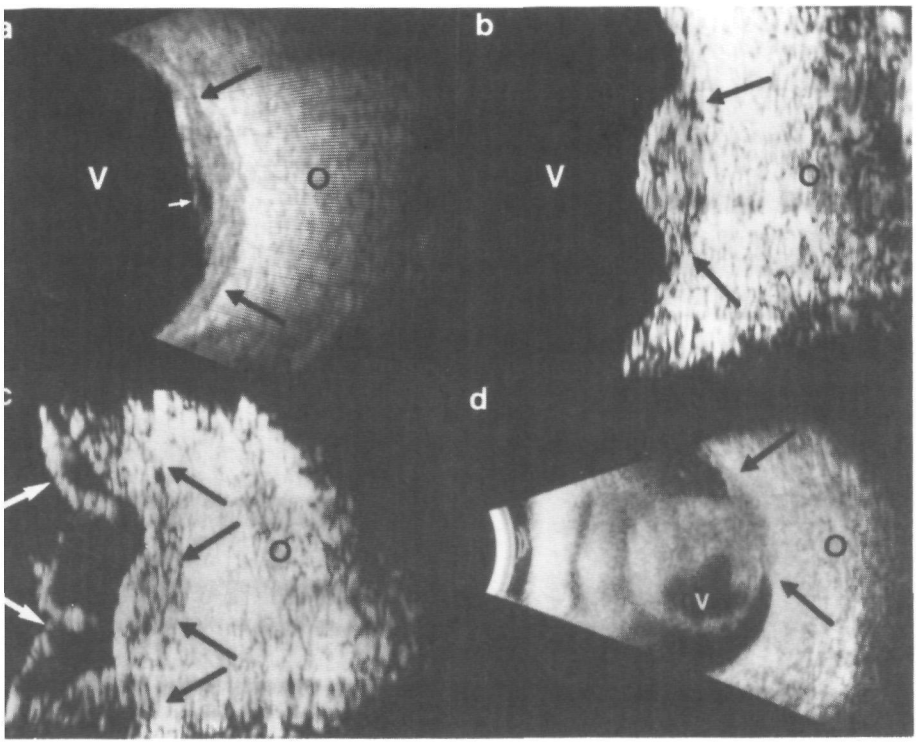
Table 2.3.4.1 *Prominence, base and prominence:base ratio according to the localizaton of the primary tumour in patients with choroidal and ciliary metastases*

	N	Mean	SD	Median	Minimum	Maximum
Prominence: (mm)						
Breast	36	2.6	1.8	2.3	0.0	8.0
Lung	18	4.7	2.9	4.0	1.0	13.0
Other	15	4.5	3.6	4.0	1.0	15.0
All	69	3.6	2.7	3.0	0.0	15.0
Base: (mm)						
Breast	26	11.7	4.7	10.5	6.0	23.0
Lung	15	12.1	4.9	11.0	5.0	23.0
Other	12	11.3	3.5	12.0	5.0	17.0
All	53	11.7	5.0	11.0	5.0	23.0
Prominence:base ratio:						
Breast	26	0.23	0.24	0.20	0.06	1.36
Lung	15	0.39	0.31	0.31	0.13	1.40
Other	12	0.41	0.30	0.37	0.11	1.15
All	53	0.32	0.28	0.25	0.06	1.40

In contrast to the predominantly flat shape of uveal metastases in the literature, in our patient population as many flat as dome-shaped tumours were observed: 41% and 39% of the patients, respectively (Table 2.3.4.2). In six patients (9%), the metastasis was lobulated. In two patients (3%), the metastasis was mushroom-shaped: once in a choroidal metastasis of a clear cell carcinoma of the kidney (Grawitz tumour) and once, in a ciliary metastasis of lung cancer. Such a mushroom shape is brought about by the tumour breaking through Bruch's membrane, a part of the tumour tissue being constricted by this membrane. It is generally assumed that such a shape is almost exclusively restricted to a malignant melanoma which grows predominantly in height, unlike the lateral growth of metastases. The present study shows, however, that a mushroom shape may also occur in metastases (Figure 2.3.4.3).

In one other patient with a metastasis of lung cancer, there were indications of a break through Bruch's membrane. In this patient this had led not to a mushroom-shaped tumour but to a lobulated shape.

In six patients (9%), the shape of the tumour could not be determined because no B-scan was available.



re 2.3.4.3 Contact B-mode echogram of choroidal metastases showing various shapes: a. I stasis (black arrows) from breast cancer with limited retinal detachment (white arrow) (O: orbital itreous). b. Dome-shaped metastasis (arrows) from lung cancer (O: orbital fat; V: vitreous). obulated metastasis (arrows) from breast cancer with a secondary retinal detachment (white arrows) orbital fat). d. Mushroom-shaped metastasis (arrows) from a clear cell carcinoma of the kid witz tumour) (O: orbital fat; v: vacuole in the tumour).

le 2.3.4.2 Shape of the intraocular metastasis according to the localization of the primary tumour in 69 patients with choroidal and ciliary metastases

The shape of the metastases was related to the nature of the primary tumour. Metastases of breast cancer were predominantly flat and less often dome-shaped. Metastases of lung cancer, on the other hand, were mostly dome-shaped and metastases of the other malignancies also more frequently showed a dome shape than a flat shape.

Flat lesions of course were hardly prominent and had a lower prominence:base ratio. In dome-shaped and lobulated lesions, higher prominences and ratios were obtained. In the two mushroom-shaped metastases, the base on average was even smaller than the prominence, so that the ratio was 1.15 and 1.40, respectively (Table 2.3.4.3).

Table 2.3 4 3 *Shape of the tumour in 63 patients with choroidal and ciliary metastases* *

Shape	N	Mean prominence (mm)	Prominence base ratio
Flat shape	** 23	1 6	0 18
Dome shaped	** 23	4 7	0 38
Lobulated shape	6	4 4	0 45
Mushroom-shaped	2	11 0	1 28
Unknown shape	** 6	4 3	**

** shape unknown in six of the 69 patients with choroidal and ciliary metastases,*
*** base unknown in five flat, four dome-shaped and all six tumours with unknown shape*

Statements concerning the ***reflectivity*** of the infrastructure of the intraocular tumour can only be made when the prominence amounts to at least 2 0 mm (Coleman et al , 1974; Ossoinig and Blodi, 1974) Several investigators described a highly irregular echographic reflectivity in metastases (Coleman, 1973; Verbeek, 1985; Poujol and Chaintron, 1988).

In our study, 51 of the 69 echographically examined uveal metastases had a prominence of at least 2.0 mm. The reflectivities of these lesions, subdivided according to the nature of the various primary tumours, are listed in Table 2.3.4.4.

Table 2 3.4.4 *Reflectivity of choroidal and ciliary metastases with a prominence of ≥ 2.0 mm according to the localization of the primary tumour in terms of percentage*

	Localization primary tumour			
	All	Breast	Lung	Other
Reflectivity	(N=51)	(N=21)	(N=17)	(N=13)
Low	29	19	47	23
Medium	53	62	41	54
High	18	19	12	23

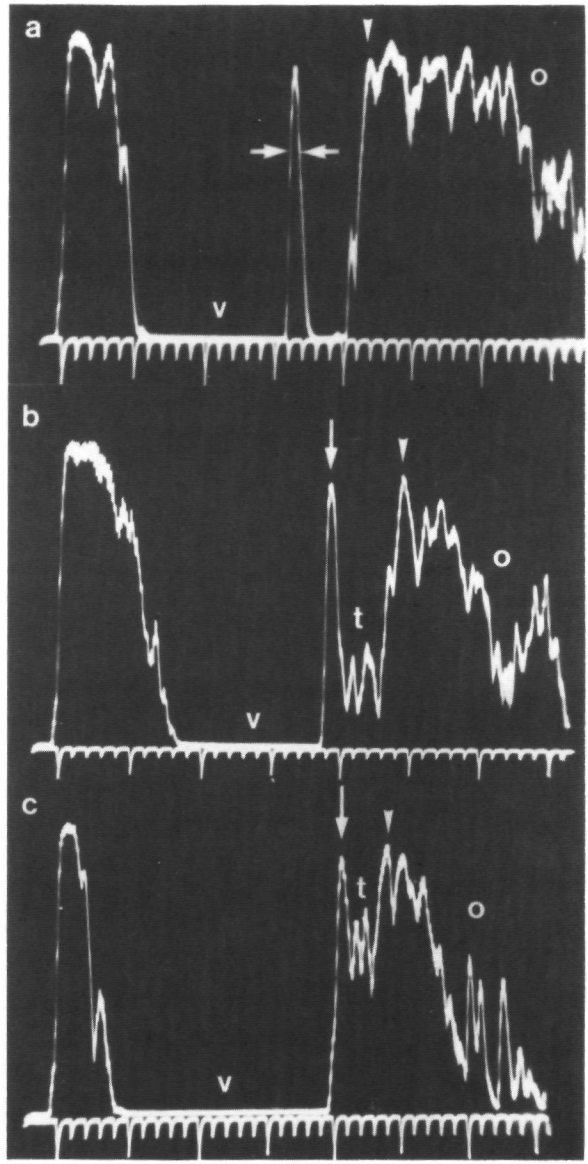


Figure 2.3.4.4 a. A-mode echogram of a retinal detachment (white arrows) (white arrowhead: sclera; O: orbital fat; V: vitreous).
b. A-mode echogram of a 5.5 mm prominent low-reflective choroidal metastasis from lung cancer (white arrow: retina; white arrowhead: sclera; O: orbital fat; t: low reflectivity of the tumour infrastructure; V: vitreous). c. A-mode echogram of a 3.5 mm prominent high-reflective choroidal metastasis from breast cancer (white arrow: retina; white arrowhead: sclera; O: orbital fat; t: high reflectivity of the tumour infrastructure; V: vitreous).

In uveal metastases, different reflectivities can be observed. They were mostly mid-reflective (53%) and less frequently low- (29%) or high-reflective (18%). Metastases, therefore, do not have a high reflectivity in the majority of the cases, as postulated in the literature. The reflectivity was not correlated with the prominence (Figure 2.3.4.4).

In a large proportion of the patients with lung cancer, namely 47%, uveal metastases were found to be low-reflective. This is in agreement with observations of other investigators (Ossoinig and Harrie, 1983; Verbeek, 1985). Metastases of breast cancer showed a low reflectivity in only 29% of the cases.

While the primary tumour in uveal metastases with low reflectivity was most often lung cancer, mid- and high-reflective tumours predominantly originated from breast cancer (Table 2.3.4.5).

Table 2.3.4.5 *Nature of the primary tumour in choroidal and ciliary metastases according to reflectivity in terms of percentage*

	Reflectivity		
Localization primary tumour	Low	Medium	High
Breast	27	48	44
Lung	53	26	22
Other	20	26	33

The tumour infrastructure may show a homogeneous echographic picture, with few variations in reflectivity, or cause a non-homogeneous irregular pattern. This is sometimes called the ***regularity*** of a tumour. Uveal metastases are described as showing an irregular echo pattern (Verbeek, 1985; Poujol, 1986; Bigar, 1988).

Evaluation of the regularity of a tumour requires several echo spikes and consequently a longer tissue tract, of 4.0 mm minimally. This was the case in 27 of the 69 patients examined echographically in our study group: eight patients with breast cancer, 10 with lung cancer and nine, with other malignancies (Figure 2.3.4.5). The reflectivity of the tumour was homogeneous in 10 patients (37%) and irregular in 16 (59%) while this element was unknown in one patient (4%). These findings are in accordance with the literature. Metastases of breast cancer in which the echographic homogeneity of the tumour was known showed an irregular infrastructure in seven of the eight tumours while only four of the 10 metastases of lung cancer and five of the nine metastases of one of the other primary malignancies were found to have an irregular reflectivity. In contrast to breast cancer metastases, lung cancer metastases, therefore, do not show the irregular picture characteristic of metastases as described by various authors. The picture of a highly irregular reflectivity, described as characteristic of metastases by various investigators (Coleman, 1973; Verbeek, 1985; Poujol and Chaintron, 1988) was described in only one patient with a metastasis of lung cancer.

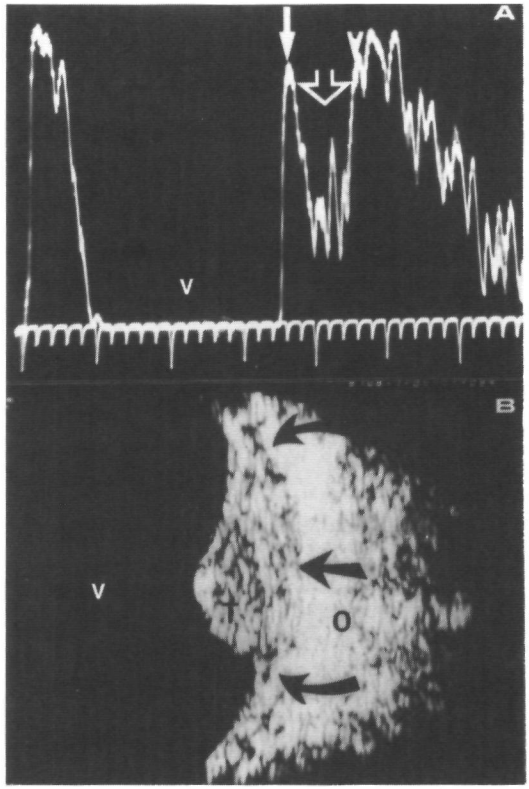


Figure 2.3.4.5 A- and B-mode echogram of a choroidal metastasis from a seminoma (with elements of teratoma) (white arrow: retina; white arrowhead: sclera; open white arrow: irregular mid-reflective tumour infrastructure; curved black arrows: choroidal metastasis; O: orbital fat; T: tumour; V: vitreous).

Low-reflective and regular tumours, more compatible with a malignant melanoma, were described four times: twice in patients with lung cancer, once in breast cancer and once, in a patient with a metastasis probably originating from a colonic carcinoma.

Most frequently (41%), a mid-reflective irregular tumour was observed: six times in patients with breast cancer, twice in lung cancer, once in a testicular carcinoma and twice, in patients with metastases of unknown origin.

In the literature interruption of the echographic continuity of the choroid, a ***choroidal excavation***, is rarely if ever described (Coleman et al., 1974; Gonvers et al., 1979; Kerlen, 1980; Neetens et al., 1984). Only Poujol (1986) described such an excavation in 42% of the metastases.

Distinct presence of a choroidal excavation was established in 11 of the echographically examined patients (16%) of our study, while in four patients (6%) this

presence was doubtful (Figure 2.3.4.6). In 45 patients (65%), no choroidal excavation was described [nine patients (13%) unknown for lack of a B-scan]. There was a distinct correlation with the reflectivity of the tumour: in low-reflective tumours a choroidal excavation was seen in 50% of the cases as against 21% of the mid-reflective and none of the high-reflective metastases. Therefore, it seems that for a choroidal excavation to be brought about, part of the choroid has to be occupied by predominantly low reflective tissue.

Consequently, the presence of a choroidal excavation was also correlated with the nature of the primary tumour. In metastases of lung cancer, a choroidal excavation was observed in 22%, in patients with one of the other malignancies in 20%. In only 11% of the breast cancer patients was the metastasis accompanied by a choroidal excavation.

The presence of a choroidal excavation proved also to be correlated with the prominence of the tumour. The mean prominence in tumours with a choroidal excavation was 5.5 mm (SD 3.5). If an excavation was doubtfully present, mean prominence was 3.9 mm (SD 2.1) and in absence of an excavation, it was 2.8 mm (SD 2.0) [unknown: 4.8 mm (SD 3.9)]. Therefore, a metastasis with a choroidal excavation had a larger mean prominence than tumours without an excavation.

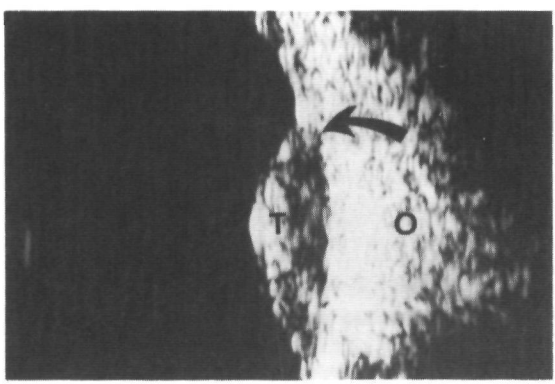


Figure 2.3.4.6 B-mode echogram of a 4.0 mm prominent dome-shaped choroidal metastasis from breast cancer with a choroidal excavation (curved arrow) (O: orbital fat; T: tumour).

An echographic ***vascularity*** of the tumour, characterized by moving echo spikes in the tumour infrastructure, is described only sporadically in the literature, just as a choroidal excavation. Determination of the presence of vascularity requires a minimal prominence of 4.0 mm (Ossoinig and Blodi, 1974; Neetens et al., 1984; Freedman and Folk, 1987).

In our study group, in 5 of the 27 tumours with a minimal prominence of 4.0 mm (19%), a distinct vascularity was observed: three times in lung cancer patients, once in a patient with a bladder carcinoma and once, in a patient with a probable colonic carcinoma. In three patients (11%) the presence of vascularity was doubtful: once in a metastasis of

breast cancer, once of lung cancer and once, of a carcinoma of the prostate. Vascularity, therefore, was established most frequently in metastases of lung cancer. In 12 patients (44%), vascularity was not demonstrable echographically, in seven patients (26%) this element was unknown.

In literature, an ***orbital shadow*** is described only in large metastases (Neetens et al., 1984; Coleman and Abramson, 1989).

In our study group an orbital shadow was established in 12 patients (17%) while in one other patient its presence was doubtful. In 47 patients (68%), no orbital shadow was described [nine patients (13%) unknown, mostly because of absence of a B-scan]. The larger the lesion, the more frequently an orbital shadow was described. Thus, in the absence of an orbital shadow, the mean prominence was 2.8 mm (SD 1.8), if the orbital shadow was doubtfully present the prominence was 3.0 mm, while in a distinctly present orbital shadow a mean prominence of 6.6 mm (SD 3.9) was measured [orbital shadow unknown: mean 3.4 mm (SD 2.6)].

An echographically manifest ***extraocular extension*** of a uveal metastasis was never established with certainty. However, it was doubtfully present in two patients (3%): once in a patient with echographic suspicion of scleral invasion and once in a patient in whom such invasion was supposed. In 57 patients (83%), this phenomenon was absent [10 patients (14%) unknown, mostly because of absence of a B-scan].

An ***acoustically silent zone*** in the tumour infrastructure was described in five patients (10%) with a prominence of the metastasis of at least 2 mm. In one other patient this was doubtfully present and in 31 patients (61%), it was absent [14 patients (27%) unknown].

As mentioned before in the chapter on ophthalmoscopy, a ***retinal detachment*** occurs frequently in patients with a uveal metastasis. A retinal detachment was observed echographically in 36 patients (52%), while it was absent in 30 patients (43%) [three patients (4%) unknown]. A correlation existed between a retinal detachment and the prominence of the tumour: the mean prominence of a metastasis with a retinal detachment was 4.1 mm (SD 2.8) as against 3.0 mm (SD 2.8) if no retinal detachment was observed (Figure 2.3.4.7).

On the basis of echographic examination alone, taking into account the above-mentioned criterias, like reflectivity, regularity, choroidal excavation, vascularity, etcetera, without considering other clinical data, an ***echographic diagnosis*** was made in 69 patients with choroidal and ciliary metastases (Table 2.3.4.6). In only half the cases was the correct diagnosis made, even if only tumours with a prominence of at least 2 mm were considered. In the other cases, the echographic diagnosis of melanoma was made most frequently, or the intraocular lesion could not be differentiated and the lesion was just classified as a 'tumour'.

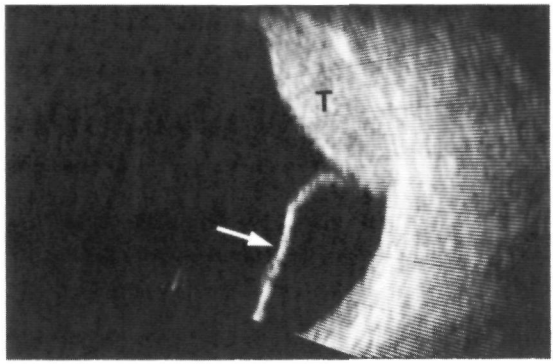


Figure 2.3.4.7 B-mode echogram of a 4.5 mm prominent dome-shaped choroidal metastasis from lung cancer with a retinal detachment (arrow) (T: tumour).

Table 2.3.4.6 Echographic diagnosis in choroidal and ciliary metastases

	All		Prominence ≥2.0 mm	
Echographic diagnosis	N	%	N	%
Metastasis	37	54	27	53
Melanoma	13	19	13	25
Naevus	0	-	0	-
Haemangioma	0	-	0	-
Choroidal detachment	1	1	1	2
Retinal detachment	1	1	0	-
'Tumour'	16	23	10	20
Normal	1	1	0	-

Echographic diagnoses are subdivided according to the nature of the various primary tumours in Table 2.3.4.7. It shows that 67% of the metastases of breast cancer were diagnosed correctly, while 8% were mistaken for a melanoma. Metastases of lung cancer, on the other hand, were diagnosed echographically as metastases in only 22% of the cases; in 39% of the cases the diagnosis of uveal melanoma was made. When only metastases with a minimal prominence of 2.0 mm were taken into consideration, the differences increased further: 81% of the metastases of breast cancer and 18% of the metastases of lung cancer were diagnosed correctly, while 14% of the metastases of breast cancer and 41% of lung cancer were mistaken for a melanoma. In metastases of one of the other malignancies, the diagnosis of metastasis was made in 58% and that of melanoma in 25% of the cases.

Table 2.3.4.7 *Echographic diagnosis in choroidal and ciliary metastases according to the localization of the primary tumour*

	Breast (N=36)		Lung (N=18)		Other (N=15)	
Echographic diagnosis	N	%	N	%	N	%
Metastasis	24	67	4	22	9	60
Melanoma	3	8	7	39	3	20
Naevus	0	-	0	-	0	-
Haemangioma	0	-	0	-	0	-
Choroidal detachment	0	-	1	6	0	-
Retinal detachment	1	3	0	-	0	-
'Tumour'	7	19	6	33	3	20
Normal	1	3	0	-	0	-

Of the 22 patients in whom no ophthalmoscopical diagnosis could be made but echographic examination was performed, 10 were diagnosed echographically as metastasis and three as melanoma.

It can be concluded that the echographic image of a uveal metastasis accepted in the literature is observed only in metastases of breast cancer. Lung cancer metastases cause major problems for echographic diagnostics because they may strongly resemble melanomas, as previously described by Verbeek (1985). Thus, they constitute a pitfall in the echographic diagnostics of uveal metastases.

At echographic examination of an ***iris metastasis***, a small convex lesion was described, with mid-reflectivity, which was suspected of being a metastasis. This metastasis originated from lung cancer.

Summary of echography in patients with uveal metastases: in our study group at echography in metastases of the choroid or the ciliary body, a frequent finding was a lesion with a slight prominence of 3.6 mm on average. The mean tumour base measured 11.7 mm. The prominence was much less in metastases of breast cancer than in metastases of other primary tumours. The shape of the metastasis was generally flat or dome-shaped. A few times lobulated or even mushroom-shaped tumours were described, especially in metastases of lung cancer.

The reflectivity of the lesions varied, but most were mid-reflective. This reflectivity proved to be correlated with the nature of the primary tumour: metastases of breast cancer were most often mid-reflective while metastases of lung cancer were low- and mid-reflective with the same frequency. The infrastructure of the tumour showed a predominantly irregular reflectivity, especially in metastases of breast cancer.

A choroidal excavation was present in 16% and vascularity in 19% of the patients.

An orbital shadow was described in 17%. Extraocular extension of the tumour was never definitely demonstrated echographically, but in two patients there were doubtful echographic indications of it. Retinal detachment was described in 52% of the patients with ciliary and choroidal metastases.

A characteristic echographic image of uveal metastases did not exist. In metastases of lung cancer a low and regular reflectivity was observed relatively frequently, the shape was convex or lobulated and one of the two mushroom-shaped tumours originated from lung cancer. The prominence was higher than in metastases of breast cancer and vascularity was observed more often. On the basis of echographic features alone, metastases of lung cancer were diagnosed correctly in only 22% of the cases, as against 67% of metastases of breast cancer and 60% of the metastases of one of the other malignancies. In most cases, a metastasis of lung cancer was mistaken for a malignant melanoma.

Table 2.3.4.8 summarizes the echographic data of all patients with ciliary and choroidal metastases; the echographic data are compared with those of other intraocular tumours.

Table 2.3.4.8 *Echographic features in patients with choroidal and ciliary metastases, melanomas, haemangiomas and naevi*

	Intraocular tumour			
	Metastasis	Melanoma	Haemangioma	Naevus
Number of patients	69	400	27	39
Prominence: mean (SD): mm	3.6 (2.7)	6.5 (3.8)	3.4 (1.1)	0.3 (0.5)
Base. mean (SD): mm	11.7 (5.0)	11.3 (5.7)	7.7 (3.2)	1.7 (2.9)
Prominence:base ratio: mean (SD)	0.32 (0.28)	0.61 (0.35)	0.44 (0.11)	0.20 (0.09)
Prominence ≥2.0 mm *	51 (74%)	357 (89%)	24 (89%)	0 (0%)
Prominence ≥4.0 mm *	27 (39%)	277 (69%)	7 (26%)	0 (0%)
Shape:				
Flat shape	41%	6%	-%	92%
Dome-shaped	39	47	70	3
Lobulated shape	9	10	-	-
Mushroom-shaped	3	22	-	-
Unknown shape	9	14	30	5
Reflectivity: #				
Low	29%	74%	-%	
Medium	53	24	4	**
High	18	2	83	
Unknown	-	1	13	

to be continued on next page

Table 2.3.4.8 (continued)

	Intraocular tumour			
	Metastasis	Melanoma	Haemangioma	Naevus
Regularity: ##				
Regular	37%	66%	29%	
Irregular	59	33	29	**
Unknown	4	1	43	
Choroidal excavation:				
Positive	16%	65%	-%	-%
Doubtful	6	1	4	-
Negative	65	21	63	65
Unknown	13	14	33	35
Vascularity: ##				
Positive	19%	52%	14%	
Doubtful	11	7	-	**
Negative	44	29	29	
Unknown	26	12	57	
Orbital shadow:				
Positive	17%	42%	4%	-%
Doubtful	1	2	-	-
Negative	68	41	67	100
Unknown	13	16	30	-
Retinal detachment:				
Present	52%	58%	33%	-%
Absent	42	35	41	100
Unknown	6	7	26	-

** percentage of all tumours with known prominence; ** all tumours prominence < 2.0 mm; # in tumours with a prominence ≥ 2.0 mm; ## in tumours with a prominence ≥ 4.0 mm*

In our patient material, ***melanomas*** of the choroid and ciliary body were more prominent than metastases, viz. 6.5 mm on average as against 3.6 mm in metastases, while the mean base of the lesions was the same for both tumours. The mean prominence:base ratio in melanomas was 0.61, which is higher than the ratio in metastases (0.32). A dome-shaped tumour was described in 47% of the patients. The mushroom shape, characteristic of melanomas, was observed in 22% of the patients, in which respect melanomas differ from metastases.

Between melanomas and metastases there was a considerable difference in reflectivity. Melanomas in the vast majority of the cases were low-reflective (74%) while in metastases mid-reflective tumours were observed in 61%. The reflectivity in melanoma was predominantly regular (66%) compared with the frequently irregular (59%)

reflectivity in metastases. Of all melanomas of which the reflectivity could be determined, 56% were low-reflective and regular as against 15% of the metastases.

A choroidal excavation occurred four times and vascularity three times as frequently in melanomas as in metastases. An orbital shadow was described three times as often in melanomas. In melanomas and metastases, retinal detachment was established with nearly equal frequency (Figure 2.3.4.8 and Figure 2.3.4.9).

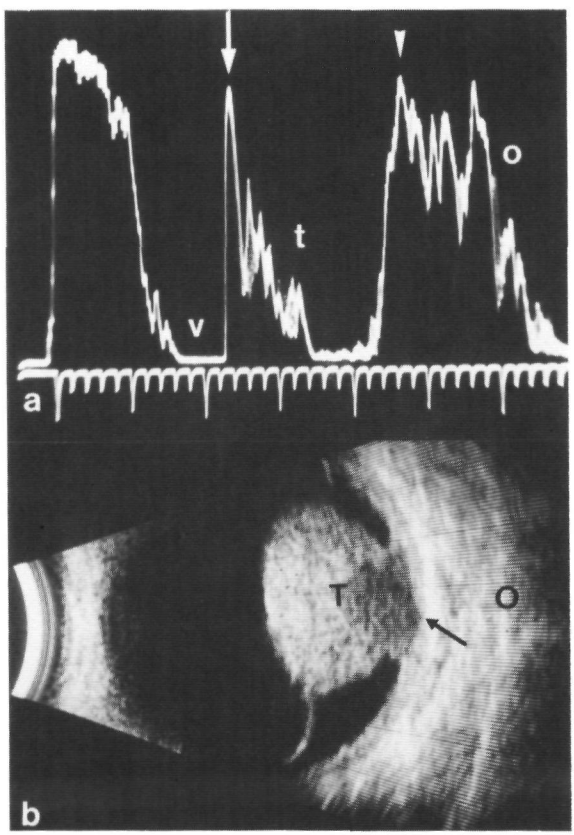


Figure 2.3.4.8 A- and B-mode echogram of a 11.0 mm prominent mushroom-shaped choroidal malignant melanoma with a low reflectivity, choroidal excavation, vascularity, and retinal detachment (white arrow: retina; white arrowhead: sclera; black arrow: choroidal excavation; O: orbital fat; t: low-reflective tumour infrastructure with vascularity; T: tumour; V: vitreous).

Figure 2.3.4.9 A-mode echogram of a malignant melanoma filling almost the entire globe with distinct vascularity (blurring of the echo spikes in the tumour infrastructure: open white arrows) (white arrowhead: sclera; O: orbital fat).

Echographic signs of extraocular spread, just as in metastases, were uncommon in melanomas also, viz. in 4% of the cases (Figure 2.3.4.10).

Noticeable features of a melanoma, therefore, are the relatively high prominence, the dome-shaped or mushroom-shaped tumour and the regular low reflectivity. Frequently, the tumour shows a choroidal excavation, an orbital shadow and vascularity.

On the echographic image alone the diagnosis in melanomas with a minimal prominence of 2.0 mm was established as melanoma in 90%, metastasis in 2% and 'tumour' in 8%.

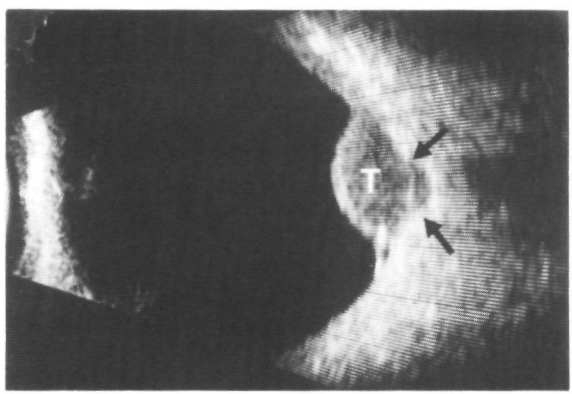


Figure 2.3.4.10 B-mode echogram of a 3.5 mm prominent dome-shaped malignant melanoma of the choroid (T) with extraocular extension (black arrows).

The following echographic criteria were selected as characteristic of melanoma:

- prominence ≥2.0 mm
- low reflectivity
- regular infrastructure
- choroidal excavation
- vascularity.

Of all the different intraocular tumours, 71 (18%) of all melanomas and one (1%) of all metastases met all these conditions (Table 2.3.4.9).

Table 2.3.4.9 *Echographic characteristics of melanomas in various intraocular tumours in terms of percentage* *

Number of echographic criteria fulfilled *	Diagnosis				
	Melanoma	Metastasis	Haemangioma	Miscellaneous tumours	Tumours of unknown nature
three	91	5	0	2	2
four	98	1	-	0	1
five	99	1	-	-	-

** prominence ≥2.0 mm; low reflectivity; regularity; choroidal excavation; vascularity*

If at least four of the five echographic melanoma criteria have to be fulfilled, 98% of the tumours are melanomas. This requirement is met by 50% of all echographically examined ciliary and choroidal melanomas and by 3% of the metastases: one patient with a metastasis probably arisen from a colonic carcinoma fulfilling all five criteria and one patient with an irregular metastasis of lung cancer fulfilling four criteria. At least three of the five criteria are met by 72% of the melanomas and 22% of the metastases.

Haemangiomas showed a prominence comparable to that of metastases, but the mean base of the lesion was smaller. In all cases, the tumour was dome-shaped. Low-reflective haemangiomas did not occur in our study group: nearly all lesions (83%) were high-reflective. Choroidal excavation and vascularity were present only exceptionally. A retinal detachment was described less frequently than in metastases or melanomas. Signs of extraocular extension were never present (Figure 2.3.4.11).

In not a single case was a haemangioma echographically diagnosed as metastasis or melanoma. In haemangiomas with a prominence of ≥2.0 mm, the echographic diagnosis was haemangioma in 79% and 'tumour' in 21%.

All ***naevi*** in our study were flat lesions with a maximal prominence of 1.5 mm. Once, a dome-shaped lesion was described. Owing to the low prominence, naevi echographically could at the most be detected but not differentiated from intraocular tumours with adequate reliability.

