Department of Ophthalmology

The Development and Early Diagnosis of Primary and Disseminated Uveal Melanoma

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Academic Dissertation
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To my Wife and Daughters

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ORIGINAL PUBLICATIONS

This dissertation is based on the following publications on metastatic uveal melanoma. The original publications in the text will be referred to by their Roman numerals I-IV:

I   Eskelin S, Pyrhönen S, Summanen P, Prause JU, Kivelä T. Screening for metastatic malignant melanoma of the uvea revisited. Cancer 1999: 85; 1151-9.

II   Eskelin S, Pyrhönen S, Summanen P, Hahka-Kemppinen M, Kivelä T. Tumor doubling times in metastatic malignant melanoma of the uvea: Tumor progression before and after treatment. Ophthalmology 2000: 107; 1443-1449.

III   Eskelin S, Pyrhönen S, Hahka-Kemppinen M, Tuomaala S, Kivelä T. A prognostic model and staging for metastatic uveal melanoma. Cancer 2003: 97(2); 465-475.

IV   Eskelin S, Kivelä T. Efficacy of referral to treatment of primary malignant melanoma of the uvea in Finland. Br J Ophthalmol 2002: 86; 333-338.

ABBREVIATIONS

ALT	Alanine Aminotransferase (enzyme)
AP	Alkaline Phosphatase (enzyme)
AST	Aspartate Aminotransferase (enzyme)
CI	Confidence interval
COMS	The Collaborative Ocular Melanoma Study
CT	Computed tomography
DT	Doubling time
DTIC	Dacarbazine (chemotherapeutic)
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organization for Research and Treatment of Cancer
FAG	Fluorescein angiography
FNAB	Fine needle aspiration biopsy
GGT	Gamma Glutamyl Transferase (enzyme)
HLA	Human leukocyte Antigen
HR	Hazard ratio
HUCH	Helsinki University Central Hospital
IOP	Intraocular pressure
LBD	Largest basal diameter
LD	Lactate Dehydrogenase (enzyme)
LFT	Liver function test
MRI	Magnetic resonance imaging
MVD	Microvascular density
N/A	Not applicable
PAD	Pathologic-anatomical diagnosis
ROC	Receiver Operating Characteristics (curve)
TNM	Tumor-node-metastasis
TTT	Transpupillary thermotherapy
UNL	Upper normal limit of a serum enzyme level
US	Ultrasonography
UV	Ultraviolet

1. ABSTRACT

This study was undertaken to advance the understanding of development of metastatic uveal melanoma and to improve treatment and prognosis of patients. Two of the studies (I, IV) concentrated on minimizing delays in diagnosis of primary uveal melanoma and metastases. The second study (II) was carried out to understand and estimate the growth kinetics of tumors and timing of the crucial processes. Study (III) tried to address the problematic lead time bias and to identify independent prognostic factors in modeling survival after disseminated disease so that the results of treatment trials could be more efficiently reported and evaluated.

I. Annual screening programs for metastatic uveal melanoma are carried out to detect metastases early, when they are small and potentially easier to treat. It was shown that two thirds of the patients were diagnosed as asymptomatic when screening is annual, and that semiannual screening would detect up to 98% patients as asymptomatic. Abdominal US revealed definite metastases or led to a diagnostic CT scan, fine needle aspiration biopsy, or both in 89% of patients. The LFTs supported the findings of abdominal US which was superior to chest radiograms. As a result chest x-rays were dropped from the program.

II. The calculated doubling times were used to roughly predict the behavior of the metastases in the period prior to diagnosis. The calculated time of micrometastasis relative to the time of treatment of the primary tumor showed that the majority of primary tumors, assuming a constant growth rate, would have metastasized within 1 to 3 years before diagnosis and treatment.

III. The analysis showed that patients who participated in the annual screening to detect disseminated disease tended to survive longer after diagnosis of metastases. This difference could be due to lead-time bias. Until now, estimating the effect of lead-time bias and stratification of patients by their estimated prognosis in treatment trials has not been possible. A multivariate model was built and a table of predicted median survival time after diagnosis of metastases was compiled for clinically relevant combinations of Karnofsky index, serum AP level and the largest dimension of the largest metastasis which all were found to have independent predictive value.

IV. Is it possible to make the diagnosis of uveal melanoma earlier so as to decrease odds of metastasis? One eighth of our patients were asymptomatic and the primary tumor was diagnosed during a routine visit. In Finland, two thirds of patients with uveal melanoma sought help directly from an ophthalmologist whether they had symptoms or not. Their chance of being immediately referred and correctly diagnosed at first visit was 88% and 71%, respectively. The observed median delay of less than 4 months from the onset of symptoms of primary tumor to treatment may not represent a serious hazard to life, but a shorter delay could potentially salvage more useful vision and perhaps prevent some metastases from developing.

At the time of micrometastasis, the primary tumor was estimated to be small, but one that should easily be detected by ophthalmoscopy. Small tumors are more likely to escape detection as even large tumors are missed by ophthalmologists, or to be interpreted as nevi.

Uveal nevi may turn malignant. Follow-up of presumed nevi is ideally based on fundus photographs and, when the nevus is elevated, on ultrasonographic measurements. The tumors in our study were on average almost twice as large by LBD at diagnosis of uveal melanoma than initially, but their median volume was seven times bigger. Earlier growth was thus likely missed or disregarded which emphasizes the importance of referring small suspicious tumors for second opinion at an early stage. The estimates of early metastatic potential might perhaps also be viewed as an indication to reconsider the policy of following small suspicious pigmented tumors without treatment.

The inability of modern treatments of primary uveal melanoma and of current chemotherapy regimens for disseminated disease to notably improve prognosis calls for efforts to help the immune system to fight micrometastasis at an early stage and to develop other adjuvant therapies to be used at the time of the treatment of the primary tumor.

2. INTRODUCTION

Uveal melanoma – a threat to both vision and life – is a relatively rare cancer but the second most common type of primary malignant melanoma in humans and the most common primary intraocular malignancy.

Uveal melanoma develops from melanocytes situated in the most vascular part of the eye, i.e. the uvea. The uvea consists of the flat choroid which covers ¾ of the posterior segment of the eye between the white hard sclera and the seeing retina, the ciliary body which supports the lens and secretes aqueous humor in the anterior segment of the eye, and the iris.

Uveal melanoma is remarkable for its purely hematogenous dissemination and a tendency to metastasize to the liver.[49;89;157] Half of the patients die of metastasis within 15 years. Iris melanomas differ greatly from other uveal melanomas by better prognosis. Until the late 1970's, an eye with a uveal melanoma was enucleated and since then various radiation and other surgical therapies have been available. These new treatments have not improved prognosis.

The prognosis of metastatic uveal melanoma has been poor with a median overall survival from 2 to 9 months.[16;58;70;110] Although median survival of up to 24 months is now reported, the factors contributing to improved prognosis have not been critically analyzed.[43;75;113] Because many enrolled patients participated in regular screening and were asymptomatic, lead-time bias must be taken into account. So far, patients enrolled in treatment trials for metastatic disease have not been categorized and no tools have been available to adjust for differences in case mix between trials. This is extremely important when evaluating treatment effect in this typically rapidly progressing phase of the disease. For this reason, working formulation for staging of patients was developed.

A logical way to improve the survival of cancer patients is to diagnose their tumors earlier when they are small, to decrease the risk of metastasis. The delays in the diagnosis and treatment of primary uveal melanoma have been studied so far only in U.K. We do not know how much earlier diagnosis would be clinically effective.

The purpose of this study was to enlighten the prognostic significance of factors related to the screening program of patients with uveal melanoma and to present an estimation of the possible lead time bias in survival in treatment trials. In addition, critical evaluation of efficacy of both the current health care system to detect and treat primary tumors and the current screening program to detect metastases was called for in order to minimize treatment delays.