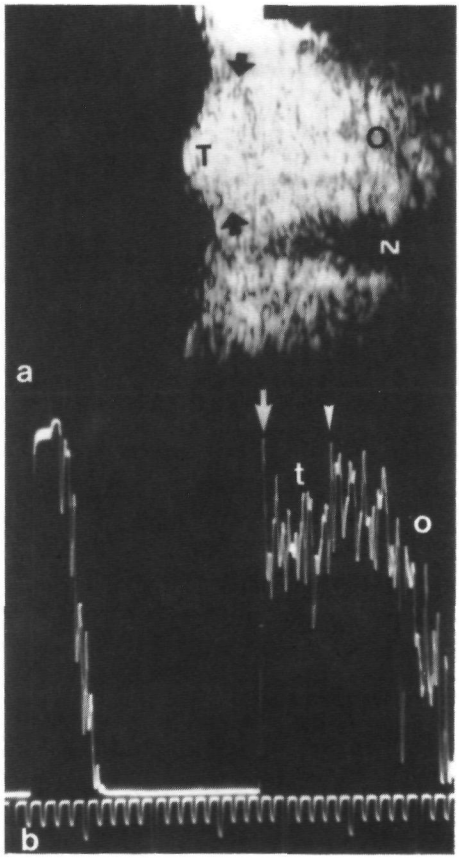


Figure 2.3.4.11 A- and B-mode echogram of a 3.5 mm prominent high-reflective dome-shaped choroidal haemangioma (black arrows: haemangioma; white arrow: retina; white arrowhead: sclera; N: optic nerve; O: orbital fat; t: high-reflective tumour infrastructure; T: tumour).

In 18 patients with a ***retinoblastoma*** echography was performed, showing a high reflectivity and shadows in the orbital fat pattern due to intratumoral calcifications in all cases. In only one patient was the echographic diagnosis 'tumour' instead of retinoblastoma (Figure 2.3.4.12).

In patients with ***miscellaneous intraocular tumours*** echography was carried out in four patients with a choroidal localization of a ***lymphoproliferative disease***. The prominence never exceeded 1.5 mm. The lesions were flat, so that echographically they could not be differentiated with adequate reliability.

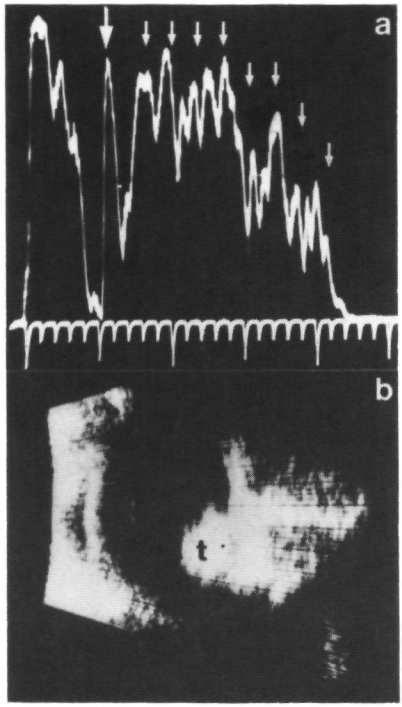


Figure 2.3.4.12 A- and B-mode echogram of a retinoblastoma almost filling the entire globe (white arrow: retinal surface; small white arrows: high-reflective tumour infrastructure: no partition from the orbital fat pattern can be distinguished; t: tumour).

In eight patients with a ***subretinal haemorrhage*** echography was performed. The mean prominence of the lesions was 3.3 mm, the mean base 10.7 mm and the mean prominence:base ratio 0.29, similar to a metastasis. The shape was flat three times, convex three times, lobulated once and mushroom-shaped once. Reflectivity was low, mid and high with equal frequency, and three times irregular and once, regular (four times: too small). A choroidal excavation was described in three patients. Vascularity was not observed. An orbital shadow occurred frequently: three times it was definitely and twice, possibly present. A retinal detachment was described in one patient. The echographic diagnosis was five times haemorrhage, once melanoma and twice, 'tumour' (Figure 2.3.4.13 a).

The mean prominence in seven patients with a ***Kuhnt Junius*** amounted to 3.4 mm with a base of 12.2 mm and a prominence:base ratio of 0.24. The lesion was predominantly dome-shaped with three times mid, twice low and once, high reflectivity (once too small). The tumour infrastructure was twice irregular and once, regular (five times too small). Choroidal excavation was described in two patients. Vascularity was

never present. Retinal detachment occurred in two patients. The diagnosis at echography was three times Kuhnt Junius, twice melanoma and twice, 'tumour' (Figure 2.3.4.13 b).

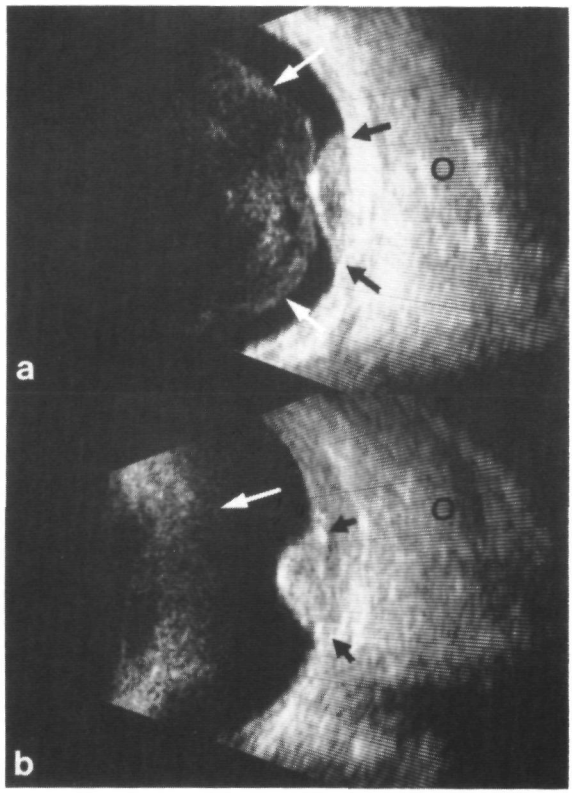


Figure 2.3.4.13 a. B-mode echogram of a 2.5 mm prominent dome-shaped subretinal haemorrhage (black arrows) with intravitreous haemorrhages (white arrows). b. B-scan echogram of a 3.0 mm prominent dome-shaped age-related macular degeneration (Kuhnt Junius: black arrows) with intravitreal haemorrhages (white arrows) (O: orbital fat).

In the five patients with a ***choroidal detachment***, a dome-shaped tumour was described with a mean prominence of 4.8 mm, a base of 7.5 mm and a prominence:base ratio of 0.53 with low reflectivity. A choroidal excavation was observed once, vascularity never. The echographic diagnosis was twice choroidal detachment, twice retinal detachment and once, 'tumour'.

The prominence and base in the three patients with a ***leiomyoma*** were 8.0 mm on average with a ratio of 1.0. The lesion was twice dome-shaped, once mushroom-shaped. The tumour was low-reflective, regular, without choroidal excavation. Once a doubtful vascularity was present, and once, a retinal detachment. The diagnosis was once melanoma and twice, 'tumour'.

The three ***retinal detachments*** which initially were mistaken for solid intraocular tumours, echographically were 4.0 mm prominent on average and dome-shaped. The echographic diagnosis caused no problems.

Conclusion: echography occupies an important place in the differential diagnostics of uveal metastases. Differentiation of the malignant melanoma of the uvea is adequately possible in many cases. However, metastases from lung cancer may give rise to problems, showing an echographic image compatible with melanoma. In many cases, metastases can also be differentiated from haemangiomas. In no patient with a metastasis was the echographic diagnosis of haemangioma made and in no patient with a haemangioma was the diagnosis of metastasis made. Retinoblastomas showed a characteristic image. In small tumours (prominence <2.0 mm) echography does not give sufficient information for adequate differential diagnosis. However, in these cases echography still may be important for detecting possible extraocular extension of the tumour.

2.3.5 Perimetry

Perimetry, or examination of the visual field, was not one of the ophthalmological examinations carried out routinely in patients with an intraocular tumour. In general, perimetry was performed only on indication, for instance because a patient complained about visual field defects or because of the insights and interests of the individual physician in charge.

In our study, perimetry was carried out in 25 patients with uveal metastases, namely in 24 patients with a choroidal metastasis and one patient with a ciliary metastasis. A visual field defect was established in 22 patients: an absolute scotoma in 16 patients, a relative scotoma in five patients and a scotoma of unknown depth in one patient. In two patients a general decrease of sensitivity was observed and one patient showed no abnormalities (Table 2.3.5.1; Figure 2.3.5.1).

In five patients with a scotoma, apart from the visual field defect, a general decrease of sensitivity was also observed and in one patient, a central decrease of sensitivity was established.

The prominence of the tumour in patients with an absolute scotoma was usually higher (mean 4.6 mm; SD 3.3) than that in patients with a relative scotoma (mean 3.0 mm; SD 2.0). No correlation could be observed between the depth of the scotoma and the nature of the primary tumour.

If perimetry had been performed, a scotoma, mostly an absolute one, was observed in 88% of the cases. This percentage must not be extrapolated to our entire study group, because the definition of the indication for this examination may affect the results.

Table 2.3.5.1 Perimetry in 25 patients with choroidal and ciliary metastases

	N	%
Normal	1	4
Scotoma:		
Absolute	16	64
Relative	5	20
Scotoma of unknown depth	1	4
General decrease of sensitivity	2	8

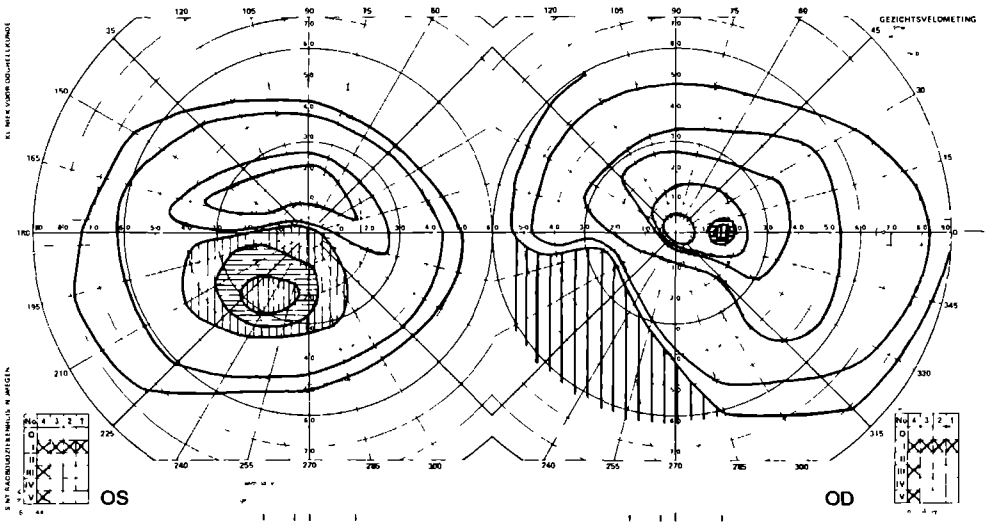


Figure 2.3.5.1 Perimetry in a patient with bilateral choroidal metastases from breast cancer. Right eye: inferotemporal absolute scotoma with a steep to sloping inclination (metastasis located superiorly of the optic disk with secondary retinal detachment extending to the macular area). Left eye: inferonasal absolute scotoma with sloping margins (metastasis located temperosuperiorly with secondary retinal detachment).

If a scotoma is present its inclination can be determined. This inclination was known in 17 of the 22 patients with a scotoma. Six times (27%) it was steep, four times (18%) sloping to steep and seven times (32%), sloping [five patients (23%) unknown]. No correlation between the depth and the inclination of the scotoma was established.

In 21 of the 22 patients with a scotoma, the ophthalmoscopical localization of the uveal metastasis and the localization of the visual field defect were known. Eighteen times (82%) the scotoma corresponded to the ophthalmoscopical localization of the metastasis. Three times (14%) the scotoma was situated in a different place: once in a patient with a tumour localized superiorly in the fundus and a secondary retinal detachment inferiorly with a related visual field defect superiorly; twice in patients with a minimal visual field defect. The cause of this discrepancy could not be ascertained. One of these two patients

was the one with a ciliary metastasis in whom a relative scotoma with a general decrease of sensitivity was established.

Summary of perimetry in patients with uveal metastases: when perimetry was carried out a scotoma, which was mostly absolute, was detected in 88% of the cases. In patients with an absolute scotoma a higher prominence of the tumour was measured than in patients with a relative scotoma. The inclination of this scotoma might be sloping or steep. This was not correlated with the depth of the scotoma. The localization of the scotoma as a rule corresponded to the ophthalmoscopical site of the metastasis (Table 2.3.5.2).

Table 2.3.5.2 *Perimetric features in patients with choroidal and ciliary metastases, melanomas, haemangiomas and naevi*

	Intraocular tumour			
	Metastasis	Melanoma	Haemangioma	Naevus
Number of patients	25	165	16	24
Visual field defect:				
None	4%	6%	-%	50%
Scotoma:	88	91	100	29
Absolute	64	77	56	4
Relative	20	10	38	17
Depth unknown	4	4	6	8
General decrease of sensitivity	8	2	-	10
Central decrease of sensitivity	-	1	-	17
Inclination of scotoma: *				
Steep	27%	36%	25%	14%
Sloping to steep	18	27	19	29
Sloping	32	5	13	14
Unknown	23	33	44	43

* *in presence of a scotoma*

In ***melanomas*** a scotoma was observed as often as in metastases. Even more frequently than in metastases this scotoma was absolute. The inclination of the scotoma was only rarely sloping.

Haemangiomas at perimetry in all cases showed an absolute or relative scotoma. Inclination of the scotoma could be either steep or sloping.

In ***naevi*** a visual field defect was described in one-half of the patients. The scotoma was usually relative, the inclination steep or sloping.

In the ***miscellaneous tumours***, perimetric examination had been performed only sporadically and insufficient data were available for differentiation of these lesions from metastases.

Conclusion: perimetry makes no contribution to the differential diagnostics of uveal metastases.

2.3.6 Electrophysiology

2.3.6.1 Electro-oculography (EOG)

In a retrospective study (Brink et al., 1989), an attempt was made to develop a method for application of EOG to the differential diagnostics of malignant melanomas, metastases and naevi of the choroid and ciliary body and rhegmatogenous retinal detachments. To this purpose a study was made of the EOG data of 64 patients with a malignant melanoma of the choroid or the ciliary body as well as of the data of 11 patients with choroidal metastases, 11 patients with choroidal naevi and 27 patients with a rhegmatogenous retinal detachment. By using the dark trough (Dt) and the light peak - dark trough ratio (Lp/Dt ratio), a diagram could be composed for the EOG classification of these lesions suspicious of tumour (Figure 2.3.6.1). This diagram could be applied exclusively to the differentiation of the above-named lesions since only for melanomas, metastases, naevi and retinal detachments a specific area is indicated. If further lesions are to be considered for the differential diagnosis, this diagram should not be used.

The EOG classifications of patients with a choroidal metastasis proved to be scattered over the entire diagram without any concentration in a particular area. This may be a consequence of the heterogeneity that is typical of metastases. It was found that not a single metastasis could be classified correctly. That an area for the diagnosis of 'metastasis' was nevertheless constructed was because the probability of one of the other three lesions in this area was even smaller than the probability of a metastasis.

In a prospective study, it was found again that metastases could not be classified correctly by means of this EOG method. Accordingly, it was concluded that metastases cannot be differentiated electro-oculographically from malignant melanomas of the uvea (Brink et al., 1990).

Electro-oculography was carried out in 16 of the 87 patients with uveal metastases in this retrospective study. In all cases the metastases were situated in the choroid. Table 2.3.6.1.1 presents a survey of the different values of the various EOG parameters in these patients, of the mean values in a normal control group of 151 persons and of the lower limit of normal. The lower limit of these normal values is defined as the value in the normal patient on the lowest fifth percentile. The percentage of abnormal values in metastases is also given.

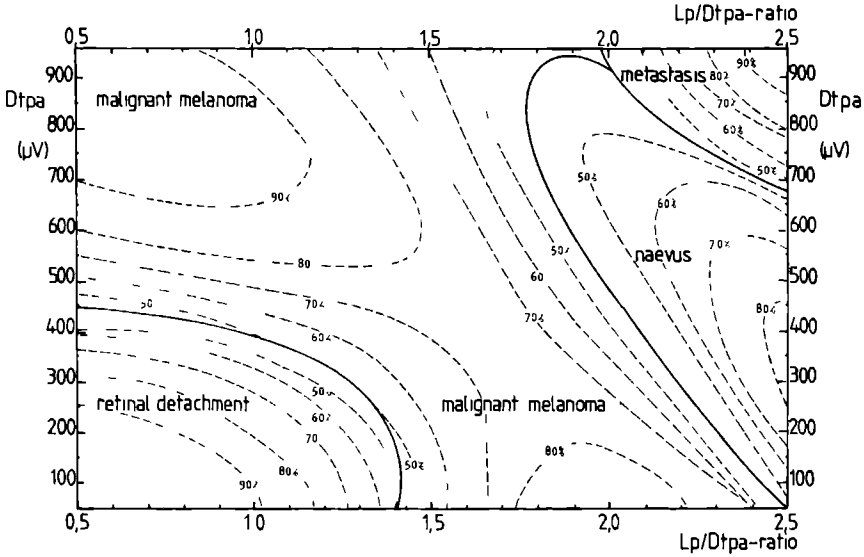


Figure 2 3.6 1 EOG probability score for various intraocular lesions. Indicated are four areas with the highest probabilities of a specific disease group, using Dtpa and Lp/Dtpa-ratio. The broken lines represent the probabilities (as indicated) of a specific disease (Dtpa: dark trough pathological eye, Lp/Dtpa-ratio. light peak divided by dark trough of the pathological eye).

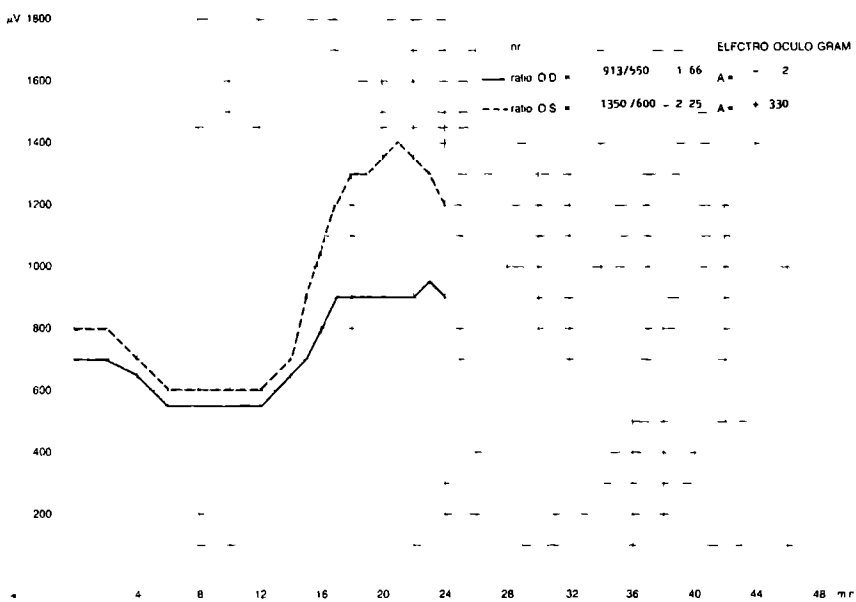


Figure 2.3.6.2 EOG registration in a patient with a metastasis from lung cancer in the right eye Abnormal results in the right eye, compatible with malignant melanoma; normal results in the left eye.

Table 2.3.6.1.1 Results of various EOG parameters in the affected eye of patients with choroidal metastases related to normals

	Iv (μV)	Dt (μV)	Lp (μV)	Lp/Dt ratio	A-criterium
Lower limit of normal:					
	300	200	500	1.78	+ 30
Normal control: (N=151)					
Mean	568	430	972	2.32	+ 244
SD	198	152	315	0.43	151
Choroidal metastases: (N=16)					
Mean	619	534	783	1.52	- 69
SD	308	206	296	0.49	263
Percentages of abnormal values in choroidal metastases:					
	0%	0%	13%	75%	75%

Iv = initial value; Dt = dark trough; Lp = light peak; Lp/Dt ratio = light peak : dark trough ratio; A-criterium = Lp - [(0.6 x Iv) + (0.9 x Dt)]

In metastases a distinctly abnormal EOG was registered, without abnormalities in initial value and dark trough, but with abnormalities in light peak and major abnormalities in ratio and A value.

This manifested itself also in the EOG classification of the choroidal metastases: in 12 patients the EOG diagnosis was malignant uveal melanoma (75%), in two patients naevus and in two other patients, retinal detachment. The diagnosis of metastasis was never made (Figure 2.3.6.2). The EOG diagram therefore is a poor method for the differential diagnostics of uveal metastases. It appears, however, that it is a good method to trace an abnormality in the natural potential difference of the eye. The cause of the abnormal EOG in uveal metastases is unknown, just as in the case of melanomas.

Table 2.3.6.1.2 presents a survey of the mean values of the various EOG parameters in the various tumours and the percentages of abnormal values. The EOG diagnoses are described in Table 2.3.6.1.3. In this connection it should be noted that EOG diagnostics of intraocular tumours, as applied by us, should be used only in the differentiation of metastases, melanomas, naevi and retinal detachments; other tumours, namely, have not been included in the calculations. For purposes of illustration, haemangiomas, miscellaneous tumours and tumours of unknown nature have nevertheless been included in Table 2.3.6.1.3.

These two tables show that in ***melanomas*** abnormal values were established in a large proportion of the cases. In 83% of the patients classification was correct.

Table 2.3.6.1.2 *Values of various EOG parameters and percentages of abnormal values in the affected eye of patients with various intraocular lesions*

		Iv (μV)		Dt (μV)		Lp (μV)		Lp/Dt ratio		A-crterium	
	N	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Value:											
Metastasis	16	619	308	534	206	783	296	1.52	0.49	- 69	263
Melanoma	116	578	251	520	229	691	339	1.38	0.47	- 123	207
Haemangioma	3	500	100	346	64	446	173	1.25	0.30	- 165	64
Naevus	36	602	213	481	190	978	317	2.12	0.44	+183	167
Other	9	572	505	511	179	822	443	1.57	0.50	+19	259
Unknown lesion	25	512	189	434	147	781	336	1.80	0.51	+83	189
Percentage of abnormal values:		%		%		%		%		%	
Metastasis	16	0		0		13		75		75	
Melanoma	116	4		2		22		82		80	
Haemangioma	3	0		0		33		100		100	
Naevus	36	3		3		3		19		19	
Other	9	0		0		22		56		56	
Unknown lesion	25	4		4		12		44		36	

Table 2.3.6.1.3 EOG diagnosis in patients with uveal metastases, melanomas and naevi and with retinal detachments

	Ultimate diagnosis											
	Metastasis		Melanoma *		Haemangioma **		Naevus		Other **		Unknown nature **	
EOG diagnosis	N	%	N	%	N	%	N	%	N	%	N	%
Metastasis	0	-	0	-	0	-	0	-	0	-	0	-
Melanoma	12	75	95	83	2	67	13	36	6	67	16	64
Naevus	2	13	11	10	0	-	23	64	2	22	7	28
Retinal detachment	2	13	9	8	1	33	0	-	1	11	2	8
Total	16	100	115	100	3	100	36	100	9	100	25	100

** one of 116 melanomas could not be classified due to a very high dark trough (1575 μV); ** when classified as metastasis, melanoma, naevus or retinal detachment*

In only three patients with a ***haemangioma*** was electro-oculography performed, at which abnormal values were found. Although Diagram 2.3.4.1.1 must not be used for the diagnostics of haemangiomas, Table 2.3.4.1.3 for purposes of comparison lists the EOG diagnoses that would have been made if the EOG criterion had been applied to melanomas.

Naevi in general show a normal EOG. Nevertheless, an abnormal ratio was registered in as many as 19% of the cases while 36% of the naevi were incorrectly classified as melanomas.

The group of ***miscellaneous tumours*** consisted of various lesions. An abnormal ratio was recorded in a patient with a choroidal detachment, a benign reactive lymphoid hyperplasia, a tuberculoma, a detachment of the retinal pigment epithelium and a Kuhnt Junius. A normal ratio was established in a patient with leiomyoma, a detachment of the retinal pigment epithelium, a vorticose vein and a subretinal haemorrhage.

In patients with intraocular ***lesions of unknown nature***, an abnormal ratio was observed in 44% of the cases. This is a significantly smaller proportion than those found in metastases and melanomas.

Conclusion: electro-oculography makes no contribution to the differential diagnostics of uveal metastases from uveal melanomas, and only a limited contribution to the differentiation from choroidal naevi.

2.3.6.2 Electroretinography (ERG)

In six patients with uveal metastases, electroretinography was found to have been performed. The electroretinograms were abnormal in four patients, subnormal in one and normal in one patient.

The number of patients examined electroretinographically was only small; therefore, no conclusions can be drawn from these figures.

Electroretinography had been performed in 16 patients with a melanoma, with normal results in seven, subnormal results in four and abnormal results in five cases.

2.3.7 Miscellaneous examination techniques

Only sporadically were other examinations than described in the preceding chapters carried out in patients with uveal metastases. With the exceptions of one patient in whom a tumour was punctured and some patients in whom transillumination was performed, all these cases concerned examinations carried out outside our clinic.

Computed tomography (CT scan) was performed in only two patients with a choroidal metastasis. Both patients echographically had a choroidal metastasis with 3 mm prominence originating from lung cancer. The outcome of the CT scanning was scleral thickening in one patient, and 'tumour' in the other.

In 17 patients with a uveal melanoma, CT scanning was performed leading to the diagnoses of melanoma four times, 'tumour' eight times and haemorrhage once, while no abnormalities could be established in four cases.

Compared with echography, the CT scan provided no additional information.

In three patients with a retinoblastoma an intraocular tumour with calcifications was observed.

Magnetic Resonance Imaging (MRI) was not carried out in any patient with a uveal metastasis.

Puncture or ***biopsy*** of the intraocular tumour was carried out in only one patient with a choroidal metastasis of unknown origin, but the quantity of material obtained was insufficient for cytological examination.

Isotope testing, for instance with the aid of isotope ^{32}P, was not carried out in any patient with a uveal metastasis in our study group.

Transillumination of the tumour was carried out in four patients with a uveal metastasis: three times clinically and once, after enucleation of the eye. The results of the clinical examinations were as follows. In a patient with a metastasis of breast cancer, prominence 1.5 mm, diaphany at the tumour site was observed. A metastasis of lung cancer with a prominence of 13.0 mm was partially diaphanous. In a metastasis of unknown origin with a prominence of 4.0 mm, complete extinction was observed. In a fourth patient, with a metastasis of lung cancer of 8.0 mm prominence and an intractible secondary glaucoma, transillumination of the enucleated eye showed complete extinction at the tumour site.

Transillumination had also been performed in 108 patients with a uveal melanoma: 36 times clinically and 72 times, after enucleation of the eye. The results of the examination were extinction in 93 cases (86%), a partially diaphanous lesion was observed 10 times (9%) and five times, the tumour was diaphanous (5%). In melanoma cases no correlation between the prominence and the diaphany of the tumour existed.

In haemangiomas, clinical transillumination of the tumour was performed five times: four times the tumour was completely and once, partially diaphanous.

Of all tumours examined by diaphanoscopy, one-half of the diaphanous lesions had a yellowish-orange colour. Tumours which at transillumination showed extinction were mostly grey. Probably, therefore, the colour of the tumour plays a more important part than the prominence at transillumination.

Diaphanoscopy makes no essential contribution to the differential diagnosis of intraocular tumours.

Conclusion: perimetry, electrophysiology, CT scanning, MRI, punctures and biopsies, isotope tests and transillumination as far as can be ascertained make no contribution to the differential diagnosis of uveal metastases.

2.3.8 Histopathological examination

In eight patients with uveal metastases, the clinical diagnosis was confirmed histopathologically. Seven times, histopathological examination was carried out while the patients were alive, after enucleation of the affected eye. Once, histopathological examination was carried out at autopsy. This concerned a patient with a metastasis of breast cancer in whom scleral invasion by the choroidal metastasis was observed.

The case histories of these patients will be briefly reviewed and a summary of the histopathological findings will be presented

In a ***female aged 33 years***, in 1974, a large yellowish-orange prominent mass situated temporosuperiorly within the macular area of the left eye was observed, with suspicion of a melanoma, with a secondary retinal detachment. There was no history of malignancies or operations. At radiological examination of the thorax and skeleton no abnormalities were established At fluorescein angiography, the lesion was suspected of being a melanoma, echographically the tumour was described as a mass with 4 mm prominence It was decided to perform enucleation of the left eye.

At histological examination the choroid was found to contain a tumoral proliferation of fairly large polygonal, partially well-delimited and partially poorly delimited tumour cells which formed solid trabeculae and nests with glandular tubuli. The cytoplasm of the cells was clearly basophilic, the nuclei dark with anisokaryosis Mitoses were encountered regularly In a few sites, necrosis and mononuclear infiltration into the tumoral stroma were observed. There was penetration of the tumour into the internal layer of the sclera. The optic nerve was tumour-free The conclusion was a moderately differentiated adenocarcinoma. Determination of the localization from the morphology was not possible.

Further examination revealed pathological lymph nodes, a space-occupying process in the liver and cerebral metastases. No primary tumour was found. The patient died three months after the initial examination.

A ***female aged 72 years*** was known for as long as 8 years with breast cancer when in 1982, temporosuperiorly in the right eye, a very large yellowish-orange pigmented tumour with a secondary retinal detachment was observed, suggestive of a metastasis. However, the fluorescein angiographic and echographic images were more compatible with a melanoma (Figure 2.3.8.1). Since no metastases elsewhere in the body were known and a malignant melanoma could not be excluded, enucleation was decided upon, partly because of possible complications.

At histological examination, a large tumour was found in the choroid, composed largely of cuboid to cylindrical cells ranged sometimes disorderly, sometimes in a mosaic pattern. Glandular tubuli and pseudorosettes were also observed. The cell nuclei were little polymorphous and mitoses were observed regularly, with central necrosis in several fields In a few places, the tumour invaded the sclera without extraocular extension. Partly

on the basis of comparison with sections of the breast carcinoma, the diagnosis of choroidal metastasis was made.

Eighteen months later, a choroidal metastasis developed in the other eye, which was treated with irradiation.

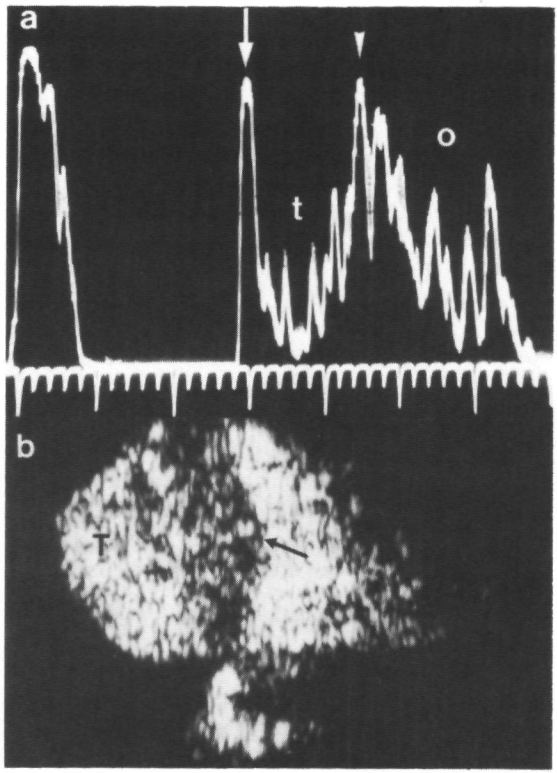


Figure 2.3.8.1 A- and B-mode echogram of a 7.5 mm prominent mid-reflective dome-shaped choroidal tumour with an irregular infrastructure (t), choroidal excavation (black arrow), vascularity, orbital shadowing and suspicion of extraocular extension: compatible with malignant melanoma. Histopathological examination: metastasis from breast cancer (white arrow: retina; white arrowhead: sclera; O: orbital fat; t: irregular tumour infrastructure; T: tumour).

A ***male aged 46 years*** in 1988 was referred to our clinic for echographical examination of a pale choroidal tumour of unknown nature, situated temporosuperiorly in the left eye. There was no history of malignancy. At fluorescein angiography, the lesion was diagnosed as a melanoma. The echographic findings mostly matched a melanoma, but a metastasis could not be excluded (Figure 2.3.8.2). In view of growth of the tumour, enucleation was decided upon.

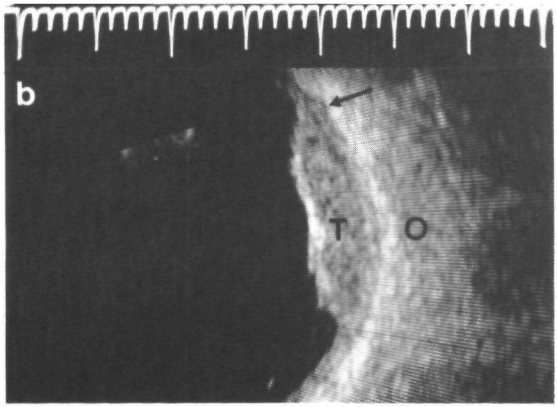


Figure 2.3.8.2 A- and B-mode echogram of a 5.0 prominent dome-shaped choroidal tumour with a base of 14.0 mm, a regular low to mid reflectivity (t), choroidal excavation (black arrow) and signs of vascularity: compatible with malignant melanoma. Histopathological examination: metastasis from prostatic carcinoma (white arrow: retina; white arrowhead: sclera; O: orbital fat; T: tumour).

In the choroid, proliferation was observed of epithelioid cells arranged in solid fields with a partly lobulated appearance. The cells contained ample cytoplasm and were not pigmented. The septa in between, however, did contain pigmented pre-existent melanocytes. Mitoses were described as sporadic. Scattered small necrotic foci and several blood-filled cavities were observed. There was invasive growth in the retina and superficial erosion of the sclera without extraocular extension. The diagnosis was malignant melanoma of the choroid of the epithelioid cell type.

Six months later, metastases were encountered in the skeleton, a primary or metastatic cerebral tumour was diagnosed and a carcinoma of the prostate was suspected. A revision of the histopathological examination of the ocular tumour was then performed with immunohistochemical processing of the preparation. The diagnosis subsequently made was a probable metastasis of a prostatic carcinoma.

After another six months the patient died and the prostatic carcinoma was confirmed at autopsy.