3. REVIEW OF LITERATURE

3.1. Epidemiology of uveal melanoma

Uveal melanoma affects from 6 to 12 patients per 1 million inhabitants per year in Caucasian populations.[18] Raivio et al. estimated in 1977 that during the years 1953-1973 the annual incidence in Finland was 5 per 1 million corresponding to a total of 25 patients per year.[109] According to more recent data the annual incidence in males and females varied from 7.5 to 11.0 and from 6.9 to 8.8 per million, respectively, during 1955-1994.[140] This apparent change may be due to the incompleteness of the Finnish Cancer registry in its early years in the 1950's. In Denmark, an annual incidence of 7.1 and in Sweden an incidence of 7.2 and, recently, up to 12 per million have been reported.[2;18;69] In large, age-adjusted series uveal melanoma is reported to be more common in males.[18;18;42] The higher rates in men may suggest an independent effect of gender or some unknown exposure that is more common among males.[42] In Finland, the difference between genders is inverse which may be due to the fact that females tend to survive longer and hence can develop more malignant tumors during their lifetime.

Melanomas of the skin and conjunctiva[150] have been increasing in frequency over the last several decades, while such a trend has not been proved as regards uveal melanoma.

Uveal melanoma is rarely bilateral. Singh and associates found eight patients with bilateral uveal melanoma in a clinical series of 4,500 cases.[133] No specific predisposing syndrome was identified other than ocular melanocytosis in two of the eight patients. The COMS group identified 10 bilateral uveal melanomas in a large clinical series of 8712 patients.[35] This results in an estimated incidence of 1 per 734 uveal melanoma patients.

Clinical metastases are evident in 0.2 – 2.5% of patients at the diagnosis of primary uveal melanoma.[35;99;153]

3.2. Predisposing Factors

3.2.1. Age

The mean age at diagnosis is 50-60 years.[42] The risk of uveal melanoma increases with age, but seems to level off after the age of 70, more so with females.[109] This is different from other adult cancers in which the risk increases with age.[42]

3.2.2. Race

Light complexion and blue eyes are also predisposing factors for increased risk for uveal melanoma.[42] Caucasians have more than 8 times greater risk of developing the disease compared with Africans.[42] The risk of uveal melanoma is also low in races of intermediate pigmentation like Orientals and native Americans.[25;42;132;154]

3.2.3. Nevi

A high number of nevi, especially dysplastic nevi, on the skin have been shown to increase the risk of cutaneous melanoma.[28] Uveal nevi seem to have low risk of progressing to uveal melanoma. The estimated incidence of choroidal nevi ranges from 3 to 20%.[158] Only rough estimates of the incidence of choroidal nevi transforming into uveal melanoma have been presented (1 in 15000).[158]

In case of small choroidal tumors, including nevi, the following high risk characteristics have been identified: presence of symptoms and subretinal fluid, tumor thickness greater than 2 mm, orange lipofuscin pigment over the tumor, and tumor margin touching the optic disc.[123;127] The COMS group has identified as additional risk factors larger basal diameter, and absence of drusen and retinal pigment epithelial changes adjacent to tumor.[144] Any one of these factors raises the risk for growth, which often is a sign of malignancy, the more so when occurring together. Shields et al. calculated the relative risk for growth to be 1.9 for one factor, 3.8 for 2 factors, 7.4 for 3 factors, 14.1 for 4 factors, and 27.1 for all 5 of their risk factors combined.[123]

3.2.4. Ocular and oculodermal melanocytosis

Ocular and oculodermal melanocytosis (nevus of Ota) are congenital pigmentary anomalies that typically involve at least episclera and uveal tract.[57] Gonder et al suggested that the ocular and oculodermal melanocytosis increase the relative risk for uveal melanoma by a maximum of 35 times.[57]

3.2.5. Sunlight exposure

Development of cutaneous melanoma has been linked to UV-light exposure. Because uveal melanomas develop from melanocytes, sunlight has been proposed as a risk factor. Contradicting evidence has been presented in favor and against the causative role of sunlight exposure in uveal melanoma, but the body of evidence favors little or no effect. If sunlight would increase the risk for uveal tumors, a general rise in incidence might be expected.[42] No

clear evidence has been presented that geographical latitude would have a consistent effect on incidence.[42;119] The incidence of uveal melanoma is not increased in xeroderma pigmentosum patients who are extremely sensitive to short ultraviolet wavelengths and develop cutaneous melanoma frequently.[102] The adult cornea and lens are effective UV-A and UV-B filters which allow virtually no transmission.[156] The juvenile lens, however, may transmit some UV radiation to the posterior segment of the eye.

Sunlight may also weaken systemic immune defense. In this case, increase in tumors would be expected, but this has not been evident.[42]

Three studies have compared sunlight exposure histories of uveal melanoma patients with those of controls. One identified sunlight as a risk factor, but of various exposure habits assessed only gardening and not protecting eyes while outside were significantly more common among patients.[149] The other did not found any association between sunlight exposure and uveal melanoma.[53] The third study identified intense exposure with increased risk but also contradictory association of birthplace below latitude 40 degrees N and outdoor work with a lower risk[119]

3.2.6. Tobacco

Smoking is suspected of altering immune defense mechanisms and may therefore enhance the growth of metastases among cancer patients. Smoking did not have any effect on the development of uveal melanoma metastases during the first years after the diagnosis of primary tumor.[40] As uveal melanoma is a slowly progressing disease, longer follow-up, up to 15 to 20 years, is needed to verify this.

3.2.7. Endocrinology

It has been suggested that pregnancy may enhance growth and metastases in melanoma.[41] However, large series of uveal melanoma patients fail to support this assertion.[125] A search for estrogen and progesterone receptors in choroidal melanoma showed no evidence for such receptors.[61;82;120]

3.3. Diagnosis

Uveal melanomas are solid intraocular tumors. Choroidal tumors are located between retinal pigment epithelium and sclera. Tumors can also arise from other parts of the uvea – from ciliary body and iris. The surface of some uveal melanomas particularly in the posterior pole shows a patchy orange pigmentation, which is lipofuscin in macrophages and retinal

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pigment epithelium. A secondary exudative retinal detachment adjacent to the choroidal tumor occurs frequently and this can be responsible partly for visual loss.[72] Usual symptoms are blurred vision and loss of visual field.[67] In addition, there can be retinal degeneration with pigmentary changes overlying the apex of the tumor. Frequently, a choroidal melanoma breaks through Bruch's membrane, extending into the subretinal space. The tumor can also grow through the retina and lead to intravitreous hemorrhages. While a circumscribed tumor is the most frequent configuration, uveal melanomas can take on a diffuse pattern in which large areas of the uveal tract are thickened. Melanomas can diffusely involve the ciliary body in a pattern called "ring melanoma". Such tumors can be difficult to diagnose because there is relatively little visible mass effect and ciliary body is a diagnostically difficult area of the eye.[23;34] In addition, patients with retinoinvasive diffuse melanoma have been reported.[73] It is a rarely diagnosed but distinct entity, different from circumscribed and most diffuse melanomas that may erode the overlying retina and infiltrate the optic nerve, but which do not invade non-adjacent retina.

The Collaborative Ocular Melanoma Study Group reports that clinical diagnosis by ophthalmic oncologist is accurate in over 98% of instances when tumor size is medium or large.[142] The smaller the tumor is, that the harder it is to diagnose it correctly when first seen. Many small tumors require follow-up to verify growth. Comprehensive indirect ophthalmoscopy or slit-lamp biomicroscopy are the main diagnostic methods supported by A- and B-scan ultrasonography, fluorescein angiography, indocyanine green angiography, and orbital CT-scan and MRI.

Ultrasound is particularly useful in the diagnosis of melanoma in eyes in which the posterior pole cannot be visualized directly. It is an inexpensive method which can give accurate measures and help in localization of the tumor. Uveal melanoma has also distinct echogram in which the reflectivity decreases linearly within the tumor in contrast to other uveal tumors. It is also an excellent follow-up method to document growth of small tumors and regression or relapse of treated tumors. High-frequency ultrasonography (ultrasound biomicroscopy) can be used in diagnosis of anterior tumors.[88]

FAG lends support to diagnosis but is not always required. Approximately two thirds of cases in one series showed a "double circulation" pattern, which is characteristic for uveal melanoma.[9] Indocyanine green angiography shows details of choroidal circulation more effectively. Combined with scanning laser confocal microscopy to study the tumor vasculature it may help in estimating the prognosis in the future.[95]

Patients are also examined thoroughly to verify the absence of other cancer.