In these three patients the suspicion of a malignant melanoma of the choroid was the reason for enucleation of an eye with a metastasis. In the third patient, with a metastasis of a prostatic carcinoma, histopathological differentiation from a melanoma also caused problems. Font et al. (1967) already mentioned the difficult differentiation between primary uveal melanomas and uveal metastases of cutaneous melanomas. Metastases of a bronchial carcinoid may also show many cytological similarities to an amelanotic melanoma (Font et al., 1966). As observed, the same may apply to a metastasis of a prostatic carcinoma.

In two other patients, enucluation was decided upon because of uncertainty about the diagnosis:

A ***male aged 67 years*** had been known for 2 years with a bladder carcinoma (transitional cell carcinoma with focally a tendency to squamous cell carcinoma) when in 1976 superiorly in the right eye a large yellowish-orange prominence with irregular pigmentation was detected. No metastases elsewhere in the body were known. At fluorescein angiography and echography, no differentiation between a metastasis and a melanoma was possible. It was decided to await the effect of radiotherapy. However, in its course the prominence increased in height and visual acuity deteriorated further. Enucleation was then considered indicated.

The histopathological diagnosis was a choroidal metastasis of a squamous cell carcinoma.

A ***woman aged 58 years*** was referred in 1981 because of a yellowish-white prominence in the macular area of the left eye with suspicion of a metastasis (Figure 2.3.8.3). The patient was otherwise healthy. At fluorescein angiography, melanoma was diagnosed, partly on the basis of a double vascularization. At echography, a 2.5 mm prominent lesion was observed, corresponding mostly to a Kuhnt Junius, possibly to a metastasis. Because of the expected complete loss of function of the eye, enucleation was decided upon.

In the choroid, a tumour was observed with extrascleral extension via nerves, blood vessels and direct scleral perforation, and a minimal rupture through Bruch's membrane. The tumour showed the characteristic appearance of an adenocarcinoma with mucin-containing tubuli. The optic nerve was tumour-free. The extrascleral tumour tissue had not been removed completely. The conclusion of the histopathological examination was a choroidal metastasis of an adenocarcinoma, arising in all probability from a breast carcinoma or from a carcinoma of the gastrointestinal tract.

Extensive examination failed to reveal a primary tumour. The patient died six months later of cachexia.

It is interesting to note that in all five patients in whom the ophthalmological diagnosis was uncertain, the colour of the tumour was pale, which corresponds to a metastasis rather than to a melanoma.

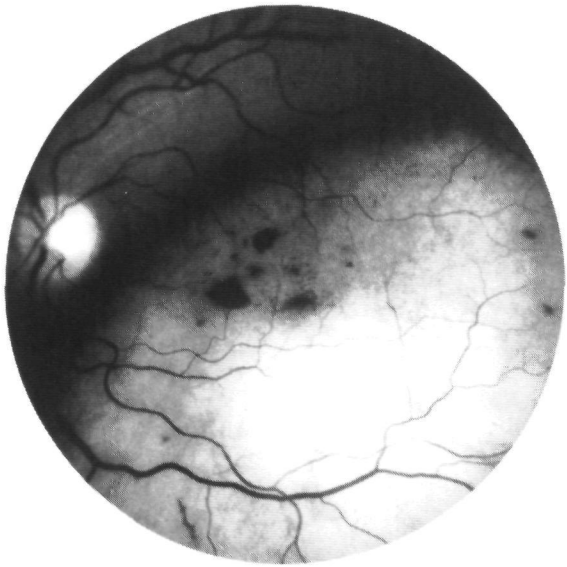


Figure 2.3.8.3 Fundus photograph showing a prominent yellowish-white choroidal tumour in the left eye of a patient with no known malignancy. Histopathological examination: metastasis of adenocarcinoma of unknown localization.

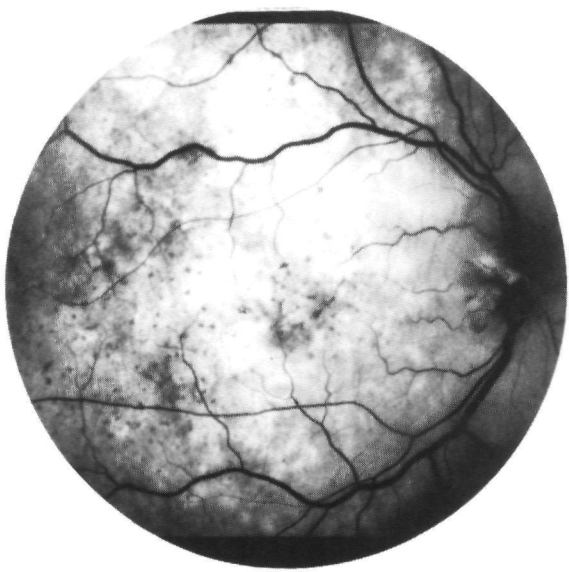


Figure 2.3.8.4 Fundus photograph showing an extensive choroidal tumour with mottled pigmentation in the right eye of a patient with no known malignancy. Histopathological examination: choroidal metastasis of adenocarcinoma of unknown localization.

In two patients, the eye was enucleated because of ophthalmological complications resulting from the intraocular tumour:

In a ***male aged 52 years***, in 1987 a large flat tumour was observed in the posterior pole of the right eye, with a light colour and a mottled appearance corresponding to a metastasis (Figure 2 3.8.4). The echographic image also strongly suggested a metastasis. A thorough examination revealed no primary tumour. Since the visual acuity of the eye decreased from 0.4 to no light perception and the eye became painful it was enucleated six months later.

The conclusion of the histopathological examination read· metastasis of a moderately to well-differentiated mucinous adenocarcinoma with as the most probable primary localization the gastrointestinal tract or the prostate. The stump of the optic nerve proved not to be free of tumour tissue.

Shortly after the operation, pathological lymph nodes and skeletal metastases were established The patient died 17 months later of cachexia without the primary tumour having been determined.

In another patient, a ***male aged 66 years***, in 1982 in the left eye a large grey tumour mass with a retinal detachment was established, with strongest suspicion of a melanoma Fluorescein angiography also pointed in that direction At echography, the diagnosis of metastasis was made (Figure 2 3 8 5 a-b) The chest X-ray showed a shadow. At further examination by means of bronchoscopy this proved to be due to a small cell undifferentiated lung carcinoma Since an intractible secondary glaucoma developed, the eye was enucleated

Histopathologically, on the iris a few dome-shaped implantation metastases were observed. There was a total serous retinal detachment and large areas of the retina showed necrosis In the choroid, a tumour was observed with invasion into the disk and optic nerve and with penetration through the sclera to epibulbar areas. Many mitoses were present as well as a few pre-existent melanocytes The larger part of the tumour was necrotic. The diagnosis was a metastasis of the pulmonary tumour (Figure 2.3 8.5 c).

In only one patient, a ***female aged 39 years*** with bilateral choroidal metastases of breast cancer, were the eyes examined post mortem. This revealed extensive metastasization of the tumour in the uvea with invasion of the sclera.

Thus, histopathological examination of uveal metastases was performed in five patients when enucleation had erroneously been considered indicated under the diagnosis of malignant melanoma of the uvea, or this lesion was assumed in a patient with a non-functional eye. Furthermore, in two patients the eye was enucleated because of ophthalmological complications. At autopsy, even when indications of uveal metastases were present, histopathological examination of the eye was carried out only once.

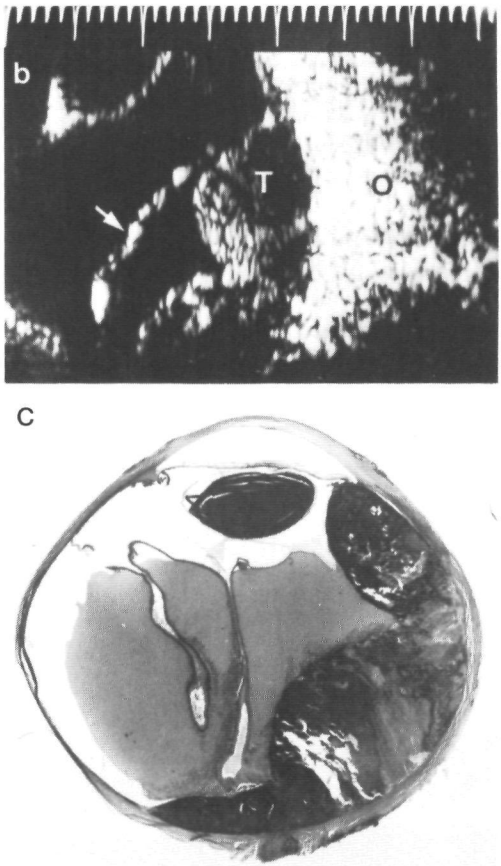


Figure 2.3.8.5 a-b. A- and B-mode echogram of a 9.0 mm prominent lobulated choroidal mass with an extensive base, an irregular low to mid reflectivity (t), vascularity, orbital shadowing and retinal detachment (white arrow in B-scan) and doubtful signs of a choroidal excavation: compatible with a choroidal metastasis (white arrow: retina; white arrow-head: sclera; O: orbital fat; T: tumour). c. Histopathol-ogical examination: metastasis from lung cancer.

2.3.9 Conclusions

Although for the differential diagnosis of intraocular tumours a large number of examination techniques are available and tumour-specific patterns can be established in a number of cases, the diagnosis of these tumours in the individual patient remains a difficult task No pathognomonic picture of uveal metastases exists. The diagnosis is frequently made by exclusion or on the basis of presence of a malignancy elsewhere in the body

The nature of the primary tumour plays an important part in the diagnostics of most uveal metastases Metastases from breast cancer show a different picture than metastases from lung cancer and can be differentiated better from other intraocular tumours In contrast to patients with uveal metastases from breast cancer, in patients with lung cancer the detection of the intraocular tumour precedes the diagnosis of the primary malignancy in one-half of the cases.

Uveal metastases have to be differentiated in particular from melanomas, haemangiomas and naevi of the uvea They also have to be differentiated from a number of less frequently occurring tumours such as leiomyomas, adenomas and osteomas and from conditions that may simulate a malignant tumour such as subretinal haemorrhages, retinal degenerations and choroidal detachments. Retinoblastomas can be differentiated from metastases without problems, owing to the early age of the patients and the clinical features of these tumours

Although there is no pathognomonic picture of uveal metastases, a number of features nevertheless are more or less specific An anamnesis with a known malignancy elsewhere in the body may call the investigator's attention to the possibility of intraocular metastasization In our retrospective patient group, in 76% of the patients with uveal metastases a primary tumour elsewhere in the body was known at the time of the ophthalmological examination. In patients with a malignant melanoma of the uvea a second primary malignancy elsewhere in the body was known in 3% of the patients. In melanoma cases, therefore, simultaneous independent malignancies elsewhere in the body may be present, although rarely, and the presence of such a malignancy does not always indicate a metastasis.

Another important finding is the presence of multiple and bilateral lesions. In melanomas and in other intraocular tumours or lesions suggestive of tumour other than metastases or retinoblastomas, this finding is rare. However, although characteristic of uveal metastases, multiple lesions occur in only 33% of the patients with intraocular metastases

Uveal metastases are limited to the choroid in 95% of the cases. Localization of metastases in the iris or ciliary body is rare.

The signs and symptoms in patients with uveal metastases are little specific and show many similarities to those described in other tumours Patients in general complain of loss of visual acuity. The median visual acuity after optimal correction is 0.5. Slight reaction of the anterior segment occurs sporadically and is mostly observed in patients with lung cancer and metastases in the iris or the ciliary body.

The signs and symptoms in patients with a melanoma are comparable with those of patients with metastases. In haemangiomas, opaque media are reported less frequently and reaction of the anterior segment occurs only sporadically. In naevi there are in general no

complaints and no reaction of the anterior segement of the eye. It should be noted that the naevi in our study group constitute a selection of lesions in which initially presence of an intraocular malignancy was suspected.

Ophthalmoscopy in metastases mostly reveals a yellowish-orange or cream-coloured choroidal tumour with a mottled surface. Metastases from lung cancer often have a grey colour. As mentioned before, multiple or bilateral development of metastases is possible. The tumour is usually localized temporally in the fundus. The shape of the tumour at ophthalmoscopy is often left undescribed. In almost one-half of the cases the tumour is accompanied by a secondary retinal detachment. An intraocular haemorrhage is reported in 15% of the patients. Metastases in the anterior segment in our study group originated in all cases from lung cancer.

Uveal melanomas are more often grey and less often yellowish-orange in colour than metastases. The orange lipofuscin pigment was described in 13% of the patients with a melanoma and only once in uveal metastases. Melanomas are localized in the temporal half of the fundus less frequently than metastases. Haemangiomas in 26% are typically salmon-pink in colour but they may show an ophthalmoscopical image similar to that of uveal metastases. More frequently than metastases and melanomas, haemangiomas are localized in the posterior pole. Intraocular haemorrhages are not observed in haemangiomas, in contrast to metastases and melanomas. Naevi are often substantially smaller than metastases and they are localized only rarely in the macular area. Mostly, naevi show a grey colour. Retinal detachment in naevi was not reported in our study group and intraocular haemorrhages were rare.

No pathognomonic ophthalmoscopic image of uveal metastases exists, although multiple and/or bilateral presence and a mottled yellowish-orange pigmentation is regularly observed in metastases.

Fluorescein angiography shows no characteristic pattern in uveal metastases. The technique is useful, however, to establish the extension of the lesion. In the early phases, hypofluorescence at the site of the metastasis is described. In the venous phase there is staining with a finely or grossly mottled pattern of hyperfluorescence. In most cases a hypofluorescent margin round the tumour is described, as well as hyperfluorescent spots on the tumour surface.

The fluorescein angiographic picture in melanomas cannot be distinguished from that of metastases. However, in melanomas tumour vessels are observed more frequently. In haemangiomas early staining of the tumour is usually observed with less frequent hyperfluorescent spots and more frequent tumour vessels than in metastases. In one-third of the patients distinct fluorescein angiographic patterns are described, in the form of spongy configurations which are characteristic of haemangiomas. Naevi in most cases remain hypofluorescent in all phases of the examination. If hyperfluorescent spots are present, these are only rarely restricted to the margin of the lesion.

Echography is of great importance for the diagnosis of metastases. Echographically, a metastasis as a rule is seen as a flat or dome-shaped mid-reflective tumour with a broad base and an inhomogeneous infrastructure. A noticeable aspect is the low and regular reflectivity that can be observed frequently in metastases of lung cancer and which corresponds more to a uveal melanoma.

Apart from a low regular reflectivity, a choroidal excavation, vascularity and an

orbital shadow are observed more frequently in melanomas than in metastases, and a melanoma is more prominent. Another characteristic feature of melanomas is the mushroom shape which is observed in 22% of the tumours. However, such a shape is also described in two patients with a uveal metastasis in our study. In haemangiomas a high-reflective dome-shaped tumour is observed without choroidal excavation or orbital shadow. Naevi in most cases are hardly or not observed echographically owing to the low prominence of the lesion.

The perimetric findings in patients with metastases, melanomas and haemangiomas are comparable, with mostly an absolute scotoma. The inclination of this scotoma is sloping significantly more often in metastases than in melanomas. In naevi, visual field defects are observed far less often. The value of perimetry for the diagnosis of uveal metastases is limited.

By means of electro-oculography an abnormality of the natural potential of the eye can be established in uveal metastases. This examination does not permit differentiation of metastases from melanomas, however.

With respect to other examination techniques such as CT, MRI, isotopes, etcetera, we have too few data at our disposal to offer a view concerning the contribution they may make to the diagnosis and differential diagnosis of uveal metastases. The value of these techniques appears for the time being to be limited.

It may be concluded that in a patient with an intraocular lesion with suspicion of tumour, in addition to a detailed ophthalmological and general anamnesis, ophthalmoscopy, echography and fluorescein angiography are necessary for the diagnosis. Although metastases do not show a pathognomonic picture, the various examinations supplement one another. Electro-oculography may be performed to provide an indication about the malignant or benign nature of the lesion. Absence of a visual field defect is an argument for the diagnosis of naevus.

Apart from a general physical examination, in patients with an intraocular tumour-like lesion roentgen examination of the thorax and biochemical testing have to be carried out in all cases to exclude a possible primary malignancy or metastases elsewhere in the body. In female patients with suspicion of intraocular metastases, mammography is also indicated. If the diagnosis remains uncertain, the lesions should be followed up accurately to detect any growth or any tumour-specific characteristics developing later.

2.4 Treatment and prognosis

2.4.1 Management and treatment

As mentioned in earlier chapters, uveal metastases in general are accompanied by serious complaints about the visual acuity. This causes major impairment of the quality of life, certainly in patients with bilateral involvement of the eyes. It is therefore of crucial importance to attempt to limit the loss of ocular function as much as possible, to arrest further deterioration and, if possible, to ensure improvement of the visual acuity. Furthermore, complications of uveal metastases such as secondary glaucoma have to be prevented.

In patients with uveal metastases, the duration of survival after detection of intraocular metastases is only brief. Therefore, treatment not only should be effective, it should also be instituted without delay, cause few or no complications and require little after-treatment.

Most patients with uveal metastases in our study group (60%) were subjected to radiotherapy (Table 2.4.1.1). Observation was decided on regularly, systemic therapy and enucleation occasionally and laser treatment once. In four patients the management after the detection of the intraocular lesion was not known.

Table 2.4.1.1 Treatment in 87 patients with uveal metastases

	Patients	
Treatment	N	%
Radiotherapy	52	60
Observation	19	22
Systemic therapy	5	6
Enucleation	6	7
Laser coagulation	1	1
Unknown	4	5

Patients with uveal metastases of breast cancer were found to have undergone radiotherapy more often (viz. 75%) than patients with lung cancer (50%) or patients with miscellaneous malignant tumours (20%). The last-mentioned two groups of patients were more frequently kept under observation, among other things for reasons of initial uncertainty on the diagnosis because at that moment no primary tumour was known. Lack of a known primary tumour was the case in 10 of the 19 patients kept under observation and four of the six patients in whom the eye was enucleated, as against only six of the 52 irradiated patients and none of the patients with systemic therapy. It was also found that in patients kept under observation and patients subjected to enucleation of an eye the prognosis quoad vitam was poorer, resulting in fewer possibilities of therapeutic intervention.

Table 2.4.1.2 Treatment in 87 patients with uveal metastases according to various parameters

	Patients		Age (yrs)		Prominence (mm)			Base (DD)			Distance from fovea (DD) *			Retinal detachment	Best visual acuity before treatment		
Treatment	N	%	Mean	SD	Median	Mean	SD	Median	Mean	SD	Median	Mean	SD	%	Median	Mean	SD
Radiotherapy	52	60	56	12	3.0	3.6	2.3	5.0	6.1	3.7	1.0	1.7	2.4	52	0.55	0.56	0.32
Observation	19	22	64	12	3.0	3.9	4.5	4.5	5.6	4.4	0.5	1.3	1.7	58	0.40	0.38	0.32
Systemic therapy	5	6	51	9	5.0	5.0	2.0	9.0	9.0	4.6	0	0.1	0.3	40	0.60	0.49	0.45
Enucleation	6	7	55	14	4.5	4.9	2.3	13.0	11.3	3.5	0	0.3	0.6	83	0.23	0.28	0.31
Laser coagulation	1	1	46			0.5			3.0			3.0		100		0.80	
Unknown	4	5	63	17	1.0	2.2	1.5	4.0	4.3	1.5	0.5	3.5	6.4	80	0.45	0.45	0.07

*DD: disk diameter; * in choroidal metastases*

Table 2.4.1.2 presents a survey of a number of important parameters for the various methods of treatment.

In patients in whom the eye was enucleated or who were treated with systemic therapy, the prominence measured echo-graphically and the tumour base as established at ophthalmoscopy were larger than in patients who were irradiated or observed while the tumour was also situated closer to the fovea. In patients in whom the eye was enucleated a retinal detachment was present more frequently. The best visual acuity prior to treatment was higher in irradiated patients (median 0.55) and in patients treated with systemic therapy (0.60) than in patients in whom the tumour was observed (0.40) or the eye was enucleated (0.23).

The various forms of treatment or management will be discussed successively, with their effect on the tumour size and the visual acuity, as well as the side effects, if any.

2.4.1.1 Radiotherapy

Radiotherapy is an accepted method of treating uveal metastases (Orenstein et al., 1972; Röttinger et al., 1976; Stephens and Shields, 1979; Mewis and Young, 1982; Lommatzsch, 1989). The literature on radiotherapy of uveal metastases is discussed in Chapter 1.6.1.4. The present chapter reports the results of a personal retrospective study of the effect of irradiation on uveal metastases in our clinic. Special attention is paid to the influence of irradiation on the prominence of the metastases and on the visual acuity.

Patients

During the period from November 1970 to November 1990 uveal metastases were diagnosed in 87 patients. Fifty-two patients (60%) were irradiated. The other 35 patients were managed in different ways as described in Chapter 2.4.2. That chapter also describes how the indication for treatment was established. Irradiation of uveal metastases was carried out in 43 females and nine males, with an average age of 56 years (range 27-79 years). All metastases were localized in the choroid. The primary tumour was usually breast cancer (75%), less often lung cancer (19%) (Table 2.4.1.1.1).

Table 2.4.1.1.1 Primary tumour in 52 patients with irradiated choroidal metastases

	Patients	
Primary tumour	N	%
Breast cancer	39	75
Lung cancer	10	19
Thyroid cancer	1	2
Bladder cancer	1	2
Seminoma	1	2

In 46 of the 52 patients the optimal visual acuity or the acuity with own correction was known. It was 0.56 on average with a median of 0.55 (range 1/300-1.25).

Ten metastases were localized inside the vascular arcade, 10 outside and 28 at the site of the vascular arcade. In four patients the exact localization of the metastasis was not known. The shortest distance between the margin of the tumour and the fovea was known in 44 patients; its mean was 1.7 disk diameter (DD) (median 1.0; range 0-13). A retinal detachment was present in 27 patients (52%).

The echographically measured prominence was known in 41 patients; its mean was 3.2 mm with a median of 3.0 mm (range 0.5-8.0). For the method of determining the prominence, the reader is referred to Chapter 2.3.4.

The follow-up after irradiation of patients with choroidal metastases was 7.1 months on average with a median of 4.2 months (range 0-30). At conclusion of the study 49 patients had died. The mean duration of survival was 13.1 months with a median of 8.5 months (range 1-42).

Irradiation equipment, dose and technique

In patients with bilateral metastases the following irradiation data refer to the eye with the metastasis diagnosed first or, if metastases were detected in both eyes at the same time, to the right eye.

Irradiation equipment: in most cases a linear accelerator was used. Use was also made of a CO-60 equipment or of a combination of linear accelerator and CO-60 (Table 2.4.1.1.2). The photon energies applied when linear accelerators were used ranged from 4 to 18 MV, the most frequently applied energies being 18 MV (eight patients) and 4 MV (seven patients). The electron energy ranged from 9 to 13 MeV (Table 2.4.1.1.2).

Table 2.4.1.1.2 Irradiation equipment in radiotherapy of 52 patients with choroidal metastases

	Patients	
Irradiation equipment	N	%
Linear accelerator (4-18 MV and 9-13 MeV)	26	50
Co-60 (1.25 MV)	19	37
Linear accelerator + Co-60	2	4
Unknown	5	10

Radiation dose and fractionation: the values stated correspond to the minimal dose in the target volume; they were determined by means of the computer planning. The dosage used and the number of fractions of the irradiation are listed in Table 2.4.1.1.3.

Table 2 4 1 1 3 Total and fraction dose in radiotherapy of 52 patients with choroidal metastases

Total dose (Gy)	Fraction dose (Gy)	Number of fractions	Patients N	Patients %
20 0	5 0	4	1	2
26 5	3 0/2 5 *	10	1	2
30 0	2 0	15	4	8
30 0	2 5	12	2	4
30 0	3 0	10	19	37
36 0	2 0	18	1	2
36 0	3 0	12	1	2
38 0	2 0	19	1	2
40 0	2 0	20	16	31
40 0	3 0/2 0/1 0 **	15	1	2
45 0	3 0	15	1	2
50 0	2 5	20	1	2
50 0	2 0	25	1	2
Unknown	unknown	unknown	2	4

** three times 3 0 Gy and seven times 2 5 Gy, ** three times 2 0 Gy, 11 times 3 0 Gy and once 1 0 Gy*

Two schedules were used most frequently: a total dose of 30 Gy in 10 fractions of 3.0 Gy (37%) and 40 Gy in 20 fractions of 2 0 Gy (31%). No other doses and fractionations were commonly used.

Virtually always 5 fractions were administered per week so that with a 30 0 Gy scheme in 10 fractions this dose was administered in 2 to 2.5 weeks with 40.0 Gy in 20 fractions in 4 to 5 weeks. In one patient, however, a total dose of 30.0 Gy was administered divided into 10 fractions over a period of 4 weeks.

Irradiation technique: as a rule, a lateral beam was used, with or without shielding of the lens Less frequently, a ventral beam was used, or a combination of these two The field size was usually 4x4 to 5x5 sq cm (Table 2.4 1.1.4).

In 10 of the 52 irradiated patients the metastasis was localized within the arcade of the major retinal vessels. In seven of these patients a lateral beam was used, in two a ventral beam and in one, a combination of the two The same distribution of beam positions was used in 10 patients with a metastasis situated outside the vascular arcade. In the 28 patients in whom the metastasis was localized at the site of the vascular arcade, a lateral beam was applied to 14 and a ventral beam to 12 metastases. In one patient, a lateral and a ventral beam were combined, in one patient the beam position was unknown.

In four patients the exact fundus localization of the metastasis was not mentioned.

Table 2.4.1.1.4 Beam positions in radiotherapy of 52 patients with choroidal metastases

Beam position	Patients N	%
Lateral beam	29	56
Ventral beam	17	33
Combined lateral and ventral beam	3	6
Unknown	3	6

Results

For the determination of the effect of irradiation four moments were selected at which the reaction of the prominence was determined as a measure of tumour size and the visual acuity as a measure of function of the eye. These moments were 1, 3, 6 and 12 months after the start of the radiotherapy. Not for all moments were data on all patients known.

For statistical reasons the tables concerning the effect of radiotherapy also include the patients with unknown results and not just patients with a known results because this would constitute a patient selection.

Effect of irradiation on prominence: Table 2.4.1.1.5 presents a review of the effects of irradiation on the prominence of the tumour. The data are always compared with the findings at the ophthalmological check-up at the most recent preceding moment. In this manner, regrowth after an initial decrease of the prominence could be established.

Table 2.4.1.1.5 Effect of irradiation on prominence in 52 patients with choroidal metastases

Interval after radiotherapy	Prominence: Decrease N	%	Stabilization N	%	Increase N	%	Unknown N	%
1 month	13	25	13	25	4	8	22	42
3 months	23	44	4	8	1	2	24	46
6 months	8	15	9	17	2	4	33	63
12 months	6	12	7	13	0	-	39	75

Of 13 patients (25%) no data on the prominence of the metastasis were known after radiotherapy. In 39 patients follow-up data were available concerning at least one moment after irradiation; data concerning all four moments were available of only eight patients. A table was compiled concerning the effect of the irradiation on tumour size without stating the time after irradiation at which these data were known. Decrease of prominence was

defined as decrease of tumour size at least once after irradiation without subsequent growth. Stabilization of the prominence was defined as a tumour of the same size after as before irradiation without a decrease or increase of prominence being established at any time Growth was involved if the tumour after irradiation was described at least once as having increased in size.

Table 2.4.1.1.6 Effect of irradiation on prominence in 52 patients with choroidal metastases

	Patients	
Prominence	N	%
Decrease	28	54
Stabilization	5	10
Increase	* 6	12
	13	25
Unknown		

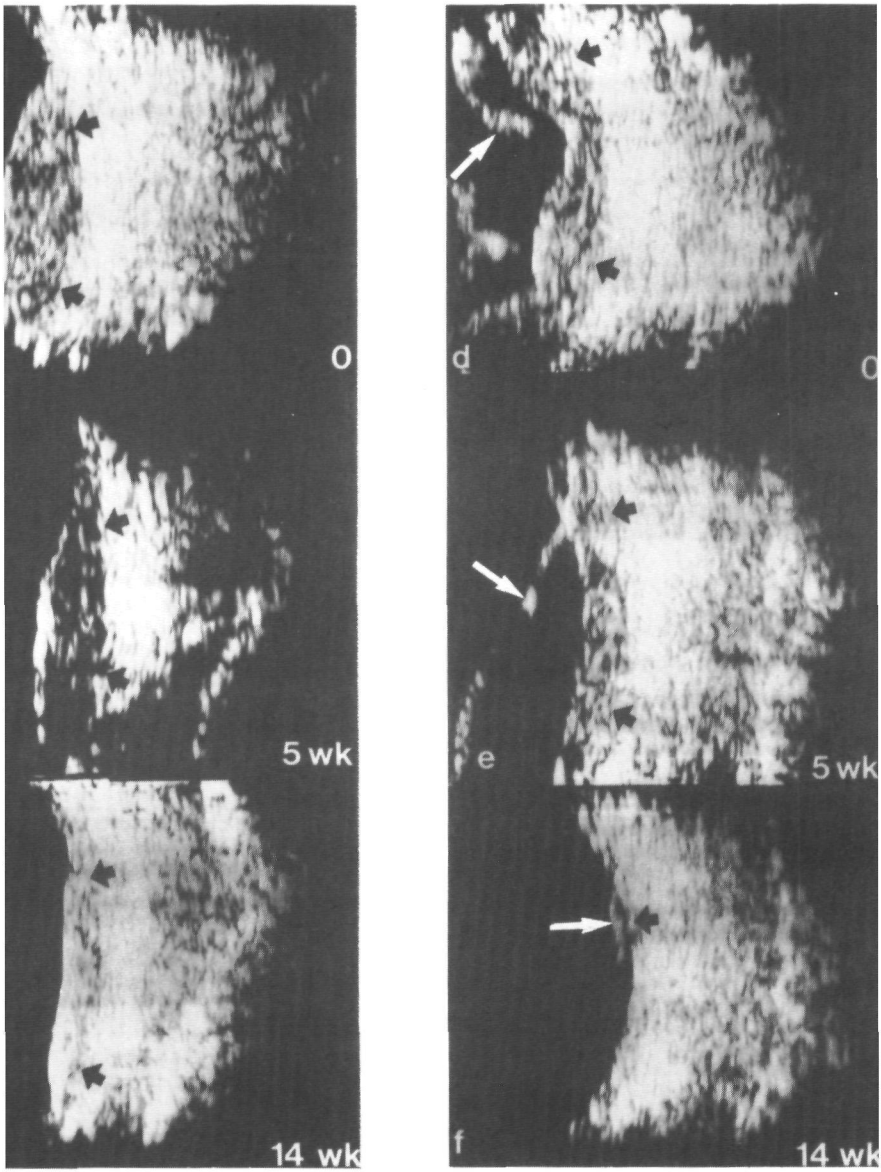
** in two patients increase of prominence one month after start of radiotherapy with subsequent decrease of prominence, in two patients increase of prominence one month after start of radiotherapy, no subsequent data known*

Table 2.4.1.1.6 gives a survey of the effect of radiotherapy on the prominence of the choroidal metastases (Figure 2.4.1.1.1). In 28 patients (54%) a decrease of the prominence was established, while in five patients (10%) the tumour did not increase in size. In six patients (12%) tumour growth occurred in spite of irradiation. In two patients this was established one month after the start of the radiotherapy, following which, however, the tumour decreased in size. In two other patients, as well, growth was established during the first month after irradiation. No further follow-up data on these patients were known. In the last two patients growth of the metastasis occurred over a period of 8 months (Figure 2.4.1.1.2).

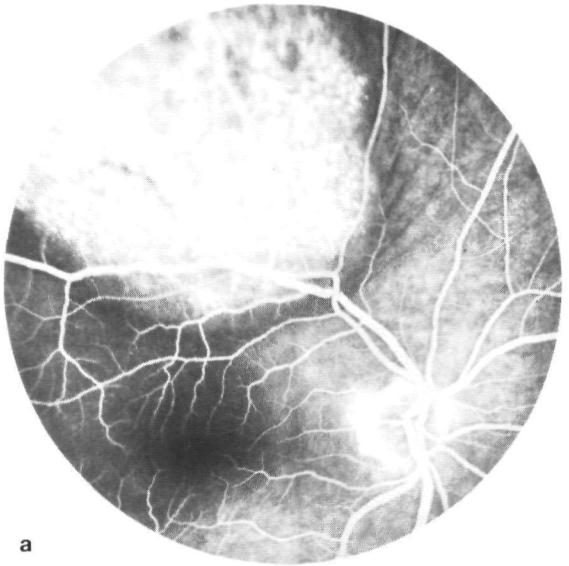
Effect of irradiation on visual acuity: more important than the effect of radiotherapy on the prominence is the effect on the function of the eye, and more in particular on the visual acuity.

In Table 2.4.1.1.7 the mean visual acuity at the various moments is compared with the most recently known visual acuity before irradiation.

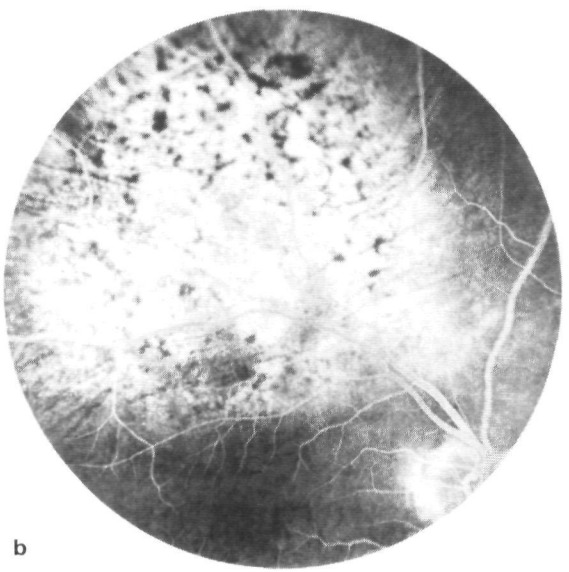
Compared with the most recently known visual acuity before the start of the irradiation, the mean visual acuity had decreased 1, 3 and 12 months after irradiation and had remained stable 6 months after irradiation. These differences are not significant, however ($p > 0.10$).