Histologic or cytologic specimens are rarely obtained for diagnosis of uveal melanoma, in contrast to most other cancers.[130] This procedure may increase the risk of local spread and vision loss, and the sampled area may not be representative of the entire tumor.[51]

A biopsy is required if the diagnosis of uveal melanoma is in doubt and alternative diagnosis would lead to different treatment. The indications for biopsy should be carefully evaluated because of complications. A needle biopsy can be taken guiding the needle through sclera or cornea directly into the tumor.[15] This method may increase the risk of extraocular growth through the canal. Others take the biopsy through the vitreous cavity under visual control.[15] This method needs also intraocular infusion to control for possible hemorrhage. With this method, intraocular dissemination within the vitreous is possible.

Differential diagnoses that have to be considered are for instance metastasis to the eye (especially breast and lung cancer), choroidal nevus, melanocytoma, hemangioma, osteoma, uveitis, and retinal detachment. The confirmation of diagnosis of uveal melanoma is based on typical clinical or intraocular US findings and on the fact that no additional tumors are found elsewhere by imaging.

3.4. Screening and follow-up

The potential effect of early diagnosis and treatment of ocular melanoma should not be disregarded, especially as they might also allow better preservation of vision in eyes that are treated with conservative methods.[3;30;31] Because the incidence of uveal melanoma is low, it is not feasible to mass screen even the age groups which would be at highest risk of developing it.[42] Moreover, a comprehensive ophthalmologic examination would be needed instead of a simple screening test. Consequently, mainly patients with suspicious choroidal nevi and congenital melanocytosis are presently reviewed by many ophthalmologists and most ocular oncologists with varying intervals.[20;57]

The question of whether to follow up choroidal nevi to detect uveal melanoma earlier, to treat suspicious nevi immediately or to refrain from follow-up has been under debate.[20;123;127;144] The time schedule of the follow-up program is currently individualized.

How patients are diagnosed to have primary uveal melanoma and how they are referred to treatment is known in detail only for the United Kingdom. [3;30;31;67] Out of 50 patients, 72% had symptoms at diagnosis, the rest were diagnosed during the course of a routine eye test. 42% of patients were considered to have experienced delays in diagnosis and treatment and they were more likely to have been treated by enucleation than eye-conserving method.[3;67]

Table 1. The number of practicing dispensing opticians, optometrists, general practitioners, and ophthalmologists per 100 000 inhabitants in Finland and U.K.

Profession	Finland	U.K.
Dispensing optician[*,†]	25.7	6.7
Optometrists[†]	N/A[‡]	14.5
General practitioner[¶,§]	69.5	57.3
Ophthalmologist[¶,**]	8.8	1.4

[*]The Association of Finnish Opticians

[†] The College of Optometrists (www.college-optometrists.org)

[‡] Ophthalmic opticians and optometrists not currently licensed, not applicable

[§] StatBase® (www.statistics.gov.uk)

[¶]Finnish Medical Association

[**]Dernouchamps J-P. UEMS Compendium of Medical Specialists 2000, Kensington Publications Ltd

United Kingdom has a special type of health care system based on many ophthalmic opticians and general practitioners and relatively few ophthalmologists (Table 1).[3;67]

In Finland, ophthalmic opticians and optometrists are not licensed, and patients contact an ophthalmologist, a family physician, or a dispensing optician instead (Table 1). The dispensing opticians, who do not do dilated fundus examinations, are obliged to refer their customer to a physician if they suspect disease. When the diagnosis of an intraocular tumor is made or suspected, staging examinations are carried out usually at regional hospitals and the patient is thereafter referred as a rule to a single ocular oncology service in Helsinki.