'.1.1.1 A- and B-mode echogram of the right (a) and left eye (d) with choroidal metastases (blac om breast cancer; prominence of the lesion in the right eye before irradiation 4.5 mm, in the le ım (note: extensive retinal detachment: white arrows). Five weeks after start of radiotherap f the prominence to 4.0 mm in the right eye (b) and to 3.0 mm in the left eye (e). Fourteen wee of radiotherapy further decrease of the prominence to 2.0 mm in the right eye (c), no lesic in the left eye (f): only a limited retinal detachment remained (white arrow).



a



b

Figure 2.4.1.1.2 a. Fluorescein angiogram in venous phase of a choroidal metastasis in the right eye in a patient with breast cancer before radiotherapy. b. Fluorescein angiogram of the same lesion nine months later: atrophy of retinal pigment epithelium as a result of the irradiation.

Table 2.4.1.1.7 Effect of irradiation on visual acuity in patients with choroidal metastases

		Visual acuity			
		Before irradiation		After irradiation	
Interval after irradiation	* N	Mean	SD	Mean	SD
1 month	27	0.49	0.32	0.39	0.34
3 months	29	0.51	0.34	0.43	0.35
6 months	21	0.52	0.34	0.54	0.35
12 months	14	0.45	0.29	0.40	0.34

** number of patients in whom the visual acuity both before and after radiotherapy was known*

Improvement of visual acuity may be defined as an increase of the acuity by at least two lines on Snellen's chart, a decrease of the visual acuity as a reduction of the acuity by minimally two lines, and stabilization as results in between (Table 2.4.1.1.8).

Table 2.4.1.1.8 Effect of irradiation on visual acuity related to the visual acuity before radiotherapy in 52 patients with choroidal metastases

	Visual acuity							
Interval after	Increase		Stabilization		Decrease		Unknown	
radiotherapy	N	%	N	%	N	%	N	%
1 month	4	8	13	25	10	19	25	48
3 months	6	12	13	25	10	19	23	44
6 months	5	10	12	23	4	8	31	60
12 months	1	2	9	17	4	8	38	73

In four patients, after irradiation the ophthalmologist in charge described an improvement in visual acuity, which was not further specified. In another such patient the visual acuity was stabilized. In a patient with deterioration of the visual acuity after one month, this acuity was found to have been measured at that moment in mydriasis, so that it was not valid. In another patient with a decrease of the visual acuity in the first month, there later occurred an increase of the acuity which was not further specified. When the effect of radiotherapy on the visual acuity in these seven patients is included in the results, and the acuity is evaluated independently of the time elapsed after irradiation, the following result is obtained (Table 2.4.1.1.9).

Stabilization or improvement of the visual acuity in relation to the visual acuity before irradiation therefore was obtained in 62% of the patients treated with radiotherapy. In 19% the eyesight deteriorated in spite of treatment (Colour plates 11 and 12). In another 19% the effect of treatment was unknown.

Table 2.4.1.1.9 Effect of irradiation on visual acuity in 52 patients with choroidal metastases

	Patients	
Effect on visual acuity	N	%
Increase	13	25
Stabilization	19	37
Decrease	10	19
Unknown	10	19

Overall effect of irradiation: although a decrease of the prominence without improvement of the visual acuity would appear not to contribute directly to an improvement of the quality of life, the risk of ocular complications is reduced in such cases, however.

The overall effect of radiotherapy is composed of the effect on the prominence and that on the visual acuity. A favourable result was defined as an increase of visual acuity by at least two lines on Snellen's chart or a decrease of the prominence; a stabilization as a change of the visual acuity of less than two lines on Snellen's chart and a stabilization of the prominence (or one of the two if the other criterion was unknown); a result was classified as unfavourable if visual acuity decreased by at least two lines on Snellen's chart and the prominence was stabilized, increased or unknown or if the prominence increased while visual acuity was stabilized or unknown. In this manner, the following result was obtained (Table 2.4.1.1.10):

Table 2.4.1.1.10 Overall effect of irradiation in 52 patients with choroidal metastases

	Patients	
Overall effect	N	%
Improvement	34	65
Stabilization	6	12
Deterioration	6	12
Unknown	6	12

In 65% of the patients a positive result of radiotherapy was established with improvement of visual acuity or decrease of prominence, while in 12% the condition was stabilized (Colour plates 13 and 14; Figure 2.4.1.1.3). Twelve per cent of the patients showed no positive response to irradiation. In 12%, the effect was unknown.

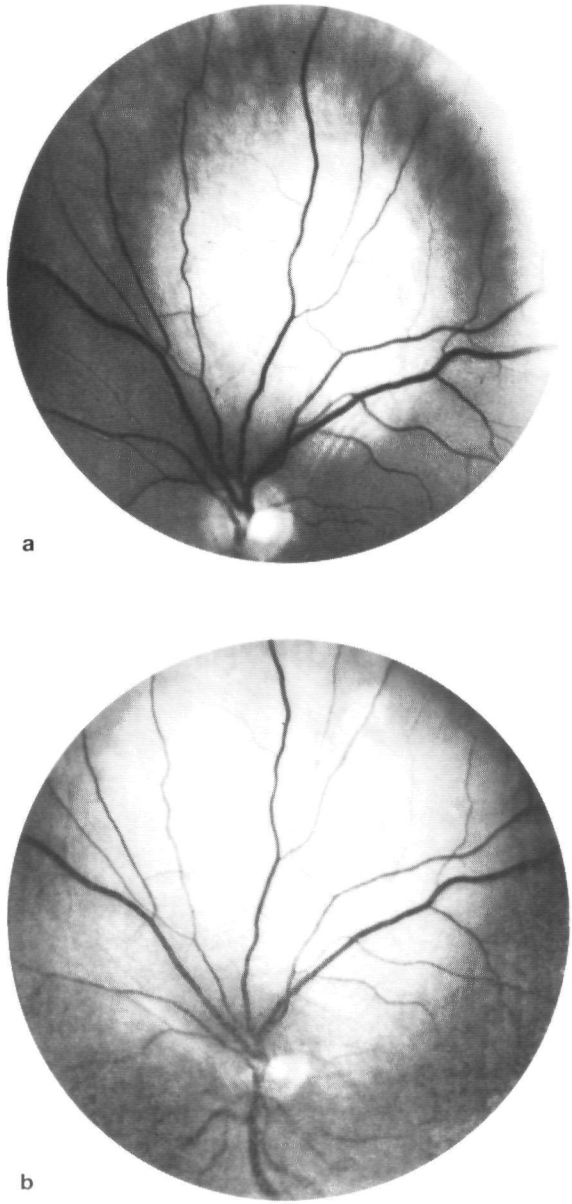
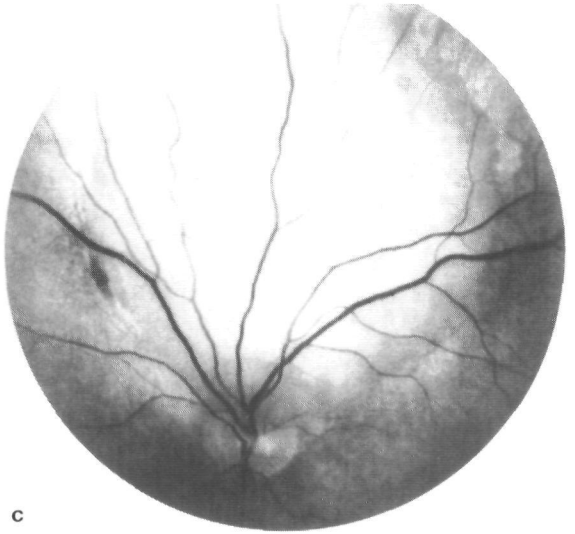
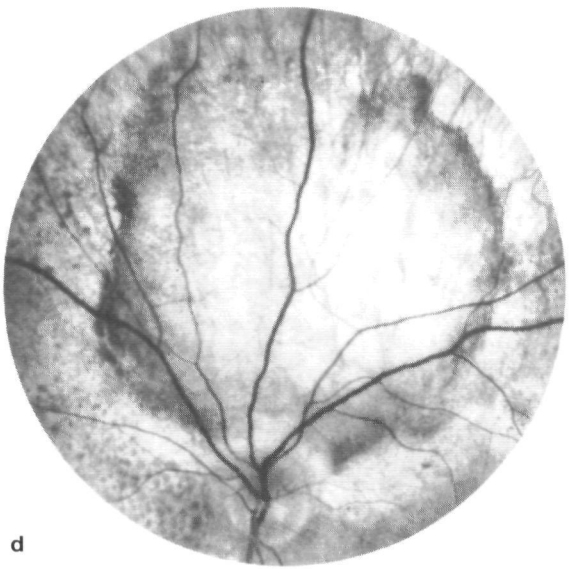


Figure 2.4.1.1.3 a. Fundus photograph showing a choroidal metastasis from breast cancer in the left eye two weeks before radiotherapy. b. Fundus photograph of the same tumour at start of radiotherapy with evident growth of the lesion extending over the optic disk.

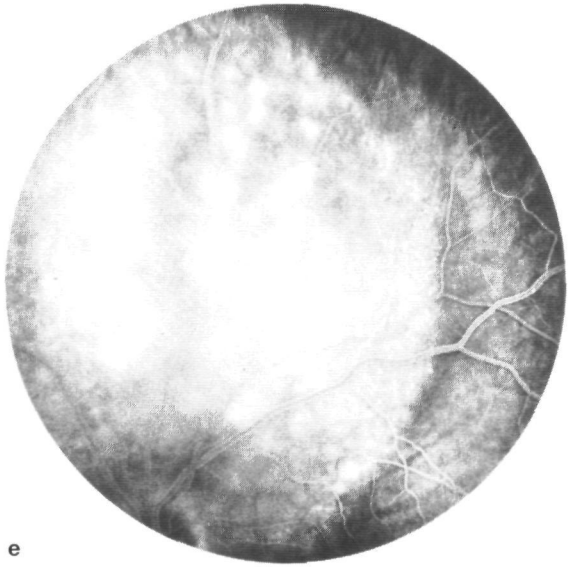


c

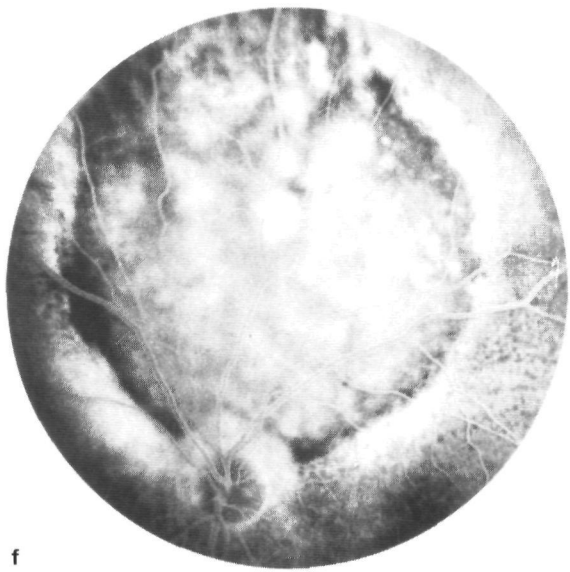


d

Figure 2.4.1.1.3 (continued) c. Fundus photograph of the same metastasis four months after start of radiotherapy. The prominence of the lesion has decreased with pigment changes on the tumour surface and at the tumour margin. d. Eleven months after start of radiotherapy only a flat pigmented choroidal scar at the site of the lesion remains.



e



f

Figure 2.4.1.1.3 (continued) e. Fluorescein angiogram in the late venous phase showing the same lesion at the start of radiotherapy (same date as fundus photograph b).
f. Angiogram in the late venous phase four months after start of irradiation with marked reaction and atrophy of the lesion (same date as fundus photograph c).

Factors influencing the effect of irradiation: a number of factors may influence the radiotherapeutic effect on visual acuity. These are:

1. the interval between the moment of diagnosis and the start of the irradiation;
2. the visual acuity before treatment;
3. the distance of the metastasis from the fovea;
4. the presence of a retinal detachment;
5. the nature of the primary tumour;
6. the effect of the irradiation on the prominence of the metastasis;
7. the radiation dose.

1. Interval between the moment of diagnosis of the choroidal metastasis and start of the radiotherapy: in 15 patients radiotherapy was administered no longer than two weeks after the moment of diagnosis of the choroidal metastasis, in 19 patients between two weeks and one month and in 18 patients more than one month after the ophthalmological diagnosis. Stabilization or improvement of the visual acuity after irradiation, compared with the acuity at the time of diagnosis occurred in these three groups in 64, 69 and 60%, respectively, of the patients of whom the visual acuity both before and after treatment was known. This difference is not statistically significant.

2. With regard to the most recently known visual acuity before irradiation, a distinction was made between a visual acuity ≤ 0.30 (social blindness), between 0.30 and 0.80 and ≥ 0.80 (normal). Table 2.4.1.1.11 shows the effect of irradiation on the visual acuity subdivided according to the last known visual acuity.

Table 2.4.1.1.11 *Effect of irradiation on visual acuity according to the last known visual acuity before radiotherapy in 47 patients * with choroidal metastases in terms of percentage*

Visual acuity		Visual acuity			
before irradiation	N	Increase	Stabilization	Decrease	Unknown
≤ 0.30	15	47	40	7	7
0.30-0.80	18	22	39	28	11
≥ 0.80	14	14	43	29	14

** visual acuity before radiotherapy in five of 52 irradiated patients unknown*

Of the patients with an initial visual acuity of maximally 0.30, 87% showed preservation or improvement of visual acuity as against 61% of patients with a visual acuity between 0.30 and 0.80, and 57% of the patients whose visual acuity prior to treatment had been at least 0.80.

3. A factor possibly influencing the effect of treatment might be the distance from the margin of the metastasis to the fovea. A tumour localized in the macular area may have caused irreversible damage to the sensory cells so that treatment has little or no

effect. In our study group, the average distance between tumour and fovea amounted to 1.8 disk diameters (DD) in patients with a favourable effect of the irradiation on the visual acuity and to 2.0 DD in those whose eyesight deteriorated. In those with stabilized visual acuity the mean distance was 0.7 DD.

4. The presence of a retinal detachment before treatment may affect the result of the irradiation. Table 2.4.1.1.12 presents a survey in which a limited retinal detachment is defined as a detachment occupying less than one-quarter of the fundus and an extensive detachment as a retinal detachment over more than one-quarter of the surface of the fundus.

Table 2.4.1.1.12 Effect of irradiation on visual acuity in relation to the presence and extent of a retinal detachment in 52 patients with choroidal metastases

	Visual acuity			
Retinal detachment	Increase	Stabilization	Decrease	Unknown
None	4	12	4	2
Occupying <25% of the fundus	6	4	4	3
Occupying ≥25% of the fundus	3	3	2	3
Unknown	-	-	-	2

In 16 of the 20 patients with a choroidal metastasis without retinal detachment in whom the effect of the irradiation on the visual acuity was known, stabilization or improvement of the eyesight was established, just as in 10 of the 14 patients with a limited and in six of the eight patients with an extensive retinal detachment. These differences are not significant ($p > 0.10$).

5. The nature of the primary tumour and the effect of irradiation on the visual acuity are listed in Table 2.4.1.1.13.

Table 2.4.1.1.13 Effect of irradiation on visual acuity according to the primary tumour in 52 patients with choroidal metastases in terms of percentage

		Visual acuity			
Primary tumour	N	Increase	Stabilization	Decrease	Unknown
Breast cancer	39	23	38	21	18
Lung cancer	10	40	20	10	30
Miscellaneous *	3	-	67	33	-

* *once seminoma (with elements of teratoma); once thyroid cancer; once bladder cancer*

Improvement or stabilization of the visual acuity was achieved in 61% of the patients with breast cancer, in 60% of the patients with lung cancer and in 67% of the patients with a different primary tumour.

6. The effect of the irradiation on the prominence of the metastasis was compared with the effect on the visual acuity. In four of the six patients with an increase of the size of the tumour in spite of irradiation a deterioration of the visual acuity was observed, in one patient the visual acuity remained stable and once it improved in spite of growth of the metastasis.

In seven of the 13 patients in whom the visual acuity improved by at least two lines on Snellen's chart, a decrease of the tumour size was established during the follow-up period. In one patient, in whom the prominence initially decreased but then increased again, improvement of the visual acuity was nevertheless observed. In five patients, the effect of the irradiation on the prominence was not known.

7. In this retrospective study, in 34 of the 52 patients two irradiation schedules were applied. These were a dose of 30.0 Gy in 10 fractions of 3.0 Gy, in 2 to 2.5 weeks (18 patients) and 40.0 Gy in 20 fractions of 2.0 Gy in 4 to 5 weeks (16 patients). One patient was given a dose of 30.0 Gy in 10 fractions in a period of four weeks. This patient, therefore, was not included in the '30.0 Gy group'. In Table 2.4.1.1.14 the patients of these two groups are compared.

Table 2.4.1.1.14 Comparison of 30.0 Gy scheme and 40.0 Gy scheme on various parameters in patients with choroidal metastases

	30.0 Gy scheme (N=18)	40.0 Gy scheme (N=16)
Age: mean (SD): yrs	60 (11)	56 (15)
Primary tumour:		
Breast cancer	13 (72%)	11 (69%)
Lung cancer	5 (28 %)	2 (13%)
Other	-	3 (19%)
Prominence: mean/median (SD): mm	3.3/3.0 (1.7)	3.5/3.0 (2.7)
Base: mean/median (SD): DD	6.0/4.0 (4.0)	6.8/5.8 (3.5)
Distance from fovea: mean/median (SD): DD	1.8/1.0 (1.8)	1.8/1.0 (3.4)
Retinal detachment	11 (61%)	10 (63%)
Visual acuity before irradiation: mean/median (SD)	0.65/0.60 (0.27)	0.40/0.40 (0.29)
Follow-up after irradiation: mean/median (SD): months	5.1/3.0 (5.6)	10.7/6.0 (11.3)

DD: disk diameter

The various basic data of these two treated groups were comparable except for the visual acuity and the duration of the follow-up. The visual acuity in the group of patients irradiated with 30.0 Gy was significantly higher ($p<0.02$) (average 0.65; SD 0.28) than in the group irradiated with 40.0 Gy (average 0.40; SD 0.29). The follow-up after irradiation was shorter in patients of the 30.0 Gy group (mean 5.1 months) than in the 40.0 Gy group (mean 10.7 months) ($p<0.10$).

As regards the prominence, a decrease of the tumour size during the follow-up occurred in eight of the 18 patients irradiated with 30.0 Gy while in two patients the size remained stable. Of the 16 patients in the 40.0 Gy schedule, 12 showed a decrease and one, stabilization (Table 2.4.1.1.15).

Table 2.4.1.1.15 Effect of irradiation on prominence in patients with choroidal metastases according to irradiation scheme

	30.0 Gy scheme (N=12) *		40.0 Gy scheme (N=15) **	
Prominence	N	%	N	%
Decrease	8	67	12	80
Stabilization	2	17	1	7
Increase	2	17	2	13

** in six of 18 patients irradiated with 30.0 Gy scheme effect on prominence unknown; ** in one of 16 patients irradiated with 40.0 Gy scheme effect on prominence unknown*

Tables 2.4.1.1.16 and 2.4.1.1.17 present a review concerning the effect of these two irradiation schemes on the visual acuity.

Table 2.4.1.1.16 Effect of irradiation on visual acuity in patients with choroidal metastases according to irradiation scheme after different intervals

Interval after irradiation	* N	Visual acuity before irradiation	Visual acuity after irradiation
30.0 Gy scheme (N=18)			
1 month	7	0.62	0.41
3 months	8	0.67	0.43
6 months	7	0.65	0.61
12 months	3	0.47	0.35
40.0 Gy scheme (N=16)			
1 month	14	0.40	0.36
3 months	12	0.42	0.44
6 months	8	0.48	0.59
12 months	7	0.39	0.46

** number of patients with known visual acuity both before and after irradiation*

Table 2.4.1.1.17 Effect of irradiation on visual acuity in patients with choroidal metastases according to irradiation scheme irrespective of interval

	30.0 Gy scheme (N=14) *		40.0 Gy scheme (N=15) **	
Visual acuity	N	%	N	%
Increase	6	43	3	20
Stabilization	3	21	9	60
Decrease	5	36	3	20

** in four of 18 patients irradiated with 30.0 Gy scheme effect on visual acuity unknown; ** in one of 16 patients irradiated with 40.0 Gy scheme effect on visual acuity unknown*

Table 2.4.1.1.18 compares the overall effect of the two irradiation schemes on both visual acuity and prominence.

Table 2.4.1.1.18 Overall effect of irradiation in patients with choroidal metastases according to irradiation scheme

	30.0 Gy scheme (N=15) *		40.0 Gy scheme (N=16)	
Overall effect	N	%	N	%
Improvement	11	73	13	81
Stabilization	1	7	1	6
Deterioration	3	20	2	13

** in three of 18 patients irradiated with 30.0 Gy scheme overall effect unknown*

The difference in overall effect between the 30.0 Gy scheme and the 40.0 Gy scheme is not statistically significant ($p > 0.10$).

Side effects of radiotherapy

The acute and late side effects of radiotherapy were minor. In 38 patients (73%) no side effects occurred. In nine patients (17%) conjunctivitis responding well to treatment was described. Once, an acute glaucoma developed due to massive tumour necrosis four weeks after the start of the radiotherapy (Figure 2.4.1.1.4). Of four patients no data on side effects were known.

During the follow-up of the irradiated patients with choroidal metastases, no cataract was reported.

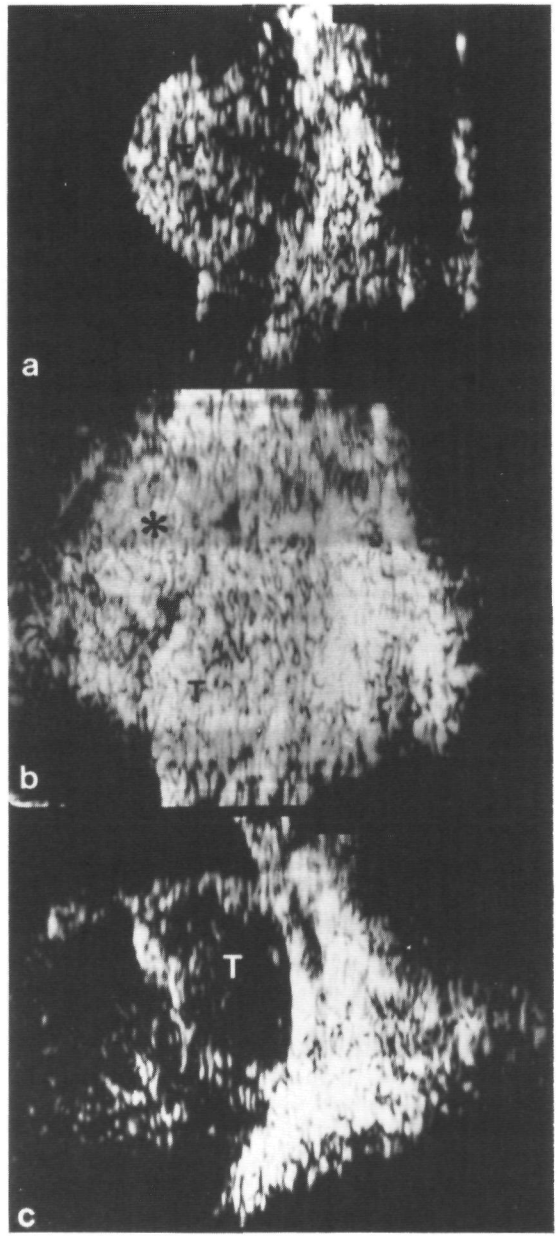


Figure 2.4.1.1.4 a. B-mode echogram of 9.0 mm prominent dome-shaped choroidal metastasis from thyroid cancer 1 week before radiotherapy. b. B-mode echogram of the same lesion during radiotherapy now showing a dense vitreous haemorrhage. c. B-mode echogram 5 weeks after start of irradiation showing clearing of the blood in the vitreous and vacuoles in the tumour suggestive of necrosis.

Discussion

A disadvantage of retrospective studies is that at evaluation some of the data of the patients examined are found not to have been recorded. One can process only a part of the total material, which automatically implies a selection from the study group, or accept that a number of data are lacking. For the descriptions in this disseration the latter option was accepted.

The purpose of irradiation of choroidal metastases is to preserve or improve the patient's eyesight and to prevent complications. In this way an important contribution may be made to the quality of the remaining period of life.

In this study group, radiation was administered by means of a linear accelerator or Co-60 equipment. Various doses and fractionations were applied. The most frequently chosen schemes were total doses of 30.0 Gy in 10 or of 40.0 Gy in 20 fractions. Beams both from lateral and from ventral were used. For metastases at the site of the vascular arcade a lateral and a ventral beam were used with the same frequency while for metastases situated within or outside the arcade of the major vessels, a lateral beam was used more often.

Owing to the brief follow-up and the short duration of survival of patients with irradiated choroidal metastases, it was not always possible to describe the long-term effect of irradiation. Moreover there was no fixed protocol concerning the moments of ophthalmological follow-up. This was also why in 44 of the 52 patients it was not possible to determine the effect of the irradiation on the visual acuity and prominence at all fixed moments, so that it was necessary to assess the effect regardless of the length of time elapsed after irradiation.

Furthermore it is to be assumed that during the interval between the time of the diagnosis of the choroidal metastasis and the start of the irradiation some proliferation of the tumour will have occurred. This proliferation, or the development of a retinal detachment will have caused further deterioration of the eyesight that may have escaped notice. Consequently, the initial values at the start of the treatment of both visual acuity and prominence probably have been more unfavourable than indicated by the above-named results.

Literature data refer to a decrease of the prominence in 57 to 80% of the patients in whom the effect of irradiation was known (see Table 1.6.1.4.5). The results of this study are similar. a decrease of the prominence was described in 54% of all patients. However, the effect of the irradiation on the prominence was unknown in 25%. Consequently, a decrease of the tumour size was established in 72% of those patients in whom the effect of radiotherapy was known. Further tumour growth in spite of irradiation was observed in 12% of the patients.

Stabilization or improvement of the visual acuity after irradiation was described in the literature in 52 to 100% of the patients. In our study group, such a result was observed in 62% of all patients and in 76% of the patients in whom the effect of irradiation on the eyesight was known. This, therefore, is also in agreement with the literature data and points to a good functional result of irradiation of choroidal metastases.

A number of possible influences on the effect of the irradiation with regard to the visual acuity were investigated in greater detail.

The first of these was the interval between the moment of the diagnosis and the start of the treatment. Among intervals of two weeks at most, two weeks to one month and one month at least, no significant difference in effect on the visual acuity was observed. This interval, therefore, does not influence the effect of irradiation.

The initial visual acuity is important because in patients with poor eyesight before treatment an improvement of the visual acuity was established more often than in patients with a high initial value. Obviously, no improvement of the eyesight is possible in patients who already have an optimal visual acuity before treatment. Consequently, for assessment of a favourable effect of radiotherapy both preservation and improvement of the visual acuity should be taken into account.

Tumours situated close to the fovea may cause irreversible damage to the macula so that radiotherapy will not lead to improvement but at best to stabilization of the eyesight. No distinct correlation could be demonstrated in our study, however.

With regard to stabilization or improvement of the eyesight no significant influence was observed of the presence or extension of a secondary retinal detachment ($p > 0.10$).

No clear relationship existed between the nature of the primary tumour and the effect of irradiation.

The effect of irradiation on the visual acuity was distinctly correlated, however, with the effect on the prominence. During further growth of the metastasis, deterioration of the eyesight was observed in four of the six patients. In seven of the 13 patients with an improvement of the eyesight, a decrease of the prominence was observed, in one patient there was growth while in five patients this was unknown.

Finally, the effect of irradiation with a 30.0 Gy scheme was compared with the effect of an irradiation scheme of 40.0 Gy.

With the 30.0 Gy scheme, regarding fixed moments after irradiation, there was a tendency to further deterioration of the mean visual acuity in spite of radiotherapy, while patients irradiated with the 40.0 Gy scheme tended more to stabilization or improvement of the mean acuity. However, it should be noted that of a relatively large number of patients on the 30.0 Gy scheme the visual acuities both before and after radiotherapy were not known at all fixed moments.

On the other hand, with the 30.0 Gy scheme, regarding the effect of irradiation irrespective of the moment of check-up, improvement of the eyesight was established in 43% of the patients as against 20% with the 40.0 Gy scheme, while stabilization was observed in 21% and 60%, respectively. It appeared, therefore, that improvement of the eyesight occurred more often with the 30.0 Gy scheme and stabilization with the 40.0 Gy scheme.

The initial visual acuity with the 40.0 Gy scheme was lower than with the 30.0 Gy scheme, viz. 0.40 and 0.65 on average which, as described before, has consequences for the effect of irradiation. Furthermore, the follow-up after irradiation in patients with a 40.0 Gy scheme was twice as long (median 6.0 months) as in patients irradiated with 30.0 Gy (median 3.0 months). Consequently, in patients irradiated with 40.0 Gy data could be collected over a longer period.

As the overall effect shows, the difference between the 30.0 Gy and the 40.0 Gy schemes regarding improvement or stabilization of the condition compared with deterioration of the disorder was not statistically significant ($p > 0.10$). However, the 30.0

Gy scheme causes less inconvenience to the patients because of the far shorter duration of the treatment.

Side effects were slight in our study group. The most frequent side effect was conjunctivitis which could be adequately controlled. In only one case did an acute glaucoma develop due to massive tumour necrosis.

Conclusions

The objective of therapy is an improvement of the quality of life. Irradiation of choroidal metastases in this retrospective study led to a decrease or stabilization of the prominence of the metastases (64%) and/or stabilization or improvement of the visual acuity (62%). The effect of radiotherapy on the eyesight was related to the effect on the prominence and to the visual acuity prior to irradiation. No influence was established of the interval between the moment of diagnosis and the start of the irradiation, of the distance of the metastasis from the fovea, of the presence or absence of a retinal detachment, of the nature of the primary tumour or of the two irradiation schemes. Side effects were few.

Consequently, radiotherapy makes an important contribution to the quality of life.

Ophthalmological follow-up of irradiated patients with choroidal metastases, with adequate determination of the visual acuity at fixed moments is necessary if the effect of radiotherapy on the visual acuity is to be described accurately. However, the palliative character of the treatment should be kept in mind. Unnecessarily frequent and extensive control examinations should be avoided.

It may be concluded that in the treatment of choroidal metastases an irradiation scheme of 30.0 Gy in 10 daily fractions gives an adequate result with few side effects. To protect the lens it is recommended in unilateral lesions to irradiate via a lateral beam directed 5° occipitally or via a half-beam technique. If metastases are present in both eyes, parallel opposed beams are advised. In metastases at the site of the equator, preference may be given to irradiation from ventral by means of photon or electron beams with shielding of the lens and of the lacrimal gland.

2.4.1.2 Observation

In the literature observation of uveal metastases in patients who are in a terminal phase of the malignant disease is an accepted course of action (Ferry, 1978). Also, an expectative attitude may be assumed in small lesions (Brady et al., 1982) and in patients in whom the fovea is not threatened by the tumour or a secondary retinal detachment (Stephens and Shields, 1979).

In our study group an expectative policy was pursued in a total of 19 patients with uveal metastases (22%). Eight of these patients had a metastasis from breast cancer, four patients one from lung cancer and seven patients, one from another primary tumour.

In 12 of the 19 patients radiotherapy was advised. However, in 10 patients the clinical condition at referral was found to be too poor, for which reason treatment was refrained from. In one patient, irradiation was postponed because of iridocyclitis that could not be controlled. The twelfth patient refused irradiation. Follow-up of these patients was limited to two months at most: in two patients deterioration of the eyesight was established, in one the eyesight improved (after cataract extraction with implantation of an artifical lens) and in one patient the visual acuity remained stable. On the other eight patients no follow-up data were available. In these patients, therefore, only little was known about the period after the ophthalmological diagnosis. Consequently, no statement can be made on the basis of these patients about the natural course of an untreated uveal metastasis.

In seven patients observation was decided upon for various other reasons.

One patient had already been irradiated all over the neurocranium because of cerebral metastases. The irradiation field included the posterior parts of both orbits. It was decided to administer no local radiotherapy to the uvea. The visual acuity improved in one month from 0.6 to 1.25. Six months later visual acuity was still 1.0.

Another patient, with a uveal metastasis of a squamous cell carcinoma of the lung was not irradiated because such a metastasis was believed to be insensitive to radiotherapy. Further follow-up data were lacking.

In two patients at the first ophthalmological examination the metastasis appeared already to be partially in regression and an expectative policy was pursued. One of these two patients was followed up for 7 months longer during which the visual acuity remained stable at 0.8.

In three patients the reason for observation was an initial uncertainty regarding the nature of the intraocular tumour. In one patient the visual acuity remained stable at 1/60 for 7 months, in a second it decreased in 5 months from 0.25 to 2/60. In the third patient, only one check of the visual acuity was known at which time it was light perception only.

2.4.1.3 Systemic therapy

Five patients at the time of diagnosis of the intraocular tumour had not yet undergone systemic treatment for the primary malignancy, three times because at the time of the diagnosis of the uveal metastasis no primary tumour was known. It was decided to await the effect of this therapy before resorting to radiotherapeutic treatment, if necessary.

The first patient was a female aged 43 years with deterioration of the visual acuity in the left eye to 1/60, in whom ophthalmoscopy revealed a lesion suspicious for a metastasis with a secondary retinal detachment. A few days later breast cancer was diagnosed for which she was treated by means of ovariectomy and chemotherapy in the form of fluorouracil. At ophthalmological check-up two weeks later, visual acuity had increased to 0.5, the prominence of the tumour had distinctly decreased and the retinal detachment had disappeared. One and a half years later, visual acuity had increased further to 0.8 and ophthalmoscopically, no tumour was present any longer. The patient died 3.5 years after the detection of the uveal metastasis.