3.5. Treatment – Primary Tumor

Irradiation with plaque brachytherapy is the main treatment method of uveal melanoma in Finland.[139] The plaque is shielded to radiate only towards eye. It is surgically placed on the sclera, over the uveal tumor, and is removed later after the calculated total radiation dose has been delivered. Several different isotopes have been used including cobalt 60, ruthenium 106, iodine 125, and palladium 103.[48]

Typically ruthenium plaques are used for melanomas less than 6 mm in height, and those that are over 6 mm in height are usually treated with iodine plaques. Enucleation is done

routinely when conservative therapy is not technically feasible. Transpupillary thermotherapy (TTT) with infrared diode laser is mainly used as adjuvant therapy and may be useful in selected cases.[122] Compared with enucleation the patient will often have useful vision remaining and will not often suffer from cosmetic disturbances. Patients may also benefit psychologically from the salvation of the globe but some may be more comfortable when "the evil" is taken away by enucleation. The treatment should be based on knowledge and understanding between the patient and ocular oncologist.[29]

The management of uveal melanoma is similar in the other Nordic countries, especially in Sweden and Denmark.[121] In other European countries enucleation, proton beam radiotherapy, gamma-knife surgery, and transscleral local resection are also used.[32;87] In U.S. most patients are treated with brachytherapy, proton beam radiotherapy, and enucleation.[130]

In Finland the management of the primary uveal melanoma is centralized into the Oncology Service of the Department of Ophthalmology, Helsinki University Central Hospital. Few patients, about 5% with advanced tumors, are still treated by enucleation in regional hospitals. In these cases the removed eye is often sent to the Ocular Pathology Laboratory, HUCH, which co-operates closely with the Oncology Service.

3.6. Prognosis

Single dose ruthenium and iodine brachytherapies have a 63-80% and 93% 5-year probability for local tumor control, respectively.[77;96;100] In few cases supplementary laser photocoagulation is performed.[65] Proton beam irradiation has a 97% 5-year probability for local tumor control.[59] Compared with proton beam irradiation, brachytherapy has less adverse effects outside globe. Because the radiation dose is delivered externally, anterior structures receive more radiation with proton beams than they would with a plaque.[48]

Local recurrence is reported to be a risk for systemic metastasis.[24;59;65] Even though regrowth is not clinically evident, viable cells are reported to be present after radiation with unknown potential for dissemination.[103;115] The possibility of cells losing their viability and still remaining positive for cell proliferation markers was addressed in Schilling's study.[115]

Secondary enucleation is done to the few patients with uveal melanoma who experience pain, phtisis, uncontrollable IOP or their tumor is resistant to the irradiation.[126]

The visual acuity and field of vision are in danger despite the shrinkage of the tumor. Radiation retinopathy is an unavoidable complication and it develops a median of 2 to 3 years after treatment.[100] The prognosis of the vision is dependent on the size and location of the tumor relative to optic disc, macula and lens, the radiation dose, and the dose rate.[48;124]

Regional disease is relatively rare nowadays as primary tumors are diagnosed early enough not to have extraocular extensions. If extraocular extensions are present in advanced uveal melanomas orbital exenteration may be justified but likely does not prevent metastasis.[129]

Malignant melanoma of the uvea is a cancer that disseminates in one half of cases within ten years.[16;21;37;69;78] Modern diagnostic and therapeutic methods have not been able to reduce the frequency of dissemination as compared with enucleation.[12;36]

3.7. Prognostic Clinical factors in Primary Uveal Melanoma

3.7.1. Size

Large studies have been published to detect prognostic factors in uveal melanoma patients. The strongest clinically detectable unfavorable factor is the large size of the tumor.[114;117] Although there is dispute about how the size should be measured – LBD, height, or volume – it seems that LBD would have the strongest significance on prognosis.

3.7.2. Location

The location of primary tumor is an independent prognostic factor of survival.[76] The survival with ciliary body tumor is poor compared with choroidal tumor, or especially with iris tumor which are small and metastasize extremely rarely.[76] Anterior location of the tumor,[118] especially the location of the anterior margin of the tumor is associated with poor survival.[117]

3.7.3. Gender

Male gender was an independent unfavorable factor with respect to time to systemic metastases.[114]

3.7.4. The Growth Rate

A high growth rate of uveal melanoma predicts poor tumor related survival.[24] The fast shrinkage of the tumor after treatment may be a sign of rapid cell cycling and indicates potentially highly malignant cell types and poor survival.[8;11;56;74] Although the high growth rate or fast cell cycling are not necessarily linked to dissemination capacity of the cells, these patients seem to have worse survival prognosis than patients with slowly deteriorating tumors.

Contradictory results based on sarcomas have been presented which suggest that some rapidly growing cancers are less radiation sensitive.[138] The uveal melanoma metastases

developing several years after primary tumor diagnosis are more likely to be associated with slowly progressing tumors.[128]

3.7.5. Exudative retinal detachment

Exudative retinal detachment due to the tumor is associated with tumor size and microvascular loops and networks but does not have independent prognostic significance on survival after adjusting for these factors.[72]

3.7.6. Histologic and Cytologic factors

Even though the staining methods have developed and more accurate diagnosis and prognosis could be established the clinical relevance of the pathologic findings of the primary tumor has diminished because of irradiation treatments. Before irradiation, almost all eyes were enucleated and pathological diagnosis was available. In case of secondary enucleation after irradiation the tumor is usually degenerating and pathological analysis does not reflect situation at diagnosis.

The tumors are categorized by their cell type by Callender classification and its later versions; spindel cell, mixed cell, and epithelioid cell melanomas. The spindel cell melanomas are slowly growing and have better survival prognosis than others. Epithelioid tumors seem to grow faster and be more likely to metastasize.[117]

3.7.7. Microvascular patterns

Intratumor vascular architecture can be estimated with loops, nets, and networks formed by extracellular vascular-like structures. Microvascular patterns of the primary tumor have been studied by Folberg et al, Seregard et al, and Mäkitie et al and they have presented quite clearly the independent prognostic significance of them.[50;51;80]

3.7.8. MVD

High microvascular density (MVD), a widely applied morphologic measure of vascularization, independently predicts death in several types of cancer and has been linked to shorter survival in uveal melanoma patients.[52] In a multivariate analysis of uveal melanoma specific survival study the MVD retained its value as independent predictor as did the microvascular patterns.[81]

3.7.9. Immunological factors

The late onset of metastatic disease could be explained partly by immunological factors. The effect may be mediated by tumor infiltrating and circulating immune cells such as lymphocytes and macrophages.[39;81;148] Increase in the count of intratumor macrophages predicts also unfavorable prognosis.[81]

Human leukocyte antigens (HLA) are essential for immune cells to recognize neoplastic cells.[79] Of HLA class I antigens, low expression of HLA-A and HLA-B antigens has been associated with better survival.[19;68]

3.7.10. Cytogenetics

Although family history of uveal melanoma is very rare, a few cases may have an inheritable component.[42] Genetic predisposition has not been studied widely and no concluding evidence of inherited genetic mutations that would increase risk for uveal melanoma exists.

Genetic studies of tumor cells have identified loss of chromosome 3 as a sign of poor survival.[1;105;135;155] In addition loss of 6q, and gain of 8q were significantly associated with poor overall survival.[1;135] In contrast, in the study of White et al. patients having chromosome 6 abnormalities seemed to have longer survival.[155] These findings concerning abnormalities in chromosome 6 are preliminary and require further studies to solve these contradictory results.

3.8. METASTASES

The ability to metastasize is the main difference between benign and malignant tumors. A benign tumor can eventually convert into a malignant one due to DNA changes in subclonal cell lines. These changes in DNA might predispose tumor cells to other mutations and lead to uncontrolled growth and invasion. The larger the tumor is, the more cell-cycles have taken place and thus the risk for changes has increased. These changes may lead to more malignant cell lines.

To disseminate malignant cells have to be able to infiltrate and invade surrounding tissues. Malignant tumors can spread locally and disseminate via lymphatics and hematogenously to distant locations depending on the type of cancer and the location of the primary tumor.