The second patient was a female aged 53 years with deterioration of the visual acuity in the right eye to 1/60 and an intraocular tumour which was suspected of being a

melanoma or a metastasis of lung cancer. Two months later, a pulmonary carcinoma with hepatic metastases was diagnosed. Chemotherapy was started with cisplatin and VM-26. After two months, the visual acuity in the right eye had increased to 0.5^{+} and ophthalmoscopically the metastasis had gone into regression. However, one month later, at the last check-up the visual acuity had decreased again to 0.25 without changes in the ophthalmoscopic image. The patient died 11 months after the diagnosis of the intraocular tumour.

The third patient, a male aged 58 years, was referred with a rapidly growing tumour in the fundus and in the iris with secondary glaucoma. No data on this patient's visual acuity were available. The same day, lung cancer was diagnosed for which the patient was treated with irradiation of the primary lesion and chemotherapy. Within one month of this a decrease of the size of the uveal metastases was observed. At the last check-up, one year after the diagnosis of the intraocular tumour, some growth had occurred again, however.

The fourth patient was a male aged 61 years in whom lung cancer had been diagnosed two months previously for which he had refused chemotherapy and had been treated primarily with radiotherapy of the pulmonary tumour. He complained of decreasing visual acuity in the left eye. Twenty-three years previously he had sustained a perforating injury in that eye, after which the visual acuity had always remained less than that in the right eye. The visual acuity in the left eye was 1/60 and temporosuperiorly in the fundus a choroidal metastasis was observed. The patient did accept chemotherapeutic treatment. This was started with a combination of cyclophosphamide, vincristine and procarbazine. However, the patient failed to return for ophthalmological check-up and died four months after the diagnosis of uveal metastasis.

The fifth patient, finally, was a female aged 39 years, known since two years with breast cancer. The visual acuity in her right eye had decreased to 0.6 due to a choroidal metastasis. Radiotherapeutic treatment of this metastasis was recommended. An appointment for this was canceled because the patient had been hospitalized for an ovariectomy and treatment with neoblastine. Two months later, she came for ophthalmological check-up at which the vision in the right eye was found to be 0.7. The prominence had disappeared apart from some pigment clumping.

In four of these five patients, therefore, the systemic therapy had a positive effect on the uveal metastases. In one patient, the effect was not known. Other investigators have already pointed out that systemic treatment of uveal metastases may be useful (Focosi and Salvi, 1961; Farnarier et al., 1973; Smith, 1976; Stolzenbach and von Domarus, 1978; Turut et al., 1987).

Such systemic hormonal or chemotherapy does not prevent uveal metastases, however: 12 of the 87 patients in our study received systemic treatment at the time of diagnosis of the uveal metastasis, while 51 patients received no systemic therapy and in 24 patients, this was unknown. In 12 patients, therefore, uveal metastases developed in spite of the systemic treatment.

It appears advisable only in a selected number of cases to await the effect of systemic therapy on the uveal metastases, viz. in patients who have not yet received systemic treatment for their malignancy. If the uveal metastasis seriously threatens the central visual acuity or has already impaired it, radiotherapeutic treatment of the eye, is recommended.

2.4.1.4 Enucleation

Enucleation of an eye with a uveal metastasis is indicated only in case of ophthalmological complications (Stephens and Shields, 1979; Char, 1989). A number of authors state that in certain cases an indication for enucleation is also present in solitary uveal metastases without metastases elsewhere in the body being known (Font and Ferry, 1976; Schreck, 1980). A controversial management is to resort to enucleation in case of a clinically distinct uveal metastasis in a patient with an unknown primary tumour, in order to attempt to determine the nature of the underlying malignancy by histopathological examination of the intraocular lesion (Hart, 1962; Daicker, 1981; Shields, 1983). However, most enucleations in patients with uveal metastases are carried out on the erroneous diagnosis of uveal melanoma (Ferry and Font, 1975; Colombo and Carnevali, 1985).

In six patients of our study group the ophthalmological treatment consisted in enucleation of the affected eye. Three times this was done on the false diagnosis of uveal melanoma and only at histopathological examination was the lesion found to be a metastasis. In one patient the diagnosis was initially uncertain. Since the eye would be functionally destroyed it was enucleated after which the diagnosis of uveal metastasis was made. In two other patients, finally, enucleation had to be performed because of ophthalmological complications: once a painful right eye and once, a refractory secondary glaucoma.

In one additional patient the eye was enucleated because the prominence of the intraocular tumour increased in height and the visual acuity deteriorated in spite of irradiation. This patient was included in the chapter on radiotherapy (Chapter 2.4.1.1).

The other findings in these patients and a brief survey of the case histories are to be found in Chapter 2.3.8.

2.4.1.5 Laser treatment

In the literature, laser treatment of uveal metastases is described only a few times. On the whole such treatment is applied only exceptionally and then in small lesions (Weve, 1960; Daicker, 1981; Brady et al., 1982).

In our study group one patient was treated with laser therapy. This was a female aged 46 years known with metastasized breast cancer when she began to complain of a spot in front of her right eye. Visual acuity was 0.8. Ophthalmoscopy revealed a choroidal metastasis with a prominence of 0.5 mm in a peripheral inferior position, with a local retinal detachment. The lesion was surrounded by a double row of laser coagulates and the tumour itself was subjected to extensive photocoagulation as well. After scar formation, the visual acuity improved to 1.2 at the last ophthalmological check-up two months later. The patient died one year after the diagnosis of the choroidal metastasis.

In this patient laser treatment was efficacious. However, this involved only one case with low prominence from the early phase of the study (1973). In later periods, on the basis of experience gained in other institutes and reported in the literature, local radiotherapy was preferred for ophthalmological intervention because more frequent and better results might be expected of it and it could also be applied to prominent tumours.

2.4.1.6 Conclusions

For the treatment of uveal metastases a number of possibilities are available. It is recommended to irradiate unilateral metastases according to a scheme of 30.0 Gy in 10 daily fractions via a lateral beam directed 5° occipitally to protect the lens, or via a half-beam technique. If bilateral metastases have been established, parallel opposed beams are advised. This treatment in most cases results in a decrease or stabilization of the prominence and/or stabilization or increase of the visual acuity.

In patients with small uveal metastases without secondary retinal detachment in whom the visual acuity is not reduced or threatened and who have not yet received systemic therapy, the effect of hormonal or chemotherapy may be awaited. However, this necessitates thorough ophthalmological check-ups so that any growth of the metastasis or deterioration of the visual acuity will be detected immediately and radiotherapy can then be administered.

Of laser treatment it is stated that it might be useful in metastases with low prominence. Our experience is limited, however.

Enucleation of an eye with a metastasis is indicated only in a patient with an intractible painful blind eye due to local complications.

Control examinations of patients with uveal metastases should be reduced to a minimum. It remains important, however, to examine the patient regularly in order that any complications or new metastases may be detected and treated as early as possible. To this purpose we recommend, if no particular events occur in the meantime, to examine patients with uveal metastases who will be irradiated in the week prior to the start of radiotherapy and 1, 2, 3, 6 and 12 months after the start of the treatment. In case of systemic therapy or an expectative policy, more frequent control examinations may be necessary.

2.4.2 Prognosis

How well the clinical course of uveal metastases can be described depends on the duration of the follow-up of these patients. Of the 87 patients with uveal metastases of our study group, nine patients were examined only once and no later clinical data were available. Seventy-eight patients had been examined ophthalmologically at least twice.

The interval between the date of detection of the uveal metastasis and the date on which the patient was examined ophthalmologically for the last time was 7.6 months on average. The median was substantially lower, namely 4.5 months. This follow-up ranged from none to over four years. In patients with uveal metastases, therefore, data on the clinical course usually were known over only a brief period.

Between the date of the last ophthalmological examination and the time of death in our patient group there was an interval with a mean of 5.7 and a median of 3.5 months. This amounts to almost one-half of the total duration of survival as known of patients with uveal metastases and described below. This is due to the fact that patients in the terminal phase of their disease in general were no longer examined ophthalmologically.

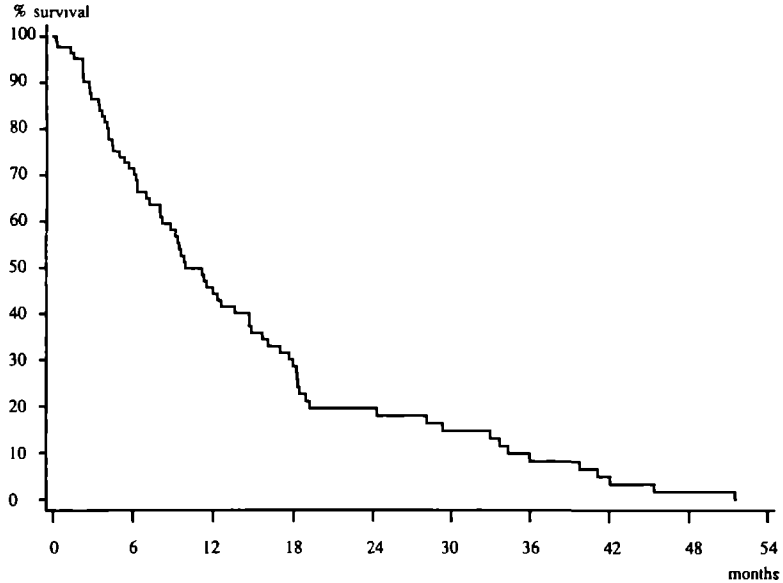


Figure 2.4.2.1 Kaplan-Meier survival curve for patients with uveal metastases (N=87).

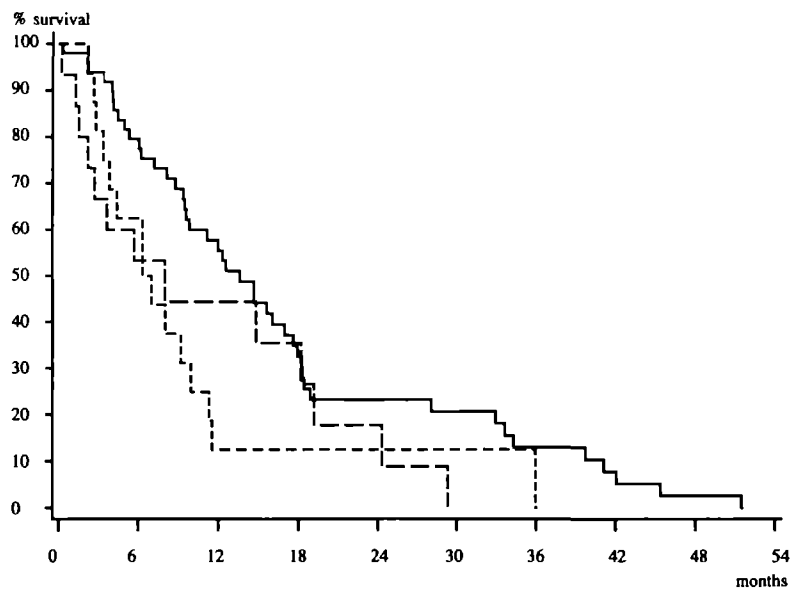


Figure 2.4.2.2 Kaplan-Meier survival curve for patients with uveal metastases, subdivided according to the nature of the primary tumours: ——— breast cancer (N=52); - - - lung cancer (N=20); — — other localizations (N=15).

Consequently, data on the evolution of the ophthalmological picture and the effect of therapy, if any, are known for only a brief period after the diagnosis of the uveal metastasis.

The Kaplan-Meier survival curve for patients with uveal metastases is shown in Figure 2.4.2.1. In Figure 2.4.2.2, the curve is subdivided according to the nature of the primary tumours.

The follow-up of uveal metastases is determined for an important part by the mortality of the patients due to the underlying malignant disease. On the termination date of the study (13 November 1990), 76 patients were known to have died (87%); six other patients (7%) were still alive at that time while of the five remaining patients (6%) data concerning this were lacking. In 72 of the 76 patients who had died the date of death was known. Median duration of survival after the diagnosis of the uveal metastasis was 9.7 months (mean 13.6). The shortest duration of survival was one week, in a patient with a metastasis of a pancreatic carcinoma, the longest 4 years and 4 months in a patient with breast cancer. Of these 72 patients, 58% had died within one year after the detection of the uveal metastases, 83% within two years and 93% within three years.

In the six patients still alive at the termination date of the study, the median follow-up after the detection of the uveal metastases was 3.7 months (mean 5.6). The longest follow-up was 20 months.

In the five patients of whom it was not known whether at the time of termination of the study they were still alive, the median follow-up was 1.6 months (mean 3.3) with a maximum of seven months.

The longest known duration of survival after detection of a uveal metastasis, and also the longest known follow-up in our patient group was 4 years and 4 months (1567 days).

There was a distinct correlation between the duration of survival after the diagnosis of the uveal metastases and the nature of the primary malignancy. The median duration of survival of patients with breast cancer, namely, was 12.7 months (range 0.3-52; mean 16.3; SD 13.2) while for patients with lung cancer it was only 6.4 months (range 2-37; mean 8.5; SD 13.2) and in patients with one of the miscellaneous malignancies 5.8 months (range 0.2-30; mean 10.3; SD 10.0). This is in agreement with data in the literature in which for patients with uveal metastases of breast cancer a median or mean duration of survival is described of from 8.5 to 23 months and for patients with lung cancer of from 5.2 to 6 months (see Table 1.6.2.2). The patients' duration of survival was also correlated with the question whether the primary tumour was already known before the ophthalmological diagnosis. If the detection of the uveal metastasis preceded that of the primary tumour, the median duration of survival was 7.1 months (range 1-42; mean 9.5; SD 10.0). If the metastasis was discovered in a patient already known to suffer from a malignancy, the median duration of survival was longer, viz. 11.4 months (range 0.2-52; mean 14.9; SD 12.6). The most probable cause of this difference is the fact that in only one patient, in whom the uveal metastasis was diagnosed before the detection of the primary malignancy, did the metastasis originate from breast cancer, as against in 11 patients from lung cancer. Patients with lung cancer, especially those with a small cell anaplastic bronchial carcinoma, have a markedly shorter life expectation than patients with breast cancer. The brief duration of survival of patients with lung cancer therefore may also account for the poor duration of survival in patients with initially unknown primary malignancies.

As already mentioned in Chapter 2.2.3, in 41% of the patients with uveal metastases no metastases elsewhere in the body were known at the moment of detection of the intraocular tumour. It is therefore definitely not true that metastases in the uvea only occur in case of extensive systemic dissemination of the malignancy. On the contrary, uveal metastases may constitute an early sign of generalization.

In contrast to the observation by Hemmes (1969) that patients with bilateral metastases of breast cancer had a better prognosis than patients with unilateral metastases, we found no difference between these groups (mean durations of survival 16 and 17 months, respectively).

The poor prognosis quoad vitam of patients with uveal metastases has been mentioned by other investigators as well (Duke-Elder and Perkins, 1966; Ferry, 1967; Gartner, 1985). The mean duration of survival as given by different authors varies from 3 to 9.3 months (see Table 1.6.1.1). Both the median duration of survival, of 9.7 months, and the mean duration of survival, of 13.6 months, which we observed in our patient group, are higher. However, the data from our study refer to a patient population from a more recent study period than those of other investigators.

Part 3
Prospective study

3.1 Aims of the study and study design

3.1.1 Aims of the study

As already mentioned in Chapter 1.3.1, determining the frequency of uveal metastases is difficult. This is due among other things to the facts that these metastases may remain asymptomatic, that they often occur in the terminal phase of the disease and that the diagnosis may be difficult.

According to Jensen (1970) and François et al. (1976), the incidence of uveal metastases is approximately 2/100.000. Other authors, however, assert that considering the total number of patients with a malignancy the incidence figures of intraocular metastases have to be higher. In the United States, according to them, on the basis of 300 million inhabitants, the incidence of uveal metastases is 5-15/100.000 (Nelson et al., 1983; Bence, 1985).

Clinically, uveal metastases are present in 0.07 to 2.3% of the patients with a known malignancy (see Table 1.3.1.3).

One of the objectives of this study is to establish the prevalence or the development of uveal metastases in patients with a known malignancy. The development of uveal metastases depends greatly on the nature of the primary tumour. It was stated in Chapter 1.3.1 that uveal metastases most frequently originate from breast cancer. For this reason it was decided to restrict the study to this patient population.

Ophthalmological complaints of patients with a malignancy may be caused by metastases in the uvea. However, cytostatic and hormonal therapy may also impair the visual acuity. In the first part of this thesis, the ophthalmological side effects of such therapies are discussed (Chapters 1.6.1.2 and 1.6.1.3: Tables 1.6.1.2.1 and 1.6.1.2.2). In the present prospective study, an attempt is made to determine to what extent any visual disorders in patients with breast cancer are caused by uveal metastases and to what extent systemic treatment is involved.

When patients with a known disseminated malignancy are examined ophthalmologically, uveal metastases are diagnosed in 2.3% of the cases (Albert et al., 1967). Mewis and Young (1982) diagnosed uveal metastases in 27% of the patients in different stages of breast cancer. Not all these patients actually had ophthalmological symptoms, however. Although uveal metastases occur frequently, they do not lead to complaints or symptoms in all cases. Consequently, one objective of the present prospective study is to determine the policy with respect to ophthalmological control examinations of patients with breast cancer for presence of ophthalmological symptoms and of uveal metastases.

With early detection of ophthalmological symptoms and early diagnosis of (still) asymptomatic uveal metastases, it may be possible to treat metastases in an earlier phase and sometimes to improve the prognosis concerning the visual acuity.

Recapitulating, the aims of this prospective study are:

- to establish the prevalence or the development of uveal metastases in patients with breast cancer;
- to determine the relationship between any visual complaints and uveal metastases or systemic treatment;
- to determine an optimal policy for ophthalmological follow-up of patients with breast cancer for presence of uveal metastases;
- to study the effect of early diagnosis of uveal metastases on the results of treatment.

3.1.2 Patients

Patients for this prospective study were referred in the period from 28 February 1989 to 2 July 1991 to the outpatient clinic for Ophthalmology, in cooperation with the department of Internal Medicine (outpatient clinic Mammary Pathology, subdepartment Endocrine Diseases) of Nijmegen University Hospital. This concerned patients with breast cancer who were considered for some form of adjuvant therapy after treatment of the primary tumour (pT1-3 N+ M-) and patients with known metastases (M+).

Patients were referred for one of the following three reasons:

1. Referral for an initial ophthalmological examination of the patient. These were patients who were referred purely in the context of this study and who in other cases would not have been examined by an ophthalmologist. If no abnormalities were observed, they were again examined after one year, unless in the interval a reason for earlier examination emerged.
2. Referral in connection with a modification of the systemic oncological treatment: this because such a change of treatment is decided upon in case of progression of the disease, which entails an increased risk of dissemination to the eye. These patients, also, in the normal course of events are not examined by an ophthalmologist.
3. Finally, all patients with ophthalmological symptoms were examined, regardless of whether they had undergone ophthalmological examination earlier, in the context of this study. These patients might possibly have been referred to an ophthalmologist if this prospective study had not been organized.

The prospective study was carried out during an uninterrupted period of 28 months. In all, 107 female patients with breast cancer were examined ophthalmologically. Their mean age was 53.4 years (SD 12; median 55; range 24-84).

In 44 of the 107 patients (41%) a curatively intended local or regional treatment of the breast cancer was performed and tumour-positive axillary glands were found (primary mammary carcinoma). In the other 63 patients (59%) distant metastases were known (Table 3.1.2.1). These were visceral metastases in 31 patients (49%). Cerebral metastases were never established; in one patient carcinomatous meningitis was diagnosed. Pulmonary metastases were observed in 18 of these patients. Bone metastases were known in 27 patients (43%) and only soft-tissue metastases in five patients (8%).

Table 3.1.2.1 Localization of metastases in 107 patients with breast cancer

Localization	N	%
Primary breast cancer (N=44)	-	-
Advanced breast cancer (N=63)		
Visceral	31	49
viz. Brain	-	-
Carcinomatous meningitis	1	2
Lung	18	29
Bone	27	43
Soft tissue	5	8

*Table 3.1.2.2 Previous therapy at the time of initial ophthalmological examination in 63 patients with advanced breast cancer **

Therapy	N	%
None	22	35
CMF	9	14
Tamoxifen	7	11
CMF, tamoxifen	3	5
CMF, tamoxifen, aminoglutethimide	2	3
CMF, tamoxifen, aminoglutethimide, MPA	1	2
CMF, tamoxifen, LH-RH analogues	1	2
CMF, tamoxifen, ovariectomy	1	2
CMF, ovariectomy	2	3
CMF, AC	1	2
Tamoxifen, ovariectomy	4	6
Tamoxifen, aminoglutethimide	2	3
Tamoxifen, aminoglutethimide, AC	1	2
Tamoxifen, fluorouracil	1	2
Tamoxifen, MPA, LH-RH analogues	4	6
Tamoxifen, 4-epirubicin, cyclophosphamide	1	2
Ovariectomy	1	2

** not stated in sequence of therapy; AC: Adriamycin (doxorubicin) + cyclophosphamide; CMF: cyclophosphamide + methotrexate + fluorouracil; LH-RH: luteinizing hormone-releasing hormone; MPA. medroxyprogesteronacetate*

The median duration of the interval between the date of diagnosis of the breast cancer and the ophthalmological examination was 21 months (range 1-310; mean 42; SD 55).

The patients with primary breast cancer had not or only just been started on adjuvant therapy. The type of treatment depended on the menopausal stage and the hormone receptor status of the tumour. Premenopausal patients were given adjuvant chemotherapy with the combination of cyclophosphamide, methotrexate and fluorouracil (CMF). Postmenopausal patients with an oestradiol receptor (ER) and/or progesterone receptor (PgR) positive tumour were given adjuvant treatment consisting of fluorouracil and tamoxifen.

In the patients with advanced breast cancer, an ophthalmological examination was made at the times of starting or altering the pharmacotherapy. Table 3.1.2.2 presents a survey of the preceding treatment in these patients.

Chemotherapy, which might or might not be combined with hormone treatment, consisted usually of CMF, once fluorouracil and once, of Adriamycin (doxorubicin) and cyclophosphamide (AC). Hormonal therapy consisted mostly of tamoxifen and of ovariectomy. Other hormonal therapy consisted of aminoglutethimide, medroxyprogesterone acetate (MPA) and ethinyloestradiol.

Since the appointment for the first ophthalmological check-up was made at the start of adjuvant therapy or at the beginning of altered palliative therapy, most patients were only actually examined after initiation of this therapy. Table 3.1.2.3 presents a review of the therapies at the time of the ophthalmological examination in all 107 patients examined.

Table 3.1.2.3 Therapy at the time of initial ophthalmological examination in 107 patients with breast cancer

Therapy	N	%
Primary breast cancer: adjuvant therapy (N=44)		
CMF	16	36
CMF + AC	1	2
Fluorouracil + tamoxifen	15	34
Tamoxifen	4	9
None	8	18
Advanced breast cancer: palliative therapy (N=63)		
CMF	25	40
Fluorouracil + tamoxifen	3	5
Tamoxifen	20	32
Tamoxifen + AC	1	2
AC	3	5
Ethinyloestradiol	1	2
None	10	15

AC: adriamycin (doxorubicin) + cyclophosphamide; CMF: cyclophosphamide + methotrexate + fluorouracil

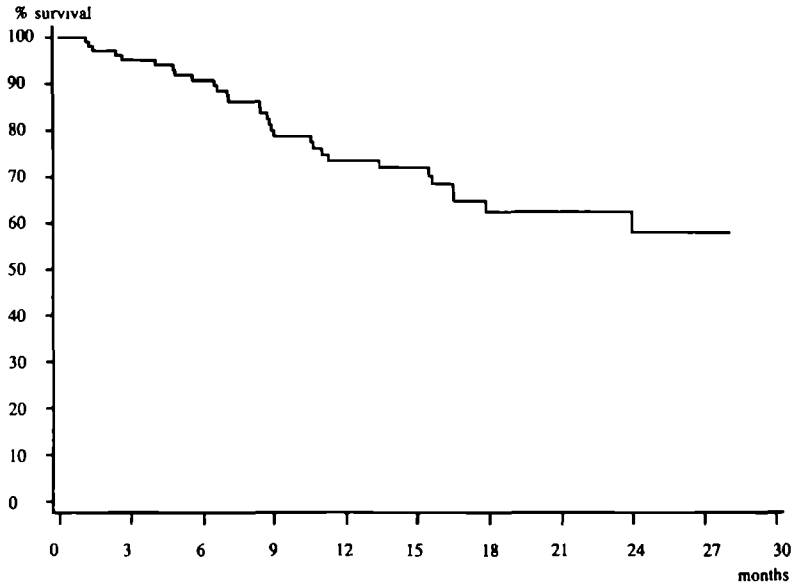


Figure 3.1.2.1 Kaplan-Meier survival curve (after ophthalmological examination) for patients with breast cancer (N=107).

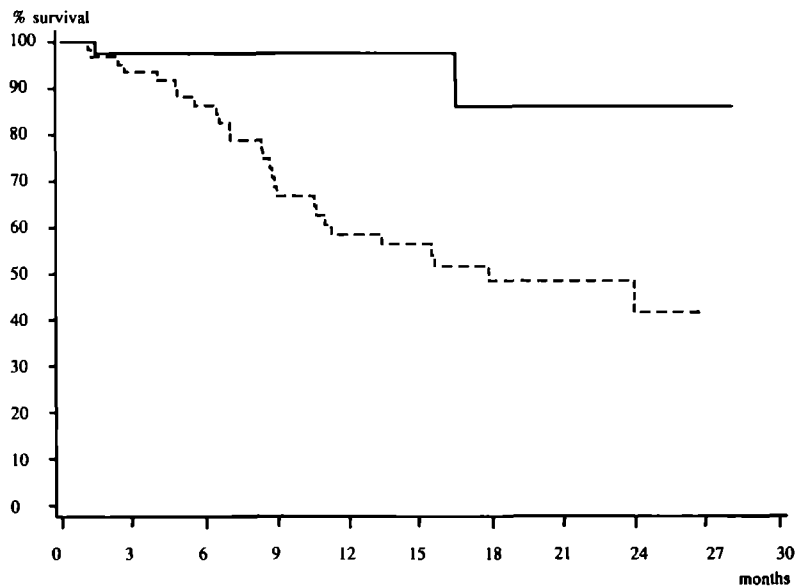


Figure 3.1.2.2 Kaplan-Meier survival curve (after ophthalmological examination) for patients with breast cancer: —— primary breast cancer (N=44); — — advanced breast cancer (N=63).

Of all 107 patients with breast cancer at the termination date of the study, 30 (28%) had died, 29 of them as a direct consequence of the breast cancer. One patient with primary breast cancer died 1.5 months after the ophthalmological examination of an acute myocardial infarction. The 30 patients included three of the 44 patients (7%) with initially primary breast cancer and 27 of the 63 patients (43%) with advanced breast cancer. The median duration of survival after the diagnosis of the primary tumour in this group was 3.1 years (range 6 months to 15 years; mean 4.6 years). The median duration of survival after the first ophthalmological examination was 9 months (range 1-24, mean 9).

The estimated durations of survival in terms of percentages after the ophthalmological examination of all 107 patients and of the patients with primary (N=44) or advanced (N=63) breast cancer, are presented in Figures 3.1.2.1 and 3.1.2.2 respectively.

3.1.3 Study design

Ophthalmological examination of the patients was performed, as described above, on three occasions, namely:

1. a first ophthalmological examination of 'new' patients with primary or advanced breast cancer without ophthalmological symptoms;
2. examination at modification of (systemic) treatment;
3. examination because of ophthalmological symptoms.

Of the 107 patients with breast cancer, 37 (35%) were referred for the first ophthalmological examination as 'new' patients, 52 (49%) because of a modification of treatment and 18 (17%) because of ophthalmological symptoms.

It was the intention that all patients would be re-examined one year after the first ophthalmological examination. Of all patients 25 (23%) were examined more than once, with a maximum of 7 times per patient (repeated examinations in general in connection with ophthalmological abnormalities or with alterations of treatment). Of the 52 patients of the first year of the study, only 15 were seen for re-examination in the second year. The other 37 patients were examined only once. Nineteen of these 37 patients had died before a second ophthalmological examination could be carried out.

At referral of the patient for the ophthalmological examination a number of data were given. The first of these was the date of diagnosis of the primary mammary carcinoma and its localization. In addition, the presence of metastases elsewhere in the body was mentioned, especially of pulmonary and cerebral metastases, with date of diagnosis. Information was also presented concerning the treatment up to time of referral. Finally, an important factor was whether the patient at the department of Internal Medicine spontaneously reported visual symptoms.

The ophthalmological examination consisted firstly of an extensive ophthalmological anamnesis including enquiries concerning the presence of visual symptoms in the form of blurred vision or decrease of the visual acuity, visual field defects or spots before the eyes, photopsia, metamorphopsia, diplopia and ocular pain.

Subsequently, in both eyes an Amsler test was carried out for detection of metamorphopsia, and perimetry according to Donders. In every patient determination of the visual acuity was performed without correction, with patient's own correction, if any, and after optimal refractionation.

During slit lamp examination, the conjunctiva and sclera were inspected for the presence of hyperaemia and dilated vessels. Subsequently, the cornea and lens were inspected, and attention was paid to the presence of Tyndall and cells in the anterior chamber and vitreous. The iris was examined meticulously for detection of metastases. Applanation tonometry was performed in both eyes. After mydriasis the fundus was inspected by indirect ophthalmoscopy and triple-mirror fundus contact lens examination.

If this examination revealed abnormalities suggestive of metastases, the patient was subjected to fluorescein angiography, echography to the extent that the suspected lesion appeared to be sufficiently prominent for further echographic differentiation, electro-oculography and, if indicated, perimetry.

In case of doubt concerning the diagnosis, the patient was kept under ophthalmological surveillance. If lesions other than metastases were discovered, these were treated in as far as necessary.

If no metastases were observed, the patient was re-examined after one year unless in the interval the systemic treatment was modified or ophthalmological symptoms developed.

If the diagnosis of uveal metastases was made, the patient was treated according to the current policy in our clinic. This means that in case of a metastasis at or in the direct vicinity of the macular area radiotherapy was advocated, just as in small lesions in the periphery with secondary retinal detachment threatening the eyesight, in large peripheral tumours and in all patients with metastases in whom a deterioration of the visual acuity was observed. An expectative policy with thorough ophthalmological follow-up was pursued in case of small metastases not threatening to impair the eyesight.

3.2 Results

3.2.1 Frequency of uveal metastases and case histories

In the course of the prospective study, uveal metastases were diagnosed in five of the 107 patients with breast cancer (5%) All five belonged to the 63 patients with advanced breast cancer (8%). Uveal metastases were never discovered in patients with primary breast cancer. The mean age of these five patients was 55 years (range 45 to 65 years). The case histories of these patients will be discussed in detail below.

Patient 1011

In May 1984, in a premenopausal woman aged 42 years, a carcinoma was diagnosed in the medial upper quadrant of the right breast A modified mastectomy according to Patey was carried out. In the axilla, one lymph node with massive tumour invasion and extranodular growth was resected. Testing for receptors in the tumour tissue gave a positive result for oestradiol receptors and a negative result for progesterone receptors. Axillary and parasternal irradiation were administered In July of the same year adjuvant chemotherapy was instituted in the form of CMF, six courses

Pulmonary metastases developed in August 1987 In November of that year metastases were also found in the skin, lymph nodes and bone. It was decided to start tamoxifen treatment In spite of this therapy, progression of the condition occurred. Further treatment with chemotherapy and other endocrine measures also failed to suppress continued progression of the disease. On 3 April 1989 in connection with an alteration of the systemic therapy, she was referred to our ophthalmological outpatient department with no known ocular signs or symptoms

At ophthalmological history-taking, the patient after all was found to have blurred vision in both eyes since six weeks with a sensation of oppression in the left eye since four months. There were no complaints about diplopia, visual field defects, ocular pain, photopsia or metamorphopsia.

Perimetry according to Donders revealed no abnormalities in either eye. The Amsler test was normal on the right; on the left, temporosuperior metamorphopsia was noted.

The visual acuity in the right eye was:

without correction (= patient's own correction):	1.0^{+}
with optimal correction (+0 25 sph):	1.25

The visual acuity in the left eye was:

without correction (= patient's own correction):	0 2
with optimal correction (+0.25 sph):	0.2

Externally, neither eye displayed abnormalities, in particular no conjunctival or scleral hyperaemia or dilated vessels.

At slit lamp examination both corneas were clear, no cells or Tyndall were observed in the anterior chamber. The iris was normal, more especially free of

metastases. The lenses were clear and no cells or Tyndall were seen in the vitreous. Applanation tonometry showed pressures of 10 mm Hg on the right and 14 mm Hg on the left.

Ophthalmoscopy revealed no abnormalities in the right eye. On the left temporoinferiorly there was a large yellowish-brown slightly elevated prominence with an offshoot into the macular area and an irregularly pigmented leopard-skinlike surface. No orange lipofuscin pigment was observed, nor haemorrhages on or round the tumour or in the vitreous. No retinal detachment was present. No disk abnormalities were observed. The picture was highly suspicious for a choroidal metastasis in the left eye (Figure 3.2.1.1).

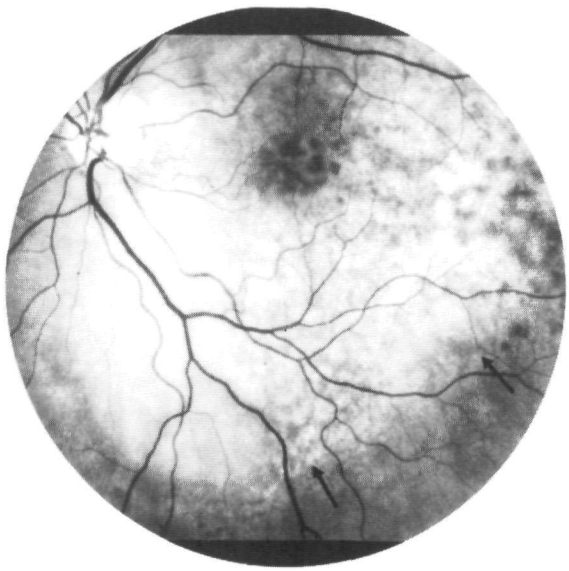


Figure 3.2.1.1 Fundus photograph of an extensive choroidal metastasis (arrows) from breast cancer in the left eye (patient 1011).

At fluorescein angiography there were no abnormalities on the right. On the left, simultaneous with the staining of the choroid at the site of the lesion, a mottled fluorescence pattern became visible which slowly increased in intensity through the remaining exposures. No double vascularization or hypofluorescent rim were observed. In the late phases, a few hyperfluorescent spots became visible at the lower margin of the lesion. The image fitted a choroidal metastasis (Figure 3.2.1.2).

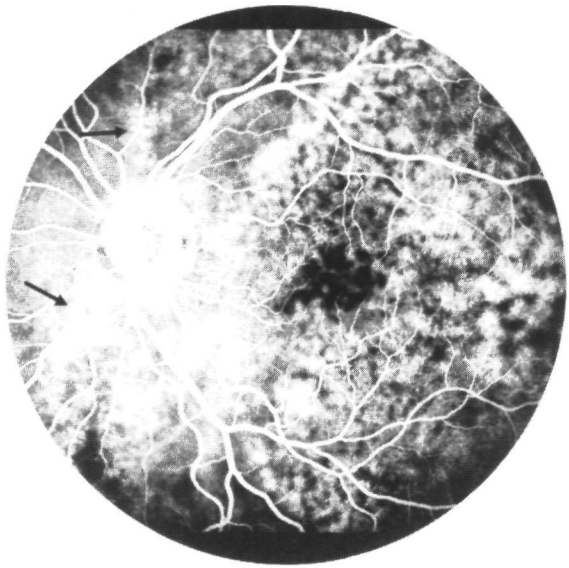


Figure 3.2.1.2 Fluorescein angiogram in the venous phase showing the same metastasis (arrows) as in Figure 3.2.1.1 with mottled fluorescence of the tumour.

At echographic examination no abnormalities were present on the right. On the left, a tumour was observed with a prominence of 1.0 mm without signs of choroidal excavation or extraocular extension. The reflectivity of the lesion was difficult to determine owing to the slight prominence. A minor serous retinal detachment was present. The diagnosis of a metastasis was made (Figure 3.2.1.3).

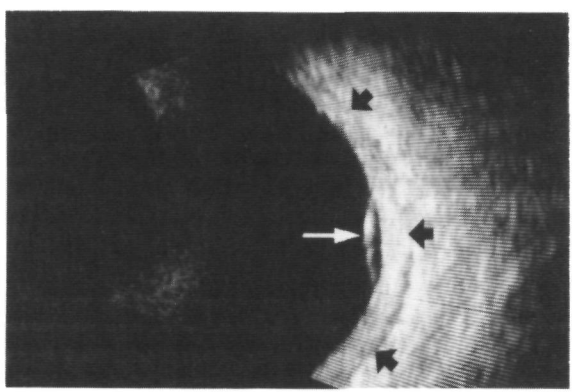


Figure 3.2.1.3 B-mode echogram of the left eye of patient 1011 with choroidal infiltration (black arrows) and a localized secondary retinal detachment (white arrow).

At electro-oculography, the following values were found for the various parameters:

OD: Iv 400 μV; Dt 275 μV; Lp 675 μV; ratio 2.45; A value +188.

OS: Iv 300 μV; Dt 275 μV; Lp 300 μV; ratio 1.09; A value -128.

Conclusion: on the left abnormal EOG, corresponding best to a retinal detachment.

At the 100 Hue test, 98 errors were indicated on the right (within normal), 489 on the left (significantly abnormal), without a distinct axis.

The diagnosis made was a choroidal metastasis in the left eye. When we saw the patient for the first time, the systemic treatment had just been switched to fluorouracil and tamixofen. Because of the patient's poor condition, it was decided first to await the effect of this systemic therapy.

At ophthalmological follow-up examination one month later the visual acuity and the ophthalmoscopic and fluorescein angiographic images had not changed. The tumour did not show distinct changes at later check-ups, either. The patient was seen for the last time in October 1989. The visual acuity then was 0.8^{++} in the right eye and 0.2 in the left eye without correction. The extension of the lesion appeared to have increased slightly, however. In view of the patient's clinical condition it was decided to perform no further examinations.

In September 1989 cerebral metastases were established and further progression of the condition occurred. The patient died on 11 October 1989 as the consequence of sepsis during neutropenia.

In this patient with a choroidal metastasis with only a small serous retinal detachment, visual complaints proved to be present which, however, were only mentioned after explicit enquiry. Because of the patient's poor general condition and the start of a different systemic treatment, no radiotherapy of the intraocular metastasis was recommended. At follow-up the ophthalmological image was found to remain stationary until just before the patient's death, at which time a slight increase of the size of the lesion was established which proved not to affect the visual acuity any further.

Patient 1023

In October 1987, in a premenopausal woman aged 44 years, a carcinomatous mastitis on the left was established with pathological lymph nodes in the neck and axilla. Mastectomy was performed. Apart from the lymph nodes, metastases were found already to be present in the lungs and the skeleton. The oestradiol and progesterone receptors were positive. Treatment with tamoxifen was instituted following which a regression of the lymph node metastases was observed. The treatment with tamoxifen was discontinued in October 1988 because of progression established one month previously. Meanwhile, secondary amenorrhoea was found to have developed owing to metastasization in the hypophysis. Because of progression of the disease in March 1989 in the by then 'post-menopausal' patient, tamoxifen treatment was resumed in combination with fluorouracil. At that time there were visual complaints in both eyes in the form of blurred vision, which cleared

after this alteration of treatment. The treatment, accordingly, led to a partial remission.

The patient was referred to us in June 1989, because of the change of therapy. Apart from watery eyes there were no visual complaints at that time.

Perimetry according to Donders and the Amsler test revealed no abnormalities in either eye.

The visual acuity in the right eye was:

without correction (= patient's own correction):	0.8^{-}
with optimal correction (+0.25 sph):	0.8

The visual acuity in the left eye was:

without correction (= patient's own correction):	0.8^{++}
with optimal correction (-0.25 sph):	1.0^{-}

Externally, neither eye exhibited abnormalities, especially no conjunctival or scleral hyperaemia or dilated vessels.

At slit lamp examination both corneas were clear, no cells or Tyndall in the anterior chamber were seen. The iris was normal, in particular no metastases were present. The lenses were clear and no cells or Tyndall were observed in the vitreous. Applanation tonometry showed pressures of 12 mm Hg in both eyes.

At ophthalmoscopical examination of the right eye, a yellow slightly prominent lesion was observed situated temporally below the level of the vascular arcade. There was no lipofuscin pigment on the tumour surface and no retinal detachment. The lesion was suspicious for a choroidal metastasis (Figure 3.2.1.4). In the left eye no abnormalities were observed.

At fluorescein angiography the lesion stained in the early phase of the examination; initially, the staining of the lesion kept pace with that of the surrounding choroid; in the late phases it showed a finely mottled hyperfluorescence. A vague hypofluorescent margin was observed; no hyperfluorescent spots were present and no tumour vessels were seen (Figure 3.2.1.5). On the left no abnormalities were observed. Conclusion: choroidal metastasis on the right.

Echography was not performed because the lesion was too flat for further differentiation.

At electro-oculography the following values were found for the different parameters:

OD: Iv 900 μV; Dt 700 μV; Lp 1400 μV; ratio 2.00; A value +230.

OS: Iv 900 μV; Dt 725 μV; Lp 1400 μV; ratio 1.93; A value +208.

Conclusion: normal EOG on both sides, best compatible with a naevus.

Perimetry revealed no abnormalities.

At the 100 Hue test, 116 errors were made with the right and 104 with the left eye (within normal).

The diagnosis made was a solitary choroidal metastasis in the right eye. Since there were no symptoms and because of the small size of the lesion, the absence of a retinal detachment and the recently instituted systemic therapy, an expectative policy was decided upon. At the outpatient and fluorescein angiographic check-ups three weeks and two months later, visual acuity had remained stable and the lesion had not increased in size.

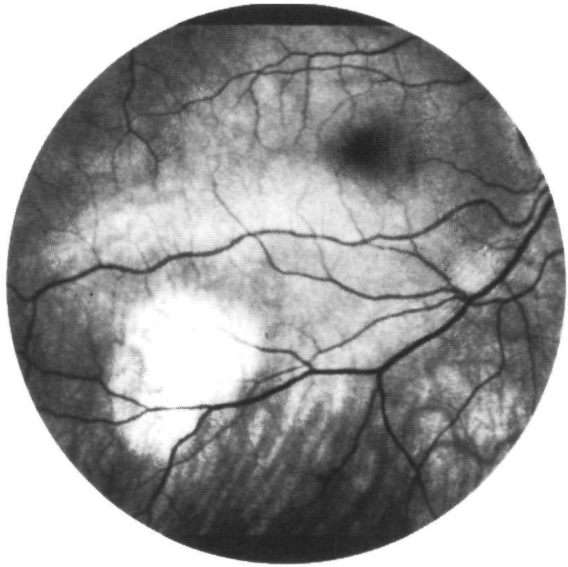


Figure 3.2.1.4 Fundus photograph of the right eye of patient 1023 showing a choroidal metastasis temperoinferior of the macular area, presumably in regression.

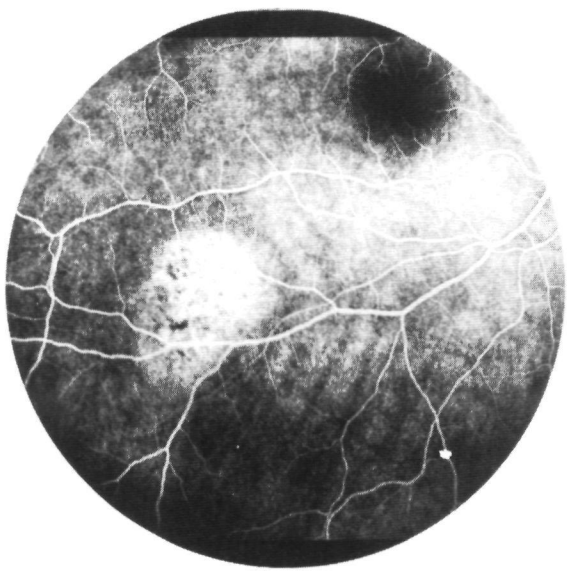


Figure 3.2.1.5 Fluorescein angiogram in the venous phase of the same lesion as in Figure 3.2.1.4 showing hyperfluorescence of the metastasis.

The systemic therapy with fluorouracil was discontinued in March 1990. The disease at that time was still in remission. The treatment with tamoxifen was continued. Immediately thereafter, however, the condition again showed progression for which reason treatment with fluorouracil was resumed in May 1990. At ophthalmoscopical control examination, the choroidal metastasis had become slightly flatter and had not increased in size. The visual acuity was 0.8 in both eyes. Because of further progression of the extraocular disease, the treatment in June 1990 was switched to courses of CMF. We examined the patient for the last time in October 1990. The ophthalmological findings at that time were unchanged.

In this patient, the choroidal metastasis was asymptomatic although shortly before the ophthalmological examination she had complained about blurred vision which disappeared post or propter treatment with fluorouracil and tamoxifen. This treatment may have controlled the metastasis in the eye as well, although later elsewhere in the body progression of the condition nevertheless occurred. Throughout the follow-up period of 16 months no change in visual acuity occurred and the lesion had grown slightly flatter. The choroidal metastasis in this patient required no local treatment and at the moment of its detection appeared already partly to have gone into regression.

Patient 1049

In January 1984, in a postmenopausal woman aged 54 years, a mammary carcinoma situated medioinferiorly on the left was established for which mastectomy was carried out. Invasion into the muscular layer was found to be present and two lymph nodes were infiltrated by tumour tissue (mammary carcinoma stage pT4N1M0). For this reason, total locoregional postoperative irradiation was administered. The oestradiol receptors were negative, those for progesterone positive.

Four years later, in July 1988, bone metastases were established for which local radiotherapy was instituted. In September 1989 progression of the disease was found to have occurred. Retesting for oestradiol and progesterone receptors in a cutaneous metastasis now gave positive results for both. Systemic therapy in the form of tamoxifen was instituted. In connection with this switch of treatment the patient, according to protocol, was referred to our outpatient department.

We examined the patient for the first time on 23 January 1990. She complained of an intermittent burning and itching sensation in both eyes. There were no complaints about the visual acuity, especially no blurred vision, spots before the eyes, visual field defects or metamorphopsia.

At perimetry according to Donders there was some decreased sensitivity nasally in the right eye, while no abnormalities were observed in the left eye. The Amsler test was normal on both sides.

The visual acuity in the right eye was:

without correction:	0.6^{-}
with patient's own correction (+1.75 sph -0.75 cx 60°):	1.25^{-}
(= optimal correction)	

The visual acuity in the left eye was:

without correction:	0.6
with patient's own correction (+1.25 sph -0.25 cx 120°):	1.25^{-}
(= optimal correction)	

Externally, neither eye showed abnormalities, especially no conjunctival or scleral hyperaemia or dilated vessels.

At slit lamp examination the corneas of both eyes were clear, no cells or Tyndall were observed in the anterior chamber. On the iris of both eyes multiple benign naevi were observed; no metastases were present. The lenses were clear. In the vitreous no cells or Tyndall were present. Applanation tonometry gave 13 mm Hg bilaterally.

At ophthalmoscopical examination of the right eye, in a peripheral temporosuperior localization in the fundus, a slightly elevated, irregularly delimited mottled yellowish-white prominence was observed with dark pigment spots on the surface (Figure 3.2.1.6). No lipofuscin pigment on the tumour surface was observed, nor haemorrhages on or round the tumour or in the vitreous. A limited secondary retinal detachment was present. The left eye was ophthalmoscopically normal. These findings might fit a solitary choroidal metastasis in the right eye.

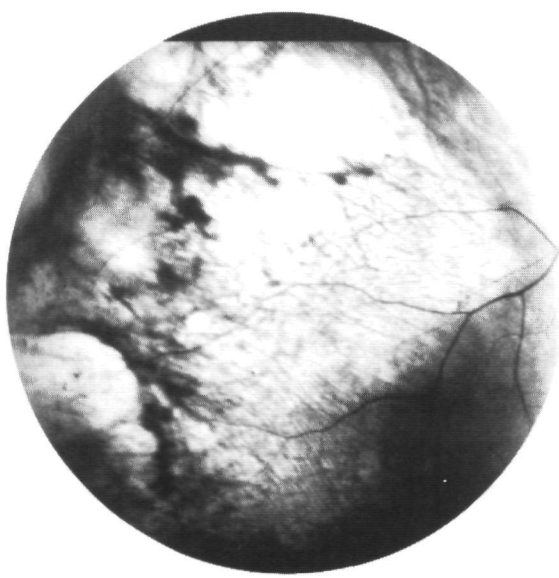


Figure 3.2.1.6 Fundus photograph of a choroidal metastasis temperosuperior in the right eye in patient 1049. Choroidal metastasis from breast cancer in regression.

At fluorescein angiography of the right eye, 16 seconds after injection of the fluorescein and 2 seconds after the staining of the retinal arteries, hyperfluorescence of the lesion developed with an irregular grossly mottled pattern. This fluorescence increased gradually and in the later phases stained the lesion diffusely. The tumour was not surrounded by a hypofluorescent margin. There were only a few hyperfluorescent spots at the tumour margin and no tumour vessels were observed. The serous retinal detachment was also described at fluorescein angiography. On the left there were no abnormalities. Conclusion: probably a choroidal metastasis in the right eye.

At echography of the right eye a flat lesion with a secondary retinal detachment was observed (Figure 3.2.1.7). Further differentiation of the lesion was not possible because of the slight prominence. On the left there were no abnormalities.

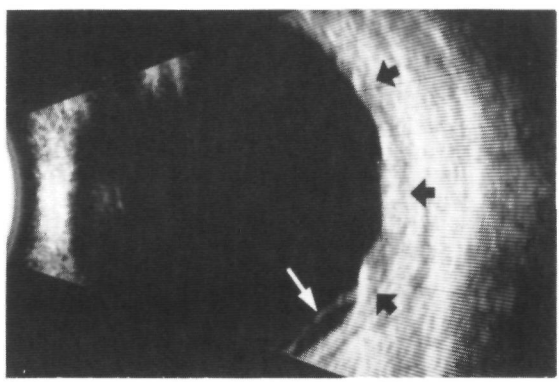


Figure 3.2.1.7 B-mode echogram of a flat choroidal tumour (black arrows) with secondary retinal detachment (white arrow) and without choroidal excavation.

At electro-oculography the following values were found for the various parameters:

OD: Iv 800 μV; Dt 688 μV; Lp 925 μV; ratio 1.34; A value -174.

OS: Iv 400 μV; Dt 300 μV; Lp 875 μV; ratio 2.92; A value +365.

Conclusion: abnormal EOG on the right, corresponding best to a melanoma.

At the 100 Hue test 88 errors were indicated on the right and 92 on the left (within normal).

Conclusion: solitary choroidal metastasis in the right eye with a secondary serous retinal detachment.

The patient was referred to the radiotherapist for irradiation of the lesion. This was started on 8 March 1990 using a linear accelerator (energy: 13 MeV). A total dose of 30.0 Gy was administered in 10 fractions of 3.0 Gy in two weeks via a ventral beam. No side effects were established.

At subsequent ophthalmological control examinations, the visual acuity remained

stable at 1.0 to 1.25 with patient's own correction. At ophthalmoscopy and fluorescein angiography, scarification of the lesion was observed. Echographically, a distinct regression was established. The EOG still showed a pathological result in the right eye although a distinct shift towards naevus had occurred.

The treatment with tamoxifen did not lead to an objective general remission but only to a brief stabilization of the disease. In June 1990, chemotherapy in the form of CMF was instituted. In view of further progression of the disease this treatment was discontinued in February 1991 and changed one month later to a combination of aminoglutethimide and MPA. This treatment did not result in tumour regression, either.

At the time of termination of the study, the patient was still alive in a reasonable general condition but with progressive metastasization.

In this patient, therefore, a choroidal metastasis was detected notwithstanding the fact that she had no complaints about the visual acuity and the acuity was normal. In this patient, also, the metastasis had partly gone into regression. Because of the associated retinal detachment it was decided, however, to irradiate the metastasis without awaiting the effect of the recently instituted systemic treatment with tamoxifen. Subsequently, the lesion decreased in size with scar formation. Throughout the follow-up of almost 1.5 years the patient remained free of ocular symptoms and the good visual acuity persisted.

Patient 1057

In December 1989, in a postmenopasual woman aged 65 years, a carcinoma in the right breast was established with carcinomatous pleurisy and bone metastases. The patient had been known since November 1986 with a collapse of the thoracic vertebral due to osteoporosis and with upper abdominal complaints due to a hiatus hernia. After excision biopsy of the mammary tumour the diagnosis was confirmed histologically. The oestradiol and progesterone receptors were positive. In January 1990 treatment with tamoxifen was instituted and the patient was referred to our outpatient department in connection with this study of uveal metastases.

We examined the patient for the first time on 20 March 1990. From the moment of diagnosis of the primary tumour she had complained about blurred vision in both eyes, worse on the right than on the left, and also of burning eyes. There were no complaints about spots before the eyes or visual field defects, photopsia, ocular pain or diplopia.

Perimetry according to Donders and the Amsler test showed no abnormalities in either eye.

The visual acuity in the right eye was:	
without correction:	0.16^{-}
with patient's own correction (+1.5 sph):	0.8^{-}
(= patient's own correction)	
The visual acuity in the left eye was:	
without correction:	0.2^{-}
with patient's own correction (+2.0 sph -0.5 cx 180°):	0.8^{+}
with optimal correction (+1.75 sph):	1.0

Externally, no abnormalities were observed in either eye, especially no conjunctival or scleral hyperaemia or dilated vessels.

At slit lamp examination both corneas were clear and no cells or Tyndall in the anterior chamber were established. In the iris, no abnormalities were observed, in particular no metastases were present. Both lenses exhibited symmetrical increases of opacity. In the vitreous there were no cells or Tyndall. Applanation tonometry gave values of 13 mg Hg bilaterally.

At ophthalmoscopical examination, no abnormalities were encountered in either eye, especially no metastases.

At the 100 Hue test, 136 errors were indicated on the right and 144 on the left (within normal).

Although visual complaints were present, the visual acuity proved to be normal; no ophthalmological abnormalities were observed, especially no metastases. The patient was reassured by these findings. An appointment was made for a check-up one year later.

The treatment with tamoxifen in the context of a clinical comparative trial (EORTC trial 10863: Beex and Rose, 1987) was administered intermittently and led to a partial remission. From December 1990 the visual acuity became impaired in both eyes, worse on the left than on the right. Consequently, she was once more referred for ophthalmological examination in January 1991.

We examined the patient for the second time in January 1991, 10 months after the initial ophthalmological examination. She stated that since December 1990 she had noticed a spot high in the left eye, accompanied by decrease of the visual acuity and a distorted image. These symptoms were progressive. She had no photopsia, ocular pain or diplopia. In the right eye there were no symptoms.

At perimetry according to Donders no abnormalities were found on the right. On the left, superiorly and nasally, a distinct restriction of the visual field was established. The Amsler test was normal on the right. On the left, part of the top and the right-hand side of the chart was not observed.

The visual acuity in the right eye was:

without correction:	0.16^{-}
with optimal correction (+1.5 sph):	0.8^{-}
the visual acuity in the left eye was:	
without correction:	3/60
with optimal correction (+3.75 sph):	0.6^{--}

Externally, neither eye showed abnormalities, in particular no conjunctival or scleral hyperaemia or dilated vessels.

At slit lamp examination the corneas of both eyes were clear and no cells or Tyndall in the anterior chamber were established. The iris showed no abnormalities, in particular no metastases. In the ocular lenses, symmetrical increases of opacity were observed. In the vitreous, no cells or Tyndall were present. Applanation tonometry gave values of 15 mm Hg on the right and 11 mm Hg on the left.

Ophthalmoscopical examination revealed no abnormalities on the right. In the left eye, temporally at the site of the vascular arcade a yellow tumour was observed, with a

fairly evenly pigmented surface without accompanying retinal detachment or haemorrhages on or round the tumour or in the vitreous. No orange lipofuscin pigment was present. The tumour appeared to consist of a conglomeration of three lesions which initially probably had been discrete. The findings corresponded completely to a choroidal metastasis in the left eye (Figure 3.2.1.8).

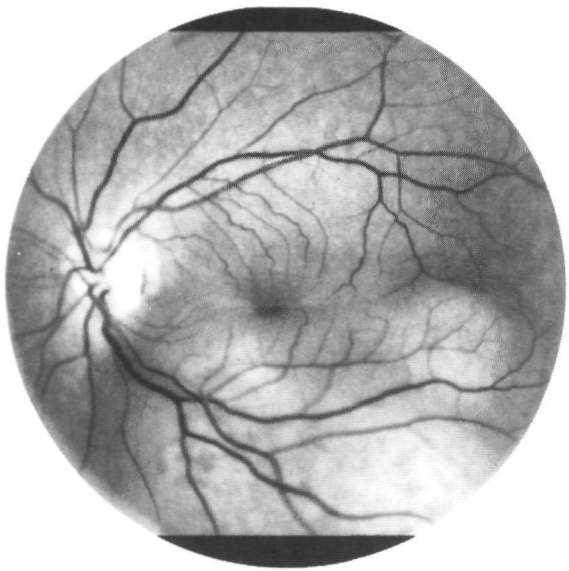


Figure 3.2.1.8 Fundus photograph of the left eye in patient 1057 showing a choroidal metastasis. The fovea is located at the tumour margin.

Fluorescein angiography showed no abnormalities in the right eye. On the left, simultaneously with the staining of the surrounding choroid, a fluorescence of the tumour appeared, with a grossly mottled pattern, the intensity of which increased slowly during the course of the examination. There was a distinct hypofluorescent margin but there were no hyperfluorescent spots nor a double circulation. No indications of a retinal detachment were present. The fluorescein angiogram, also, was suggestive of a fusion of three lesions (Figure 3.2.1.9). Conclusion: choroidal metastasis on the left.

At echography, no abnormalities were encountered on the right. Temporoinferiorly in the left eye a dome-shaped tumour was present, with a prominence of 4.0 mm, low-reflective, only moderately regular without choroidal excavation or vascularity, without signs of scleral extension or orbital shadowing and without a retinal detachment (Figure 3.2.1.10). These data corresponded best to the diagnosis of choroidal metastasis.

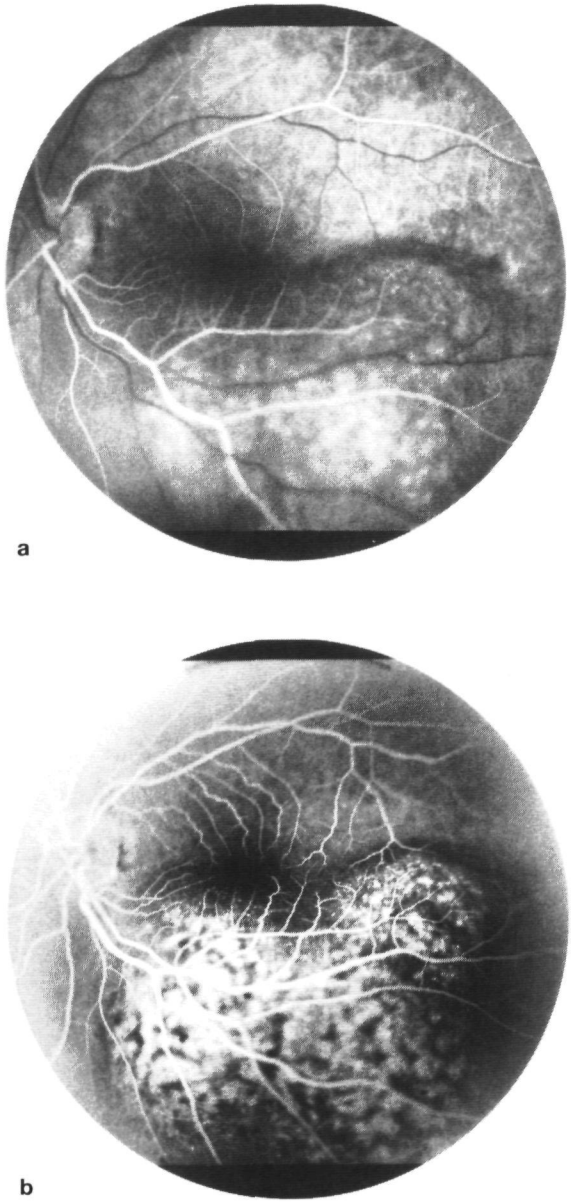


Figure 3.2.1.9 Fluorescein angiogram of the left eye of patient 1057. a. Arterial phase with fluorescence of the tumour of almost the same intensity as the surrounding choroid and mottled hyperfluorescence. b. Venous phase with hypofluorescent margin.

At electro-oculography, the following values were found for the various parameters:

OD: Iv 700 μV; Dt 425 μV; Lp 1000 μV; ratio 2.35; A value +198.

OS: Iv 500 μV; Dt 450 μV; Lp 763 μV; ratio 1.70; A value +58.

Conclusion: abnormal EOG on the left, best fitting a melanoma.

At the 100 Hue test, 176 errors were indicated on the right (within normal) and 328 on the left (significantly abnormal).

Accordingly, there was a large choroidal metastasis in the left eye, 10 months after a thorough ophthalmological examination at which no abnormalities had been established. The tumour had led to a hypermetropization of 2.0 diopters.

The patient was referred to the Department of Radiotherapy for irradiation of the metastasis. A CT scan of the orbit revealed a hyperdensity at the tumour site.

Starting 25 February 1991, the patient was irradiated by means of a linear accelerator (6 MV) through one lateral beam with a total dose of 30.0 Gy in 10 fractions of 3.0 Gy in two weeks.

On 26 February 1991 she came to our ophthalmological outpatient department for a check-up. On that occasion, just as four weeks previously, a visual acuity of 0.6 was determined. However, the hypermetropization had increased from 2.0 to 3.5 diopters. Echography revealed that the prominence of the tumour also had increased distinctly, from 4.0 to 5.5 mm. This demonstrated rapid growth of the metastasis.

Two weeks after the start of the radiotherapy the hypermetropization had stabilized compared with February and the prominence of the lesion had decreased by 0.5 mm. From that time, the positive effect of the radiotherapy became increasingly clear (Table 3.2.1.1; Figure 3.2.1.10).

Table 3.2.1.1 *Course of optimal visual acuity, refraction and prominence in the left eye of patient aged 66 years with a choroidal metastasis from breast cancer*

	20.03.90 *	29.01.91 **	28.02.91 ***	19.03.91	09.04.91	07.05.91	04.06.91	02.07.91
Optimal visual acuity:								
	0.8^{+}	0.6^{-}	0.6	$0.6^{\cdot}$	0.8	0.6	0.6	0.8
Spherical equivalent optimal refraction:								
	+1.75	+3.75	+5.25	+5.25	+4.62	+3.75	+3.25	+3.0
Prominence: (mm)								
	-	4.0	5.5	5.0	3.5	4.0	3.0	2.5

** no abnormalities found; ** diagnosis of choroidal metastasis; *** one day after start of radiotherapy*

Thus, after local irradiation a distinct decrease of the prominence of the metastasis was observed; the optimal visual acuity was unchanged with reduction of the required correction. The visual acuity with patient's own correction increased in the process from 0.125 in April 1991 to 0.16 in May, 0.25 in June and 0.4 in July. Five months after the start of the radiotherapy, therefore, a beneficial effect of the irradiation still persisted.

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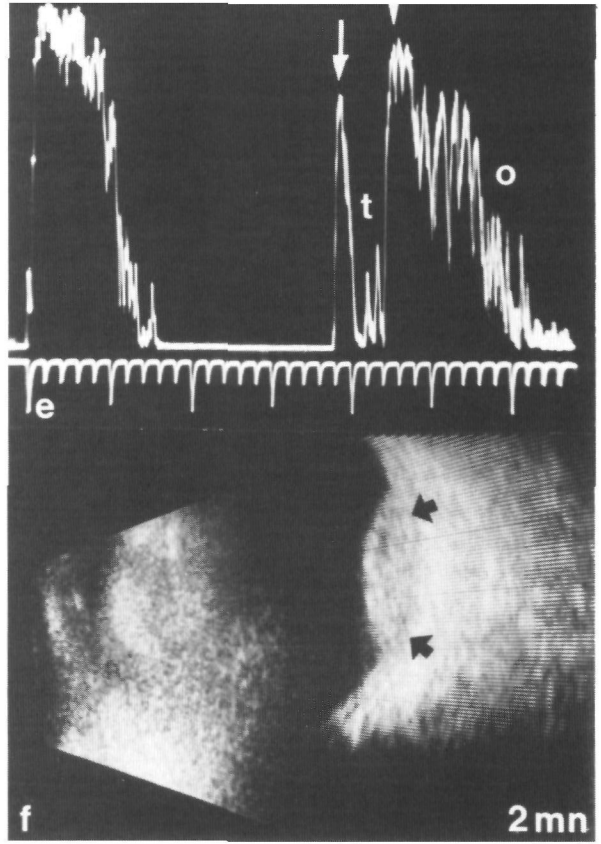
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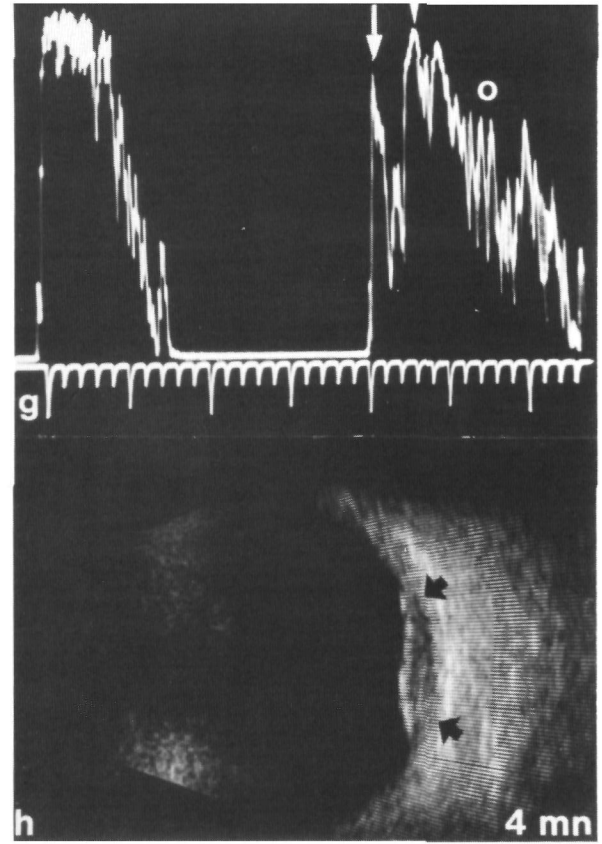
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At repetition of the fluorescein angiography in April 1991, the image had changed only little from that of January. Only the fluorescence pattern had grown more grossly mottled and less regular.

In the right eye, the various control examinations revealed no abnormalities and the optimal visual acuity remained stable at 1.0.

Because of the detection of the choroidal metastasis, the treatment with tamoxifen was discontinued in February 1991. In June, cutaneous metastases were observed after which treatment with aminoglutethimide was instituted.

Accordingly, a little over one year after the diagnosis of breast cancer in this patient, a choroidal metastasis was detected in the left eye. Shortly after the diagnosis of the mammary tumour, the patient had already undergone an extensive ophthalmological examination in the context of this study of uveal metastases, at which examination no abnormalities had been observed. Ten months later, a metastasis was found to have developed in the left eye. The tumour showed rapid growth and responded well to radiotherapy. During this treatment, the prominence of the tumour decreased distinctly and the visual acuity with patient's own correction increased. The optimal visual acuity remained stable at 0.6 to 0.8 while the hypermetropization decreased. Five months after the start of the radiotherapy a distinct effect of the irradiation continued to be present.

Patient 1078

In August 1988, in a postmenopausal woman aged 53 years a carcinoma was diagnosed mediosuperiorly in the left breast (T2NOMO) which was treated with a modified radical mastectomy according to Madden. Subsequently, the patient was irradiated over the parasternal lymph nodes. Oestradiol receptor testing gave a positive, progesterone receptor testing a low positive result.

In March 1990, hepatic metastases were established and three months later, pulmonary and bone metastases as well. Because of the extensive hepatic metastases, chemotherapy in the form of CMF was instituted. The patient spontaneously reported being troubled intermittently by decreased vision in the left eye, present for some time. In view of these symptoms and of the start of the chemotherapy, the patient according to protocol was referred to our ophthalmological outpatient department.

We saw the patient for the first time on 31 July 1990. She complained about blurred vision in both eyes since five months, especially in the left eye. In addition, since the start of the chemotherapy, she had suffered from burning eyes. She did not suffer from spots before the eyes, visual field defect, photopsia, ocular pain or diplopia.

At perimetry according to Donders, no abnormalities were observed in either eye. The Amsler test was unimpaired on the right, on the left central metamorphopsia was established.

The visual acuity in the right eye was:

without correction:	0.6
with patient's own correction (+0.5 sph -2.0 cx 105°):	1.0
with optimal correction (+0.5 sph -1.0 cx 95°):	1.0

The visual acuity in the left eye was:

without correction:	0.3
with patient's own correction (+0.5 sph -2.0 cx 85°):	0.16
with optimal correction (-0.5 sph -1.5 cx 80°):	0.3

Old records showed that previously the patient had had a visual acuity of 0.8 in both eyes with her own glasses.

Externally, no abnormalities were seen in either eye, especially no conjunctival or scleral hyperaemia or dilated vessels.

At slit lamp examination the corneas of both eyes were clear and no cells or Tyndall were observed in the anterior chamber. The iris was normal; in particular no metastases were present. The lenses showed symmetrical slight increases of opacity. In the vitreous no cells or Tyndall were established. Applanation tonometry gave 10 mm Hg on the right and 8 mm Hg on the left.

At ophthalmoscopical examination there were no abnormalities on the right apart from a few scattered exudates. In the left eye temporally from the macula extending into the periphery, a large light-coloured dull yellowish-orange tumour was present with a mottled surface (Figure 3.2.1.11). No lipofuscin pigment on the tumour surface was observed, nor haemorrhages on or round the tumour or in the vitreous. Peripherally to the lesion there was a folded serous retinal detachment. Temporoinferiorly a small naevus was observed. The optic disk was not well delimitated. The findings as a whole indicated a solitary choroidal metastasis in the left eye.

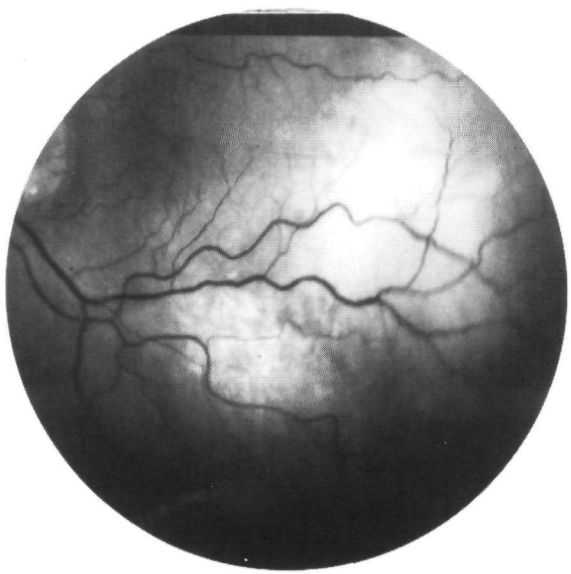

Figure 3.2.1.11 Fundus photograph of a choroidal metastasis in the left eye (patient 1078).

At fluorescein angiography the right eye showed no abnormalities, apart from the exudate already observed at ophthalmoscopy. In the left eye, 14 seconds after injection of the fluorescein and simultaneously with the staining of the retinal arteries, a staining developed in the lesion below the macula in the form of a few tumour vessels. In the process the other parts of the tumour initially remained dark but from the venous phases it locally developed an irregular hyperfluorescence in the form of a grossly mottled pattern which was superimposed on the hypofluorescence. The area with the tumour vessels immediately below the macula, on the other hand, in its entirety developed a mottled hyperfluorescent pattern and in the late phases showed a nearly completely diffuse hyperfluorescence. Nasally to the disk and temporoinferiorly, a few hypofluorescent areas were observed. The tumour was not surrounded by a hypofluorescent margin, nor were hyperfluorescent spots observed. The serous retinal detachment was described at fluorescein angiography as well (Figure 3.2.1.12). Conclusion: choroidal metastasis in the left eye.

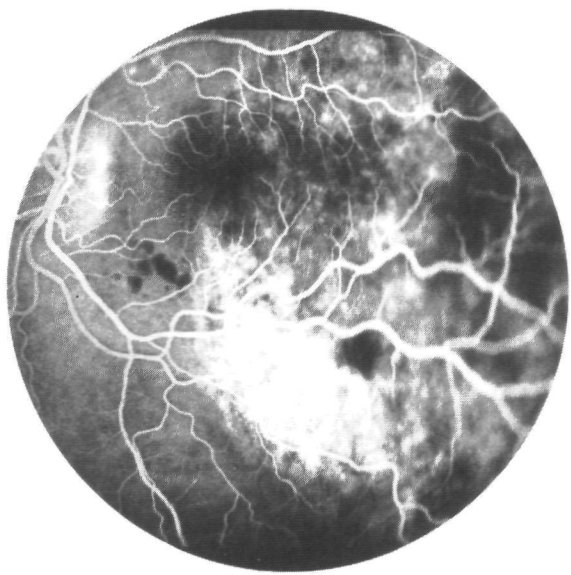

Figure 3.2.1.12 Fluorescein angiogram in the venous phase showing grossly mottled fluorescence of the choroidal metastasis in patient 1078.

At echography no abnormalities were established on the right. Temporally, in the left eye a flat to dome-shaped irregular mid-reflective tumour was observed with a prominence of 5.0 mm and a very large base (>20 mm) without choroidal excavation, vascularity or signs of scleral invasion or extraocular extension, and with a doubtful orbital shadow. The serous retinal detachment was confirmed echographically as well (Figure 3.2.1.13). Diagnosis: choroidal metastasis.

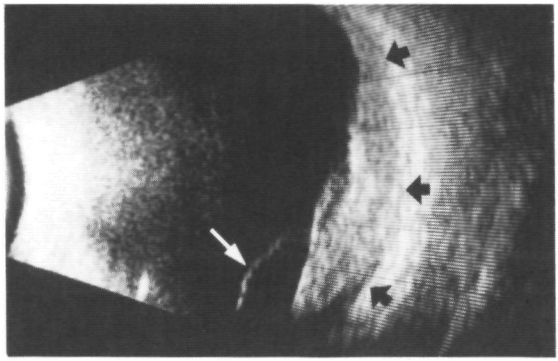

Figure 3.2.1.13 B-mode echogram of a 5.0 mm prominent choroidal metastasis (black arrows) with secondary retinal detachment (white arrow) without choroidal excavation.

At electro-oculography the following values were found for the various parameters:

OD: Iv 500 μV; Dt 400 μV; Lp 813 μV; ratio 2.03; A value +153.

OS: Iv 700 μV; Dt 613 μV; Lp 600 μV; ratio 0.98; A value -372.

Conclusion: abnormal EOG on the left, corresponding best to a melanoma.

Perimetry revealed a slight central decrease of the sensitivity on the right. On the left there was an absolute scotoma superiorly as well as an enlarged blind spot with in addition a decrease of the central sensitivity. The localization of the scotomas did not accord with the site of the tumour.

At the 100 Hue test, 104 errors were indicated on the right (within normal) and 524 on the left (significantly abnormal) with an axis between deutan and tritan.

The diagnosis made was a solitary choroidal metastasis of breast cancer in the left eye; the patient was referred to the radiotherapist for irradiation of the intraocular tumour. This was started on 13 August 1990, two weeks after the detection of the choroidal metastasis, using a linear accelerator (energy 13 MeV). A total dose of 30.0 Gy was administered in 10 fractions of 3.0 Gy in two weeks, via a lateral beam. No side effects were noted.

At control examination one week later, visual acuity in the right eye proved to have remained stable at 1.0 with patient's own correction. On the left, the optimal visual acuity was 0.4^{++} with a correction of +1.25 sph -1.0 cx 65°. At ophthalmoscopy, there were no abnormalities in the right eye, in the left no changes had occurred apart from an increase of the serous retinal detachment. The echographic image was stable.

Two months after the start of the radiotherapy, a subjective improvement of the visual acuity was present. Objectively, the visual acuity in the right eye was 0.8 with patient's own correction (no further correction possible) and 0.3 in the left eye with patient's own correction (no further correction possible). The anterior segment showed no abnormalities in either eye. Ophthalmoscopically, bilateral papilloedema was observed. On the right, apart from the exudates, no further abnormalities. On the left, the tumour had

decreased in prominence but the retinal detachment had become more extensive. Echography, also, revealed bilateral papilloedema. The prominence of the choroidal metastasis in the left eye had decreased from 5.0 mm to 3.0 mm, the retinal detachment had increased. Accordingly, after radiotherapy subjectively there was some improvement of the visual acuity, objectively stabilization of the visual acuity and a decrease of the prominence. Because of deterioration of her general condition, the patient did not return to our ophthalmological outpatient department after October 1990.

In spite of the chemotherapy, ascites developed and further progression of the bone metastases. Therefore the chemotherapy was switched to courses of Adriamycin (doxorubicin) and cyclophosphamide. This failed to influence the progression of the condition. From January 1991, the patient's clinical condition quickly grew worse and she died on 17 February 1991. No autopsy was performed. In the course of the disease, no clinical indications of the presence of cerebral metastases had been observed.

In this patient with breast cancer, therefore, a solitary choroidal metastasis situated temporally in the left eye was diagnosed. Ophthalmological examination was only carried out after the patient complained spontaneously of reduced eyesight, which symptom had been present long before known metastasization of the disease elsewhere in the body had developed. This emphasizes the importance of a concise ophthalmological anamnesis in patients with a malignancy.

The intraocular metastasis responded well to local radiotherapy with preservation of the eyesight and decrease of the prominence. However, in spite of the chemotherapy, distinct progression of the malignancy elsewhere in the body occurred and the patient died seven months after the detection of the intraocular metastasis.

3.2.2 Discussion concerning uveal metastases

In all five patients with uveal metastases the tumours were localized in the choroid. In four patients the metastasis was detected at the first ophthalmological examination. In one patient, the first examination revealed no abnormalities and the choroidal metastasis was only observed at a control examination one year later. During that year the patient had been treated with tamoxifen almost continuously. This apparently had failed to prevent the development of a uveal metastasis. In one other patient, also, a metastasis had developed in spite of systemic treatment.

In two of the five patients with uveal metastases the intraocular lesion at the moment of detection was found already to have gone into partial regression.

In one patient cutaneous and hepatic metastases developed in spite of treatment with tamoxifen. At that time there also were complaints about the eyesight which, however, subsided after resumption of tamoxifen in combination with fluorouracil. When we examined the patient three months later we diagnosed a choroidal metastasis. This abnormality had probably been the cause of the earlier complaints. The combination of tamoxifen and fluorouracil had already caused the lesion to go into partial regression. Ophthalmologically, therefore, an expectative policy was pursued.

In a second patient a treatment with tamoxifen had been instituted only two weeks before the ophthalmological examination, in connection with progression of the disease. The uveal metastases discovered at that moment appeared already to have gone into partial regression. Since it would appear that the duration of the systemic treatment at the time had been too short for such an effect it may be speculated that a 'spontaneous regression' had been involved here. Since the lesion was still partially active, radiotherapeutic treatment of the choroidal metastasis was started.

It is interesting to note that in three of the five patients with metastases the reason for referral was a change of treatment. One patient (with a metastasis in regression) had no complaints about visual acuity even at the ophthalmological examination. The other patient with a metastasis in regression complained of itching eyes. In a third patient, finally, no complaints were known at the time of referral but on specific history-taking complaints were nevertheless found to be present.

Of the two patients with known ophthalmological complaints, one was referred for that reason alone and the other also in connection with a change of treatment.

The mean visual acuity at the time of detection of the choroidal metastases in these five patients was 0.63 (range 0.20-1.25).

All five patients were suffering from already extensively disseminated breast cancer which at the time of the ophthalmological examination showed progression. Two of the five patients died within the period with which the prospective study was concerned.

3.2.3 Further ophthalmological description of the study group

Of the 102 patients with breast cancer ***without*** uveal metastases, 16 (16%) were referred to our outpatient clinic in connection with ophthalmological complaints. The most frequently mentioned complaint was decrease of the visual acuity (Table 3.2.3.1).

Table 3.2.3.1 *Signs and symptoms in 16 patients with breast cancer without uveal metastases referred because of ophthalmological complaints*

Sign or symptom	* N
Decrease of visual acuity	13
Burning eyes	2
Epiphora	2
Diplopia	2

** total number exceeds 16 because of patients with multiple signs or symptoms*

Accordingly, 86 patients were referred for some other reason than ophthalmological complaints, namely in connection with an initial ophthalmological examination or because of a change of the systemic treatment. However, 21 of these 86 patients when asked specifically in the ophthalmological outpatient department proved to have complaints after

all. Of these complaints, the main ones were decrease of the visual acuity and a burning sensation in the eyes (Table 3.2.3.2).

Of these 21 patients, eight had primary and 13 advanced breast cancer.

Table 3.2.3.2 *Signs and symptoms in 21 patients with breast cancer without uveal metastases referred because of reasons other than ophthalmological complaints*

Sign or symptom	* N
Decrease of visual acuity	11
Burning eyes	9
Visual field defect	3
Photopsia	3
Diplopia	1
Muscae volitantes	1
Ocular strain	1

** total number exceeds 21 because of patients with multiple signs or symptoms*

In all, therefore, ophthalmological complaints existed not only in four of the five patients with choroidal metastases but also in 37 of the 102 patients without metastases in the uvea. The causes of the complaints in these 41 patients are listed in Table 3.2.3.3. Complaints were present in 15 of the 44 patients (34%) with primary breast cancer and in 26 of the 63 patients (41%) with advanced breast cancer.

Table 3.2.3.3 *Cause of ophthalmological complaints in 41 patients with breast cancer*

	Patients	
Cause of complaints	N	%
Choroidal metastasis	4	* 10
Cataract	8	20
Membrane	1	2
Abnormalities in refraction	3	7
Stenosis lacrimal ducts	1	2
Retinal degeneration	1	2
Carcinomatous meningitis	1	2
No ophthalmological cause known	22	** 54

** in a fifth patient with a choroidal metastasis no signs or symptoms were present, ** because of poor general condition in one patient only limited ophthalmological examination possible*

In eight patients a sight-impairing cataract was the cause of the complaints. Within the study period one patient was operated for this reason. In one patient, after-cataract caused impairment of the vision for which she was subjected to YAG laser treatment. The mean visual acuity in these nine patients was 0.51 (0.30-0.80). Slight increases of the opacity of the lens were also present in 29 other patients.

Abnormalities of refraction were diagnosed in three patients. In two patients these could be corrected adequately and a prescription for glasses was given. One patient had variable refraction without clear cause for which she is being followed up.

One patient since the start of a treatment with fluorouracil and tamoxifen suffered from epiphora which proved to be due to occlusion of both lacrimal points. Although the lacrimal points could be opened surgically, the lacrimal ducts were also occluded and the symptoms persisted.

In one patient thin atrophic retinal areas were observed in both eyes, with in the left eye a small defect. These retinal degenerations were surrounded by laser coagulates following which the visual acuity in both eyes remained stable at 1.0.

In the last patient, extensive ophthalmological abnormalities were present. She was referred because of decrease of the visual acuity and a pupil not reacting to light on the left. She also complained of spots before the eyes and ocular pain on the left. Vision in the right eye reportedly was also reduced. Visual acuity was 0.4 in the right and 1/300 in the left eye, both without correction and in both with no further correction possible. On the left, the pupil was partly dilated and reacted to light directly but not consensually. On the left there was a ptosis to halfway the pupillary aperture. On the right, the ocular movements were slightly restricted in all directions. On the left, abduction was almost completely abolished, elevation and downward gaze greatly limited and adduction virtually normal.

Ophthalmoscopy revealed papilloedema in the right eye without further abnormalities of the fundus. On the left there were no abnormalities.

At echography a diffuse thickening round the optic nerve was seen in both eyes but more pronounced in the left than in the right eye, possibly due to metastastic infiltration of the sclera or the orbit directly behind the globe.

In view of this involvement of several cranial nerves and indications of pressure on the optic nerve, the probability diagnosis of carcinomatous meningitis was made. At CT scanning no abnormalities of the cerebrum and orbits were observed apart from a central cortical atrophy. The lumbar puncture was traumatic. No malignant cells were observed in the cerebrospinal fluid.

In one week the ptosis increased further and marked chemosis of the conjunctiva on the left developed. In spite of the fact that no distinct metastases were found, radiotherapeutic treatment of the base of the skull was decided upon for neurological reasons. The orbits were included in the radiation field, in connection with the orbital abnormalities and the progression of the clinical picture. In spite of the irradiation, the ptosis increased further an a distinct proptosis developed as well. Echographically no changes were established. On local antibiotic treatment the chemosis initially increased further but subsequently abated. The patient died one month after the initial ophthalmological examination. No autopsy was performed.

In this patient orbital metastases may have been present.

Apart from five choroidal metastases, 15 other patients with breast cancer showed pronounced ophthalmological abnormalities. In all, therefore, ophthalmological abnormalities were present in 20 of the 107 patients examined (19%). In all cases these lesions had not been known previously. The mean visual acuity in these patients was 0.67 (0.20-1.25).

In 22 patients with breast cancer who had ophthalmological complaints no distinct abnormalities could be found. The clinical condition of one woman was too poor for an adequate ophthalmological examination.

Of the other 21 patients, 13 complained among other things about reduced visual acuity and eight of burning eyes. All but three of these patients were being treated systemically at the time of the examination. Eleven were being treated with CMF, four with tamoxifen combined with fluorouracil, two with tamoxifen alone and one, with CMF and aminoglutethimide. Of tamoxifen and fluorouracil, in particular, ophthalmological side effects are known to occur (Griffin and Garnick, 1981; Vizel and Oster, 1982; Fraunfelder and Meyer, 1983; Imperia et al., 1989). This systemic therapy may have been the cause of the ophthalmological complaints. The mean visual acuity in these patients was 1.11, ranging from 0.80 to 1.25. However, no distinct relationship existed between the complaint and the nature of the systemic therapy.

Of the 26 patients with advanced breast cancer and ophthalmological complaints, four (15%) were found to have choroidal metastases.

In the entire group of 107 patients with breast cancer the mean visual acuity was 0.95 (SD 0.30; median 1.00; range 0.12-1.60).

The mean intraocular pressure in the 107 patients was 13.4 mm Hg, ranging from 6.0 to 21.0 mm Hg (median 14.0; SD 3.4). In other words, raised intraocular pressure was never encountered.

In three patients, abnormalities were observed during perimetry according to Donders. These were one patient with a choroidal metastasis, one with cataract and one, with after-cataract.

Abnormalities at Amsler testing were established in eight patients, two of them with metastases. Two other patients had cataracts and in four patients, no underlying ophthalmological abnormalities could be found.

3.3 Discussion and conclusions

During a period of 28 months we examined 107 successive patients who came for control examination in the outpatient clinic for Internal Medicine because of breast cancer which had been given primary surgical treatment. These included 44 patients with primary breast cancer (41%) and 63 patients with advanced breast cancer (59%). In all, uveal metastases were diagnosed in five of the 107 patients (5%); they were localized in the choroid in all cases. These five patients at that time were in a progressive phase of the disease with extensive dissemination already present. Uveal metastases therefore were diagnosed in 8% of the patients with advanced breast cancer and never in patients with primary breast cancer. Four of the five patients had ophthalmological complaints. In two patients, the uveal metastasis at the time of the examination appeared already to have gone into partial regression.

Albert et al. (1967) over a period of 24 months examined 213 patients with various disseminated malignancies. They observed choroidal metastases in five patients (2.3%). In four of these patients the metastasis originated from breast cancer (n=52), in one from lung cancer (n=50). Choroidal metastases therefore were present in 8% of the examined patients with breast cancer.

Mewis and Young (1982) examined 250 patients with breast cancer. The length of time during which the study was carried out was 7.5 years. Patients with known dissemination as well as patients without metastases were examined. Choroidal metastases were encountered in 67 patients (27%): 58 of the 152 patients with ophthalmological symptoms (38%) and nine of the 98 asymptomatic patients (9%).

The percentages found by us, 5% of all patients with breast cancer and 8% of patients with advanced breast cancer, in which uveal metastases were diagnosed, are in agreement with the findings of Albert et al. (1967). Mewis and Young (1982), however, observed metastases far more frequently. We are unable to explain this discrepancy adequately. Admittedly, the proportion of patients with ophthalmological symptoms in the population of Mewis and Young was higher, namely 61%. In our study group, this category accounted for only 39%. Also, the duration of our study was substantially shorter. Of the 67 patients with choroidal metastases of Mewis and Young, 22 were examined only once; in one-half of the cases because of the short duration of observation before death. The investigators do not state what proportion of the total study population with breast cancer was examined more than once or whether perhaps a large proportion of these patients were followed up over a long period of time which might explain the more frequent occurrence of uveal metastases. In this connection it should also be noted that these authors give only a very limited description of the composition of the patient population.

In our prospective study, ophthalmological complaints were established in a large number of the patients with breast cancer examined, viz. in 41 of the 107 patients (38%). The complaints most frequently mentioned concerned deterioration of the visual acuity or burning eyes. In 20 of these patients (19% of the total study population), distinct ophthalmological abnormalities were established. Apart from choroidal metastases, these

were sight-impairing cataracts in most cases. In a few patients the symptoms were brought about by abnormalities of refraction. In the remaining patients major abnormalities were present in the form of complete occlusion of the lacrimal ducts, retinal degeneration and carcinomatous meningitis possibly with orbital metastases. In one patient, the clinical condition was too poor for adequate investigation of the complaints.

In the 21 patients without a clear ophthalmological cause of the complaints, systemic treatment (in 18 patients) may have been responsible. However, no distinct correlation was found between any particular therapy and the ophthalmological symptoms.

Mewis and Young (1982) encountered ophthalmological complaints in a larger proportion of the patients with breast cancer (61%). Choroidal metastases were established in one-third of these patients. The authors omit to mention the causes of the complaints in the remaining patients.

In a large proportion of the patients with advanced breast cancer in our study group, therefore, there were ophthalmological complaints which in one-half of the cases were due to a distinct ophthalmological abnormality. It is therefore of crucial importance that such complaints should be taken seriously and the patients be referred to an ophthalmologist for examination. In over one-half of these cases no ophthalmological complaints were known to the referring internist at the time of the referral for this prospective study. It was only during the visit to the ophthalmological outpatient department that these complaints were made clear. It is therefore advisable in patients with a malignancy to enquire specifically after ophthalmological symptoms and, if these are present, to refer the patient to an ophthalmologist. This is especially important in patients with progression of the malignancy because in them the probability of presence of a uveal metastasis is highest. However, specifically ophthalmological abnormalities may also occur in other patients with a malignancy.

If only patients with ophthalmological symptoms are referred, a small proportion of existent uveal metastases may escape notice. Since these lesions are asymptomatic and during systemic therapy already instituted will not necessarily cause complaints in the future, either, they are clinically of limited importance and do not justify the screening for uveal metastases of all truly asymptomatic patients.

The above data concern patients with breast cancer. This is the malignancy in which uveal metastases are diagnosed most frequently. In patients with other malignancies, however, intraocular metastases may also develop, although in smaller proportions. Whether ophthalmological abnormalities occur as frequently in these patients as in patients with breast cancer is not known. If, however, visual symptoms occur in such patients, the possibility of presence of uveal metastases or of other ophthalmological abnormalities should always be taken into account.

Good visual acuity is important for everyone. This applies more in particular to patients who, because of their disease, have a reduced quality of life in any case. This study has proved that in many of these patients visual symptoms may occur which are often due to distinct ophthalmological abnormalities, including metastases in the uvea. In the majority of the cases these abnormalities can be treated with good functional results, thereby contributing to improvement of these patients' quality of life.

Summary

In this thesis an attempt is made to present as complete a description as possible of the ophthalmological aspects of uveal metastases in order, where possible, to improve the diagnostics and treatment and thus to contribute to these patients' quality of life.

The study consists of three parts. In the first part, an extensive review is presented of the literature on uveal metastases. The second part deals with the results of a retrospective study of intraocular tumours and lesions suspicious for tumours, with emphasis on uveal metastases. The third part concerns a prospective study in patients with breast cancer, with the objective to determine the frequency of ophthalmological symptoms and of uveal metastases in these patients and to consider to what extent screening for ophthalmological abnormalities is advisable.

Part 1: Review of the literature

The earliest publication on uveal metastases is a treatise by Perls from 1872 concerning the histological findings in a patient with lung cancer. Hirschberg in 1882 published the first clinical description of a choroidal metastasis.

Regarding the pathogenesis of uveal metastases much remains uncertain. Metastases can only reach the uvea via a haematogenous route. The uvea receives its blood supply from the short and long posterior and from the anterior ciliary arteries, which are branches of the ophthalmic artery. The choroid receives most of its blood through the 20 short and in part through the two long posterior ciliary arteries. The four anterior ciliary arteries together with the two long posterior ciliary arteries supply the anterior uvea (ciliary body and iris) with blood. Owing to this vascularization, ophthalmological metastases are localized most frequently in the choroid. Apart from circulatory factors, however, local environmental factors also play a part in the development of uveal metastases. Uveal metastases concern extracerebral localizations.

Uveal metastases are the most frequently occurring, although not the most frequently diagnosed intraocular tumours. The primary tumour is usually breast cancer. Metastases of lung cancer are observed much less frequently, and those of other malignancies only rarely. The question why the primary tumour is so often breast cancer cannot be answered unequivocally. Uveal metastases according to several authors only occur áfter the development of pulmonary metastases and simultaneously with cerebral metastases.

The interval between the diagnosis of the primary tumour and that of the uveal metastasis is approximately three to four years, depending on the nature of the primary tumour. In 10 to 46% of the patients the detection of the uveal metastasis precedes that of the primary tumour. This happens only rarely in patients with breast cancer and frequently in patients with lung cancer.

In connection with the frequent occurrence of breast cancer as the primary tumour most patients with uveal metastases are of the female sex. The mean age is between 50 and 60 years. Uveal metastases are rarely described in children.

The most frequent complaint of patients with uveal metastases is decrease of the visual acuity. Defects of the visual field are also established regularly. Inflammatory reactions and raised intraocular pressure are described in patients with metastases in the anterior segment. A small proportion of the patients has no complaints.

Ophthalmoscopically, a metastasis is described in general as a flat, round to oval, light-coloured lesion with a mottled surface situated temporally in the posterior pole of the eye. In the literature bilateral and multiple lesions are described with various percentages. The tumour is frequently accompanied by a secondary retinal detachment and sometimes by intraocular haemorrhages. Dark-coloured metastases are also described, especially in patients with lung cancer. Metastases in the iris are predominantly small diffuse lesions, light in colour, and with vessels on the tumour surface. Ciliary metastases are described only sporadically.

At fluorescein angiography, no pathognomonic pattern is observed. In early phases of the examination, the tumour as a rule remains hypofluorescent, with spotty staining in the arteriovenous phase and a diffuse late fluorescence. Hyperfluorescent spots are described regularly.

Echographically, a metastasis characteristically is a flat tumour with a relatively large base, a high irregular infrastructure and often without choroidal excavation or vascularity. Metastases of lung cancer are frequently low-reflective.

Other examination techniques are applied only infrequently. At CT scanning and MRI variable images are observed. Perimetry may reveal a relative or absolute scotoma. Electro-oculographically an abnormal ratio is described. Puncture or biopsy might be useful in case of diagnostic doubt.

Differential-diagnostically, a choroidal metastasis has to be distinguished particularly from (amelanotic) malignant melanoma, naevus and haemangioma.

The choroidal melanoma in a number of cases can be distinguished adequately from metastases. This is the case in unilateral and solitary melanomas with frequently pronounced pigmentation, possibly a mushroom shape and the echographic characteristics of low regular reflectivity, choroidal excavation and vascularity. At fluorescein angiography differentiation is difficult and the picture shows many similarities to that of uveal metastases. Other methods of examination make no essential contributions.

Naevi of the choroid are flat and predominantly darkly pigmented and in general show no growth. At fluorescein angiography, no staining of the tumour is observed in most cases. If a scotoma is present it is nearly always relative. Electro-oculographically, naevi can be distinguished adequately from metastases in the choroid.

Choroidal haemangiomas are unilateral and solitary, and have an orange-red salmon colour with frequently a typical thickened and cystoid retina and a characteristic fluorescein-angiographic pattern. At echography they show high reflectivity and, just as in CT scanning, sometimes calcium deposits.

Choroidal metastases have also to be differentiated from lymphoproliferative and inflammatory conditions, from serous and haemorrhagic detachments of the retina, the retinal pigment epithelium or the choroid, from subretinal haemorrhages and from other uncommon intraocular tumours.

Metastases in the ciliary body are extremely rare. The principal differential diagnosis is from malignant melanoma. In addition it has to be distinguished from leiomyoma and from medulloepithelioma.

A metastasis in the iris has to be differentiated from amelanotic melanoma, from leiomyoma and from various inflammatory conditions.

The natural course of uveal metastases according to the literature is characterized by rapid growth of the lesions with further deterioration of the visual acuity.

Radiotherapy is the most widely used treatment of uveal metastases. Radiation in general is administered using a lateral or ventral beam with a total dose of 30 to 40 Gy. A favourable effect in the form of decrease of the tumour size and preservation or even improvement of the visual acuity is described in highly varying percentages. External irradiation of uveal metastases has only few side effects, apart from conjunctivitis which responds well to treatment.

Observation is justified only in patients who are in a terminal phase of their disease and in patients with a peripherally localized metastasis that does not directly threaten the eyesight, and which patients are being treated systemically with hormonal or chemotherapy. However, many uveal metastases have developed in spite of such systemic treatment.

Enucleation may be necessary in a patient with a painful blind eye. Mostly, however, enucleation is carried out under the erroneous diagnosis of malignant melanoma.

Treatment in the form of laser or cryocoagulation has been applied only incidentally.

The development of uveal metastases allegedly means a poor prognosis quoad vitam.

Part 2: Retrospective study

During a period of 20 years (November 1970 - November 1990) data were collected on 762 patients with intraocular tumours or lesions suspicious for tumour. These included 87 patients with a metastasis, 422 with a malignant melanoma, 27 with a haemangioma, 60 with a naevus, 25 with a retinoblastoma and 53 with miscellaneous intraocular lesions. In 88 patients the ultimate diagnosis remained unknown. The frequency of diagnosis of uveal metastases proved to have increased during the study period.

The uveal metastases originated from breast cancer in 60% of the patients, from lung cancer in 23% and from some other malignancy in 9%. In 8% of the patients the primary tumour was not known. In nearly one-quarter of the cases the uveal metastasis preceded the detection of the primary tumour. In most of these cases a metastasis from lung cancer was involved. In patients in whom the primary tumour was already known, the uveal metastasis proved to be the first sign of dissemination in 23% of the cases. No relationship with pulmonary or cerebral metastases could be demonstrated.

Of the patients with uveal metastases 75% were of the female and 25% of the male sex. The mean age was 57 years.

The metastasis was localized in the choroid in 83 patients, in the ciliary body in two and in the iris in one. In one patient, metastases were observed in the choroid as well as in the iris.

The signs and symptoms in patients with uveal metastases were of low specificity. Most concerned deterioration of the visual acuity. Slight reaction of the anterior chamber

occurred sporadically, mostly in patients with lung cancer and metastases in the anterior segment. A similar pattern of signs and symptoms was observed in our study group in other intraocular tumours. Naevi as a rule caused no symptoms.

Ophthalmoscopy in uveal metastases as a rule showed a yellowish-orange or cream-coloured choroidal tumour with a mottled surface. Multiple lesions were present in 33% of the patients, bilateral metastases were diagnosed in 29%. The tumour as a rule was localized temporally in the fundus. In nearly one-half of the cases the tumour was accompanied by a secondary retinal detachment. An intraocular haemorrhage was established in 15% of the patients. Metastases of lung cancer were often solitary, grey-coloured and consequently difficult to differentiate from malignant uveal melanomas. Metastases in the anterior segment in our study group originated from lung cancer in all cases. Malignant melanomas of the uvea were predominantly grey in colour and more prominent than metastases. Amelanotic tumours were also observed in our study group. Haemangiomas showed a characteristic salmon colour or a picture similar to that of uveal metastases. Naevi in the majority of the cases had a grey colour and were not accompanied by a retinal detachment. Ophthalmoscopically, uveal metastases appeared not to have clear pathognomonic features for the differential diagnosis from other tumours or lesions suspicious for tumour. Multiple and/or bilateral lesions were observed not only in metastases but also in retinoblastomas. Retinoblastomas, however, show a characteristic ophthalmoscopical image.

At fluorescein angiography, uveal metastases exhibited no specific pattern. In the early phases hypofluorescence was observed at the site of the lesion; in the venous phase the lesion stained with a finely or grossly mottled pattern of hyperfluorescence. In most cases a hypofluorescent margin round the tumour was observed, as well as hyperfluorescent spots on the tumour surface. The findings in melanomas were highly similar. However, in melanomas tumour vessels were observed more frequently. In haemangiomas, early staining of the tumour was observed as a rule with hyperfluorescent spots observed less frequently and tumour vessels more frequently than in metastases. In one-third of the patients characteristic sponge-like configurations were observed. Naevi in most cases were hypofluorescent in all phases of the fluorescein angiography.

Echographically, a metastasis in general was depicted as a flat or dome-shaped predominantly mid-reflective tumour mass with a large base and often, an irregular infrastructure. A noticeable aspect in metastases of lung cancer was the frequently low and regular reflectivity which is more typical of a uveal melanoma. In melanomas a choroidal excavation, vascularity and orbital shadow were described more frequently than in metastases, and in 23% of these patients the mushroom-shape characteristic of melanomas was observed. Haemangiomas showed a high-reflective dome-shaped tumour without choroidal excavation or vascularity. Naevi as a rule were hardly or not visible owing to the low prominence. Retinoblastomas showed a characteristic picture with high reflectivity and calcifications.

At perimetry metastases, melanomas and haemangiomas gave similar pictures, of a scotoma which as a rule was absolute. The inclination of this scotoma was significantly more frequently sloping in metastases than in melanomas. In naevi, visual field defects were encountered less frequently.

At electro-oculography, in uveal metastases an abnormal light peak, ratio and A value were registered. Metastases could be differentiated from naevi but not from melanomas.

With regard to other examination techniques, only few data were available in our study group. They appeared to make no essential contribution to the diagnostics of uveal tumours.

The diagnosis of uveal metastases was often difficult, especially in the case of metastases of lung cancer. In patients with lung cancer the uveal metastasis in one-half of the cases preceded the detection of the primary tumour. In patients with suspicion for an intraocular tumour it is necessary in all cases apart from the anamnesis to perform ophthalmoscopy, echography and fluorescein angiography and sometimes, electro-oculography as well. If the diagnosis cannot be made with certainty, the course of the condition should be followed up accurately. In addition, a general physical examination and chest X-ray have to be carried out to detect any primary tumours or metastases elsewhere in the body. When a uveal metastasis is suspected, mammography has to be carried out as well.

In most patients with uveal metastases (60%), radiotherapy was applied; in 22% the tumour was kept under observation, in 6% systemic therapy was administered, in 7% the eye was enucleated and in one patient the tumour was subjected to laser coagulation.

Radiotherapy in general consisted of a total dose of 30.0 Gy in 10 or of 40.0 Gy in 20 daily fractions via a lateral or, less frequently, a ventral beam and use was made of a linear accelerator or Co-60 equipment. Unfortunately, in many patients data on the evolution after irradiation were not available. After radiotherapy a decrease of the prominence was observed in 54% of the patients, stabilization in 10% and further growth in 12% (25% unknown). The visual acuity improved in 25% of the patients, remained stable in 37% and deteriorated further in 19% (19% unknown). The overall effect (on prominence as well as visual acuity) amounted to improvement in 65% of the patients, to stabilization in 12% and to deterioration in 12% (12% unknown). The effect of the irradiation on the visual acuity was correlated with the effect on the prominence and visual acuity prior to treatment. There was no correlation with the duration of the interval between time of diagnosis and start of irradiation, with the distance of the metastasis from the fovea, with presence or absence of a secondary retinal detachment or with the nature of the primary tumour. No statistically significant difference was established between the results of the 30.0 Gy and 40.0 Gy schemes. Side effects of radiotherapy were slight and mostly consisted of well-manageable conjunctivitis. Only once did a major side effect develop, in the form of acute glaucoma.

In 22% of the patients with uveal metastases an expectative policy was pursued, although radiotherapy had been advised in two thirds of the cases. The principal reason not to apply irradiation was a poor general condition of the patient.

In five patients, the effect of not previously instituted systemic therapy was awaited, with a positive result in four patients.

Enucleation as first therapy was performed six times: three times under the erroneous diagnosis of melanoma, twice because of uncertainty of the diagnosis and once because of intractible complications.

In one case, a choroidal metastasis was treated with laser coagulation, with a good result.

It is recommended to irradiate uveal metastases with a total dose of 30.0 Gy in 10 daily fractions via a lateral beam directed 5° occipitally or with use of a half-beam technique. If metastases are present in both eyes, parallel opposed beams are advised. In

metastases at the level of the equator, preference may be given to irradiation from ventral with protection of the lens and of the lacrimal gland. In patients who have small uveal metastases without retinal detachment, not impairing or directly threatening the visual acuity, and who have not yet been given systemic treatment, the effect of hormonal or chemotherapy may be awaited.

The median duration of survival of patients with a uveal metastasis was 9.7 months and was related to the nature of the primary tumour: 12.7 months in patients with breast cancer, 6.4 months in patients with lung cancer and 5.8 months in patients with one of the remaining primary tumours.

Part 3: Prospective study

In a period of 28 months (February 1989 - July 1991) repeated ophthalmological examinations were carried out in 107 female patients with breast cancer with metastases only in locoregional lymph nodes (N=44: primary breast cancer) or with distant metastases (N=63: advanced breast cancer).

At the time of the ophthalmological examination, 83% of these patients were being treated systemically with adjuvant or palliative hormonal and/or chemotherapy.

In five of the 63 patients with advanced breast cancer (8%), uveal metastases were observed, which in all cases were localized in the choroid. Metastases in the uvea were seen in not a single patient with primary breast cancer. In two of the five patients with uveal metastases, the lesions at the time of detection were found already to have gone into partial regression. Ophthalmological symptoms were present in four of the five patients. In all these cases the malignancy was already extensively disseminated. Of these patients, the case histories are described.

Eighteen of the 107 patients with breast cancer were referred in connection with ophthalmological symptoms. At examination at the ophthalmological outpatient clinic, however, ophthalmological complaints were found to be present in a total of 41 patients. These complaints consisted mainly of decrease of the visual acuity and burning eyes. They were found to be due to uveal metastases in four patients, to cataract in eight patients and to stenosis of the lacrimal ducts, to retinal degenerations and to carcinomatous meningitis in one patient each. In one-half of the patients with ocular complaints, however, no ophthalmological abnormalities could be demonstrated; in these patients, the systemic therapy may have been responsible for the symptoms.

From these data it can be concluded that complaints about the eyesight are present in a large proportion of the patients with breast cancer. The probability that these complaints are due to uveal metastases in patients with known distant metastases amounts to 15%.

Since ocular abnormalities are observed in such a large proportion of the patients with breast cancer, it is recommended in patients with a malignancy to enquire specifically about ocular complaints and, if these are present, to refer them to an ophthalmologist for further examination. Screening for uveal metastases in patients with primary breast cancer appears not to be justified. In patients with advanced breast cancer, and in patients with other disseminated malignancies, on the other hand, the possibility of development of uveal metastases should be constantly kept in mind.

Samenvatting

In dit proefschrift wordt getracht een zo compleet mogelijke beschrijving te geven van het oogheelkundig beeld van uveametastasen om daarmee de diagnostiek en behandeling zo mogelijk te verbeteren en zo een bijdrage te leveren aan de kwaliteit van leven van deze patienten.

Het onderzoek bestaat uit drie delen. In het eerste deel wordt een uitgebreid overzicht gegeven van de literatuur over uveametastasen. Het tweede deel behandelt de resultaten van een retrospectief onderzoek naar intraoculaire tumoren en voor tumor verdachte aandoeningen, waarbij de nadruk ligt op uveametastasen. Het derde deel betreft een prospectief onderzoek bij patienten met een mammacarcinoom met het doel de frequentie van voorkomen van oogheelkundige klachten en van uveametastasen bij deze patienten vast te stellen en te bezien in hoeverre screening op oogheelkundige afwijkingen bij hen zinvol is.

Deel 1: Literatuuroverzicht

De eerste publicatie over uveametastasen betreft een verhandeling van Perls uit 1872 omtrent de histologische bevindingen bij een patient met een longcarcinoom. Hirschberg publiceerde in 1882 de eerste klinische beschrijving van een chorioideametastase.

Over de ontstaanswijze van uveametastasen bestaat nog veel onzekerheid. Metastasen kunnen de uvea alleen via haematogene weg bereiken. De bloedvoorziening van de uvea geschiedt vanuit de korte en lange achterste en vanuit de voorste ciliair arteriën, welke zijtakken van de arteria ophthalmica vormen. De chorioidea ontvangt daarbij voornamelijk bloed via de 20 korte en voor een deel via de twee lange achterste ciliair arteriën. De vier voorste ciliair arteriën voorzien samen met de twee lange achterste ciliair arteriën de uvea anterior (corpus ciliare en iris) van bloed. Oogheelkundige metastasen zijn, als gevolg van de vaatvoorziening, het meest frequent in de chorioidea gelokaliseerd. Bij het optreden van uveametastasen spelen naast circulatoire factoren echter ook lokale omgevingsfactoren een rol. Uveametastasen betreffen extracerebrale lokalisaties.

Uveametastasen zijn de meest frequent voorkomende, hoewel niet de meest frequent gediagnostiseerde, intraoculaire tumoren. De primaire tumor is meestal een mammacarcinoom. Veel minder frequent worden metastasen van een longcarcinoom gezien en zelden van andere maligniteiten. Er bestaat geen eenduidige verklaring voor het zo frequent optreden van het mammacarcinoom als primaire tumor. Uveametastasen zouden volgens verschillende auteurs pas optreden ná het ontstaan van longmetastasen en tegelijk met hersenmetastasen.

Het interval tussen het ontdekken van de primaire tumor en van de uveametastase is ongeveer drie tot vier jaar, afhankelijk van de aard van de primaire tumor. In 10 tot 46% van de patienten gaat de uveametastase aan het ontdekken van de primaire tumor vooraf. Dit gebeurt slechts zelden bij patienten met een mammacarcinoom en frequent bij patienten met een longcarcinoom.

Samenhangend met het zo frequent optreden van het mammacarcinoom als primaire

tumor zijn de meeste patienten met uveametastasen van het vrouwelijk geslacht. De gemiddelde leeftijd ligt tussen de 50 en 60 jaar. Bij kinderen worden uveametastasen zelden beschreven.

De meest gehoorde klacht bij patienten met uveametastasen is een visusdaling. Daarnaast worden regelmatig gezichtsvelddefecten vastgesteld. Inflammatoire reacties en verhoogde oogdruk worden beschreven bij patienten met metastasen in het voorsegment. Een klein deel van de patienten heeft geen klachten.

Fundusscopisch kenmerkt een metastase zich over het algemeen als een vlakke, ronde tot ovale, licht gekleurde laesie met een mottig oppervlak welke temporaal in de achterpool van het oog is gelegen. In de literatuur worden bilaterale en multipele laesies in wisselende percentages beschreven. De tumor gaat frequent gepaard met een secundaire netvliesloslating en soms met intraoculaire bloedingen. Ook donker gekleurde metastasen worden beschreven, met name bij patienten met een longcarcinoom. Metastasen in de iris zijn overwegend kleine diffuse laesies, licht van kleur, en met vaten op het tumoroppervlak. Ciliaire metastasen zijn alleen als casuistiek beschreven.

Fluorescentie angiografisch wordt geen pathognomonisch beeld gezien. In vroege fasen van het onderzoek blijft de tumor meestal hypofluorescent om in de arterioveneuze fase vlekkig aan te kleuren met een diffuse late fluorescentie. Regelmatig worden hyperfluorescente spots beschreven.

Echografisch kenmerkt een metastase zich als een vlakke tumor met relatief brede basis, een hoge irregulaire infrastructuur, veelal zonder chorioidale excavatie of vasculariteit. Metastasen van een longcarcinoom zijn vaak laag reflectief.

Andere onderzoekstechnieken worden slechts weinig toegepast. Bij CT-scan en MRI wordt een variabel beeld gezien. Bij perimetrie kan een relatief of absoluut scotoom worden vastgesteld. Electro-oculografisch wordt een abnormale ratio beschreven. Punctie of bioptering zou zinvol kunnen zijn bij twijfel over de diagnose.

Differentiaal diagnostisch moet een chorioideametastase met name worden gedifferentieerd van het (amelanotische) maligne melanoom, de naevus en het haemangioom.

Het chorioideamelanoom kan in een aantal gevallen goed van metastasen worden onderscheiden. Het betreft dan unilateraal en solitair voorkomende melanomen met een veelal sterke pigmentatie, mogelijk een paddestoelvorm en echografische karakteristieken met een lage regulaire reflectiviteit, chorioidale excavatie en vascularitеit. Fluorescentie angiografisch is differentiatie moeilijk en vertoont het beeld vele overeenkomsten met dat van uveametastasen. Andere onderzoeksmethoden leveren geen essentiële bijdrage.

Naevi van de chorioidea zijn vlak, overwegend donker gepigmenteerd en vertonen over het algemeen geen groei. Bij fluorescentie angiografie wordt meestal geen aankleuring van de tumor gezien. Indien een scotoom optreedt is dit vrijwel altijd relatief. Electro-oculografisch zijn naevi goed te onderscheiden van metastasen in de chorioidea.

Chorioideahaemangiomen treden unilateraal en solitair op, hebben een oranje-rode zalmkleur met veelal een typische verdikte en cystoiede retina en een karakteristiek fluorescentie angiografisch patroon. Echografisch vertonen zij een hoge reflectiviteit en kunnen er, evenals bij CT-scan onderzoek, kalkafzettingen worden waargenomen.

Chorioideametastasen moeten tevens worden gedifferentieerd van lymfo-proliferatieve en inflammatoire aandoeningen, van sereuze en haemorrhagische loslatingen

van het netvlies, het retinale pigment epitheel of de chorioidea, van subretinale bloedingen en van andere weinig voorkomende intraoculaire tumoren.

Metastasen in het corpus ciliare zijn uiterst zeldzaam. De voornaamste differentiaal diagnose wordt gevormd door het maligne melanoom. Daarnaast moet worden gedifferentieerd van het leiomyoom en het medulloepithelioom.

Een irismetastase moet worden gedifferentieerd van het amelanotische melanoom, het leiomyoom en van verschillende inflammatoire aandoeningen.

Het natuurlijk beloop van uveametastasen wordt volgens de literatuur gekenmerkt door snelle groei van de laesies met verdere achteruitgang van de visus.

Radiotherapie is de meest geaccepteerde behandeling van uveametastasen. Over het algemeen wordt bestraald met een laterale of ventrale bundel met een totaal dosis van 30 tot 40 Gy. Een positief effect in de vorm van afname van de tumorgrootte en behoud of zelfs verbetering van de visus wordt in zeer wisselende percentages beschreven. Behalve een goed behandelbare conjunctivitis treden bij uitwendige bestraling van uveametastasen slechts weinig bijwerkingen op.

Observatie is alleen verantwoord bij patienten die in een terminale fase van hun aandoening verkeren en bij patienten met een perifeer gelegen metastase welke de visus niet direct bedreigt en waarbij de patient systemisch wordt behandeld door middel van hormonale of chemotherapie. Veel uveametastasen zijn echter ontstaan ondanks een dergelijke systemische behandeling.

Enucleatie kan noodzakelijk zijn bij een patient met een pijnlijk blind oog. Meestal wordt enucleatie echter verricht onder de foutieve diagnose maligne melanoom.

Therapie in de vorm van laser- of cryocoagulatie is slechts incidenteel toegepast.

Het optreden van uveametastasen zou op een slechte levensprognose wijzen.

Deel 2: Retrospectief onderzoek

Over een periode van 20 jaar (november 1970 - november 1990) werden de gegevens van 762 patienten met intraoculaire tumoren of voor tumor verdachte laesies verzameld. Het betrof 87 patienten met een metastase, 422 met een maligne melanoom, 27 met een haemangioom, 60 met een naevus, 25 met een retinoblastoom en 53 met overige intraoculaire aandoeningen. Bij 88 patienten is de uiteindelijke diagnose onbekend gebleven. De frequentie van diagnose van uveametastasen bleek in de onderzoeksperiode te zijn toegenomen.

Bij 60% van de patienten was de uveametastase afkomstig van een mammacarcinoom, bij 23% van een longcarcinoom en bij 9% van een andere maligniteit. Bij 8% van de patienten was de primaire tumor niet bekend. In bijna een kwart van de gevallen ging de uveametastase aan het ontdekken van de primaire tumor vooraf. Het betrof dan in de meeste gevallen een metastase van een longcarcinoom. Bij patienten bij wie de primaire tumor reeds bekend was, bleek de uveametastase in 23% van de gevallen het eerste teken van disseminatie te zijn. Er kon geen relatie met long- of hersenmetastasen worden aangetoond.

Van de patienten met uveametastasen was 75% van het vrouwelijk geslacht en 25% mannelijk. De gemiddelde leeftijd was 57 jaar.

Bij 83 patienten was de metastase in de chorioidea gelegen, bij twee in het corpus ciliare en bij één in de iris. Bij één patient werden zowel metastasen in de chorioidea als in de iris vastgesteld.

De klachten en verschijnselen bij patienten met uveametastasen waren weinig specifiek. Over het algemeen betroffen het klachten in de vorm van een visusdaling. Prikkelingsverschijnselen van het oog traden sporadisch op en werden meestal gezien bij patienten met een longcarcinoom en metastasen in het voorsegment. Een zelfde beeld van klachten en verschijnselen werd in onze onderzoeksgroep bij andere intraoculaire tumoren vastgesteld. Naevi veroorzaakten over het algemeen geen klachten.

Fundusscopisch werd bij uveametastasen meestal een geel-oranje of crème-kleurige chorioidale tumor vastgesteld met een mottig oppervlak. Bij 33% van de patienten waren multipele laesies aanwezig, bij 29% werden bilaterale metastasen vastgesteld. De tumor was over het algemeen temporaal in de fundus gelokaliseerd. In bijna de helft van de gevallen werd de tumor begeleid door een secundaire netvliesloslating. Bij 15% van de patienten werd een intraoculaire bloeding geconstateerd. Metastasen van een longcarcinoom waren vaak solitair, grijs van kleur en daardoor moeilijk te differentieren van maligne uveamelanomen. Metastasen in het voorsegment waren in onze onderzoeksgroep in alle gevallen afkomstig van een longcarcinoom. Maligne melanomen van de uvea waren overwegend grijs van kleur en meer prominent dan metastasen. Amelanotische tumoren kwamen in ons onderzoek eveneens voor. Haemangiomen toonden een karakteristieke zalmkleur of een met uveametastasen vergelijkbaar beeld. Naevi hadden in de meerderheid van de gevallen een grijze kleur zonder dat een netvliesloslating aanwezig was. Fundusscopisch leken geen pathognomonische differentiaal diagnostische kenmerken voor uveametastasen aanwezig te zijn ten opzichte van andere tumoren en voor tumor verdachte laesies. Multipele en/of bilaterale laesies traden behalve bij metastasen eveneens bij retinoblastomen op. Retinoblastomen vertonen echter een kenmerkend fundusscopisch beeld.

Bij fluorescentie angiografie was bij uveametastasen geen specifiek patroon aantoonbaar. In de vroege fasen werd een hypofluorescentie ter plaatse van de aandoening geconstateerd welke laesie in de veneuze fase aankleurde met een fijn- of grofvlekkig patroon van hyperfluorescentie. In de meeste gevallen werd een hypofluorescente rand om de tumor vastgesteld evenals hyperfluorescente spots op het tumoroppervlak. Het beeld bij melanomen vertoonde hiermee veel overeenkomsten. Wel werden bij melanomen vaker tumorvaten waargenomen. Bij haemangiomen werd meestal een vroege aankleuring van de tumor vastgesteld met minder vaak hyperfluorescente spots en vaker tumorvaten dan bij metastasen het geval was. Bij één derde van de patienten werden kenmerkende sponsachtige configuraties waargenomen. Naevi waren in de meeste gevallen hypofluorescent in alle fasen van de fluorescentie angiografie.

Echografisch beeldde een metastase zich over het algemeen af als een vlakke of bolvormige overwegend midreflectieve tumormassa met een brede basis en vaak een irregulaire infrastructuur. Opvallend bij metastasen van het longcarcinoom was de veelal lage en regulaire reflectiviteit die meer kenmerkend is voor een uveamelanoom. Bij het melanoom werd daarnaast frequenter een chorioidale excavatie, vasculariteit en orbitaschaduw beschreven dan bij metastasen en werd bij 23% van de patienten de voor melanomen kenmerkende paddestoelvorm vastgesteld. Haemangiomen lieten een hoog reflectieve bolvormige tumor zien zonder chorioidale excavatie of vascularitеit. Naevi beeldden zich door de geringe prominentie meestal niet of nauwelijks af. Retinoblastomen

vertoonden een karakteristiek beeld met een hoge reflectiviteit en kalkspatten.

Bij perimetrie werd bij metastasen, melanomen en haemangiomen een vergelijkbaar beeld vastgesteld van een scotoom dat meestal absoluut was. De helling van dit scotoom was bij metastasen beduidend vaker glooiend dan bij melanomen. Bij naevi werden minder vaak gezichtsveldafwijkingen vastgesteld.

Bij electro-oculografie werd bij uveametastasen een abnormale light peak, ratio en A-waarde geregistreerd. Metastasen konden wel van naevi, maar niet van melanomen worden gedifferentieerd.

Over andere onderzoekstechnieken waren in onze onderzoeksgroep slechts weinig gegevens beschikbaar. Zij leken geen essentiële bijdrage te leveren aan de diagnostiek van uveatumoren.

De diagnostiek van uveametastasen was vaak moeilijk, met name in het geval van metastasen van een longcarcinoom. Bij deze patienten met een longcarcinoom ging de uveametastase in de helft van de gevallen aan het ontdekken van de primaire tumor vooraf. Bij patienten met verdenking op een intraoculaire tumor moet, naast anamnese, in alle gevallen fundusscopie, echografie en fluorescentie angiografie worden verricht en eventueel electro-oculografie. Indien de diagnose niet met zekerheid kan worden gesteld dan moet het beloop van de aandoening nauwkeurig worden vervolgd. Daarnaast moeten een algeheel lichamelijk onderzoek en röntgenonderzoek van de thorax worden verricht om eventuele primaire tumoren of metastasen elders in het lichaam op te sporen. Bij verdenking op een uveametastase moet tevens mammografie worden verricht.

Bij de meeste patienten met uveametastasen (60%) werd radiotherapie toegepast; bij 22% werd de tumor geobserveerd, 6% werd met systemische therapie behandeld, bij 7% werd het oog geënucleëerd en bij één patient werd de tumor met lasercoagulatie behandeld.

Bij radiotherapie werd over het algemeen een totaaldosis van 30,0 Gy in 10 of 40,0 Gy in 20 dagelijkse fracties toegepast via een laterale of, minder vaak, ventrale bundel en werd gebruik gemaakt van een lineaire versneller of Co-60 apparatuur. Bij veel patienten ontbraken helaas gegevens over het beloop na bestraling. Na radiotherapie werd bij 54% van de patienten een afname van de prominentie vastgesteld, bij 10% een stabilisatie en bij 12% verdere groei (25% onbekend). De visus verbeterde bij 25% van de patienten, stabiliseerde bij 37% en verslechterde verder bij 19% (19% onbekend). Het overall effect (op zowel prominentie als visus) hield bij 65% van de patienten een verbetering in, bij 12% een stabilisatie en bij 12% een verslechtering (12% onbekend). Het effect van de bestraling op de visus was gerelateerd aan het effect op de prominentie en aan de visus vóór behandeling. Er bestond geen relatie met het interval tussen het tijdstip van diagnose en de aanvang van bestraling, met de afstand van de metastase ten opzichte van de fovea, met de eventuele aanwezigheid van een secundaire netvliesloslating en met de aard van de primaire tumor. Er werd geen statistisch significant verschil gevonden tussen de resultaten van het 30,0 Gy en het 40,0 Gy schema. Bijwerkingen van radiotherapie waren gering en betroffen meestal goed behandelbare conjunctivitiden. Slechts één maal trad een ernstige bijwerking op in de vorm van acuut glaucoom.

Bij 22% van de patienten met uveametastasen werd een expectatief beleid gevoerd, hoewel in twee derde van de gevallen radiotherapie was geadviseerd. Voornamelijk kon bestraling niet worden toegepast in verband met de slechte algehele conditie van de patient.

Bij vijf patienten werd het effect van niet eerder ingestelde systemische therapie afgewacht met een positief resultaat bij vier patienten.

Enucleatie als eerst ingestelde therapie werd zes maal verricht: drie maal onder de foutieve diagnose 'melanoom', twee maal wegens onbehandelbare complicaties en één maal in verband met onzekerheid over de diagnose.

Eén maal werd een chorioideametastase met goed resultaat behandeld met lasercoagulatie.

Geadviseerd wordt uveametastasen te bestralen met een totale dosis van 30,0 Gy in 10 dagelijkse fracties via een laterale bundel die 5° occipitaal wordt ingeschoten of via een halve bundel techniek. Indien metastasen in beide ogen zijn gelokaliseerd worden parallelle opponerende bundels geadviseerd. Bij metastasen ter plaatse van de equator kan de voorkeur worden gegeven aan bestraling van ventraal met bescherming van de lens en de traanklier. Bij patienten met kleine uveametastasen zonder netvliesloslating welke de visus niet hebben aangetast of direct bedreigen en die nog niet systemisch zijn behandeld kan het effect van hormonale of chemotherapie worden afgewacht.

De mediane overlevingsduur bij patienten met een uveametastase was 9,7 maanden en was gerelateerd aan de aard van de primaire tumor: 12,7 maanden bij patienten met een mammacarcinoom, 6,4 maanden bij patienten met een longcarcinoom en 5,8 maanden bij patienten met één van de overige primaire tumoren.

Deel 3: Prospectief onderzoek

In een periode van 28 maanden (februari 1989 - juli 1991) werden 107 vrouwelijke patienten met een mammacarcinoom met metastasen alléén in locoregionale lymfeklieren (N=44: primair mammacarcinoom) of metastasen op afstand (N=63: gemetastaseerd mammacarcinoom) herhaaldelijk oogheelkundig onderzocht.

Ten tijde van het oogheelkundig onderzoek werd 83% van deze patienten systemisch behandeld met adjuvante of palliatieve hormonale en/of chemotherapie.

Bij vijf van de 63 patienten met een gemetastaseerd mammacarcinoom (8%) werden uveametastasen vastgesteld die in alle gevallen in de chorioidea waren gelegen. Bij geen enkele patient met een primair mammacarcinoom werden metastasen in de uvea aangetroffen. Bij twee van de vijf patienten met uveametastasen bleken de laesies op het moment van ontdekken reeds voor een deel in regressie te zijn gegaan. Bij vier van de vijf patienten bestonden oogheelkundige klachten. In alle gevallen betrof het reeds uitgebreid gemetastaseerde aandoeningen. Van deze patienten wordt de ziektegeschiedenis beschreven.

Achttien van de 107 patienten met een mammacarcinoom werden verwezen in verband met oogheelkundige klachten. Bij onderzoek op de polikliniek oogheelkunde bleek echter bij in totaal 41 patienten sprake te zijn van oogklachten. Deze klachten bestonden met name uit visusdaling en branderige ogen. Zij bleken bij vier patienten te berusten op uveametastasen, bij acht patienten op cataract en bij respectievelijk één patient op een stenose van de traanwegen, op retinale degeneraties en op een meningitis carcinomatosa. Bij de helft van de patienten met oogklachten konden echter geen oogheelkundige afwijkingen worden vastgesteld en was mogelijk de systemische therapie voor de klachten verantwoordelijk.

Op grond van deze gegevens kan worden geconcludeerd dat klachten van de ogen

in een hoog percentage van de patienten met een mammacarcinoom voorkomen. De kans dat deze klachten berusten op uveametastasen is bij patienten met reeds bekende metastasering op afstand 15 %.

Aangezien oogafwijkingen in een zo hoog percentage van de patienten met een mammacarcinoom werden vastgesteld, wordt geadviseerd bij patienten met een maligniteit gericht te vragen naar oogklachten en indien deze aanwezig zijn hen voor nader onderzoek naar een oogarts te verwijzen. Screening op uveametastasen bij patienten met een primair mammacarcinoom lijkt niet gerechtvaardigd. Bij patienten met een gemetastaseerd mammacarcinoom, evenals bij patienten met andere gemetastaseerde maligniteiten, moet men daarentegen voortdurend bedacht zijn op de ontwikkeling van uveametastasen.

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Dankwoord

Mijn dank gaat in eerste instantie uit naar mijn promotores, prof.dr. A.F. Deutman en prof.dr. F. Hendrikse en mijn co-promotores dr. L.V.A.M. Beex en dr. J. Hoogenhout voor al hun inspanning, steun en begeleiding. Ondanks hun eigen drukke werkzaamheden kon ik te allen tijde bij hen terecht.

De stafleden en arts-assistenten van de afdeling oogheelkunde bedank ik voor de grote interesse die zij voor mijn onderzoek hebben getoond en voor de hulp die ik daarbij van hen kreeg. In het bijzonder wil ik drs. A.M. Verbeek bedanken die met zijn enorme enthousiasme aan de wieg van dit onderzoek heeft gestaan. Ik keek altijd uit naar zijn wekelijkse echo-spreekuur, waarvan ik veel heb geleerd en waarbij ook tijd was voor luchtiger zaken. Ook dr. A.J.L.G. Pinckers ben ik bijzonder erkentelijk voor de gastvrijheid op zijn 'bijzondere' afdeling, zijn niet aflaatbare stroom van suggesties en zijn grote persoonlijke betrokkenheid.

De medewerkers van de afdeling Fotografie, en met name A.L. Aandekerk, H. Bongaarts en E.J. Steenbergen, hebben zorg gedragen voor de vele foto's in dit proefschrift, waarmee zij een onmisbare bijdrage aan dit boek hebben geleverd.

Dr.ir. J.M. Thijssen en drs. W. Brouwer bedank ik voor de adviezen en suggesties die zij ten aanzien van een aantal hoofdstukken hebben verleend.

Alle medewerkers van de afdeling oogheelkunde bedank ik voor de plezierige samenwerking. Liesbeth, bedankt voor jouw belangstelling en de gezellige tijd! Anja, Mariëtte en Yvonne, fijn dat jullie mij zo veel ruimte gaven om te werken! Yolanda, bedankt voor het wegnemen van een aantal logistieke obstakels.

Theo de Boo en Wim Lemmens bedank ik voor hun statistische adviezen en bewerkingen. Ook hun meedenken over andere facetten van dit onderzoek zijn van veel waarde geweest voor de totstandkoming van dit proefschrift.

Griet Henkes en Kees Visser bedank ik voor de voortreffelijke vertaling en de bijzonder plezierige samenwerking.

De medewerksters van het secretariaat Endocriene Ziekten bedank ik voor hun hulpvaardigheid bij het vergaren van patienten gegevens.

Alle oogartsen, internisten, radiotherapeuten, huisartsen en andere beoefenaars van de geneeskunde die mij informatie hebben verstrekt bedank ik voor hun medewerking.

Lieve Annelies, dank je wel.

Curriculum vitae

Hendrik Brink werd op 15 maart 1961 geboren te Valkenswaard. Na het behalen van het diploma OVWO aan het Kruisheren College te Uden, werd in 1980 een aanvang genomen met de studie geneeskunde aan de Katholieke Universiteit Nijmegen.

Als onderdeel van de postdoctorale studie geneeskunde verrichtte hij onderzoek naar de diagnostiek en therapie van chorioideametastasen (Drs. A.M. Verbeek) in de Oogheelkundige Kliniek van het Academisch Ziekenhuis Nijmegen St. Radboud (Hoofd: prof.dr. A.F. Deutman). Hiermee werd de basis gelegd voor dit proefschrift.

In oktober 1987 werd het artsexamen behaald. Aansluitend breidde hij voornoemd onderzoek uit met onderzoek naar de diagnostiek van uveamelanomen en naar de invloed van intraoculaire tumoren en autoimmuunprocessen op het electro-oculogram (Dr. A.J.L.G. Pinckers).

In de periode van 1 juli 1988 tot 1 januari 1990 werd de militaire dienstplicht vervuld als reserve-officier-arts bij het Provinciaal Geneeskundig Detachement Noord-Brabant met als standplaats Grave. In deze periode werd tevens een aanvang genomen met dit promotieonderzoek.

Sinds 1987 is hij getrouwd met Annelies van Ede.

Stellingen

behorende bij het proefschrift

Uveal metastases
A clinical survey

door

Hendrik M.A. Brink

Nijmegen, 24 januari 1992

1. Uveametastasen zijn de meest frequent voorkomende maligne intraoculaire tumoren

2. Uveametastasen dienen beschouwd te worden als extracerebrale gelokaliseerde uitzaaiingen

3. Van de beschikbare oogheelkundige onderzoekstechnieken dragen fundusscopie en echografie het meest bij aan de diagnostiek betreffende de aard van chorioidea-tumoren

Dit proefschrift

4. Electro-oculografie kan een bijdrage leveren aan de differentiaal diagnostiek van intraoculaire tumoren.

Brink et al.: Doc Ophthalmol 1990, 75: 329-334

5. De eerste keuze voor behandeling van symptomatische uveametastasen is bestraling met een totaal dosis van 30 Gy te geven in 10 dagelijkse fracties van 3 Gy

Hoogenhout et al.: Strahlenther Onkol 1989; 165: 375-379 / Dit proefschrift

6. Een afwachtend oogheelkundig beleid bij patienten met uveametastasen is alleen verantwoord bij kleine asymptomatische perifeer gelegen laesies welke niet gepaard gaan met een secundaire netvliesloslating

7. Screenend onderzoek naar de aanwezigheid van uveametastasen bij patienten met een mammacarcinoom die geen oogheelkundige klachten hebben, levert geen wezenlijke bijdrage aan de vroegdiagnostiek van deze afwijking Daarentegen is bij klachten oogheelkundig onderzoek in alle gevallen aangewezen

Dit proefschrift

8. Bij patienten met een gemetastaseerd mammacarcinoom die gunstig reageren op chemotherapie levert vroegtijdige beëindiging van deze behandeling geen bijdrage aan de verbetering van kwaliteit van leven.

Coates et al.: N Eng J Med 1987; 317: 1490-1495
Muss et al.: N Eng J Med 1991; 325: 1342-1348

9. Reductie van de ten aanzien van operatieve oogheelkundige ingrepen ter beschikking staande anaesthesietijd leidt niet tot een afname van het aantal oogoperaties, maar wel tot onaanvaardbaar lange wachttijden voor operaties waarvoor anaesthesie noodzakelijk is.

10. Het onderscheid tussen kijken en zien is nog te weinig bekend. Binnen de oogheelkundige oncologie kan dit leiden tot verwarring van bol met hol.

11. Conclusies welke alléén gebaseerd zijn op statistische bewerking van patientengegevens zeggen weinig over de onderzochte populatie maar des te meer over de onderzoeker.

12. De citatie-index voor medische literatuur nodigt uit tot manipulatie.

13. Geneeskunde laat zich niet tot kantooruren beperken. Promotie onderzoek evenmin.

14. Men hoeft een boek niet gelezen te hebben om ervan te houden.

ISBN 90-9004777-8