Most malignancies will develop metastatic tumors in characteristic locations and organs. This can be anticipated and taken into account when treating patients. Breast cancer e.g.

usually metastasizes to axillary lymph nodes and later to lungs and bone. When treating breast cancer surgically at least sentinel nodes are removed for pathologic examinations.

Usually cancers that disseminate hematogenously develop metastases in lungs. Despite the mechanical pressure and circulatory logic, cells of certain cancers such as uveal melanoma seem to have a natural propensity to home themselves into other suitable locations such as the liver.

3.8.1. Epidemiology of Disseminated Uveal Melanoma

Malignant melanoma of the uvea causes clinical metastases in one half of patients within ten years.[16;21;37;69;78] It is often a slowly growing, early metastasizing cancer. Diagnosis is usually based on fine-needle aspiration biopsy (FNAB) or thru-cut biopsy, more so with patients who are eligible for treatment. Other patients are diagnosed based on typical clinical and imaging findings, progression, absence of any evidence of second cancer, and in few, not earlier than at autopsy.

The metastases are diagnosed on average 2 to 5 years after primary tumor.[58;60;114;159]

3.8.2. Zimmermanns' theorem and COMS

In 1978 Zimmermann and McLean postulated that the enucleation or some factor related to it promotes dissemination of melanoma cells into the systemic circulation.[92;159]

They based their hypothesis on the finding that initially low mortality rises abruptly following enucleation, reaching a peak by the second year.

They suspected that either the operation might interfere with the immune defense system and lead to survival and accelerated growth of the disseminated cells or the mechanical stress of the operation on the eye globe would enhance dissemination. Presumably, compression on the globe during the enucleation procedure caused tumor cells to exit via the vortex veins, thus causing metastasis.

In early 1980's radiation therapy made its way into the everyday management of uveal melanoma. Some clinicians still rigorously believed in the superiority of enucleation.[84;86] Zimmermanns' theorem was widely discussed and the question whether to treat patients with enucleation or irradiation led to a massive clinical multicenter trial in USA. The Collaborative Ocular Melanoma Study was launched. The patients were divided into three groups; small, medium, and large tumors. Those with small tumors (up to 3 mm in elevation) were observed for tumor growth; if growth was sufficient to place the tumor in the medium group and if the patient remained eligible and willing, the eye was randomized for treatment. The two main

questions of the study were: - would adjuvant external beam therapy be of benefit with enucleation of large melanomas, – would iodine 125 brachytherapy versus enucleation of medium melanomas be of benefit.[36]

The accrual of 1317 patients ran 11 years and the patients were followed up from 2 to 13 years.[35;36] The preliminary results were published in 2001, and the survival did not differ between the treatments.[36] These results strengthen the idea of dissemination taking place before the primary tumor is treated but they do not address the possibility of not treating.

3.8.3. Metastatic Behavior

The behavior of uveal melanoma differs greatly from that of its cousin, cutaneous melanoma (melanoma of the skin). Cutaneous melanoma usually spreads to regional lymph nodes, skin, lungs, bones, and in one fifth of cases into liver. As the uveal melanoma is situated in the intraocular space which is devoid of lymphatics it disseminates solely hematogenously and the regional lymph nodes are spared. Delayed dissemination is rather frequent.[21;37;69] Its propensity to disseminate first to the liver has been designated one of the most unusual phenomena in tumor biology.[44]

Usually, hepatic metastases are initially present in 40 to 60% of patients with disseminated uveal melanoma.[17;21;44;58;90;110] Eventually the liver is involved in up to 95% of patients, [5;17;58;69;70;110;139;145] even though up to 50% have later developed also extrahepatic metastases, most often in the lungs, bone, skin, and brain. [5;17;21;58;69;70;110;145]

3.8.4. Metastatic Disease - Diagnosis

The diagnosis of metastatic uveal melanoma is usually suspected after imaging by chest radiograms, abdominal ultrasonography (US), computed tomography (CT), and magnetic resonance imaging (MRI) techniques. The diagnosis is based on FNAB or other tissue specimen of the metastatic tumor in about 65% of cases.[145] A post-mortem autopsy is rarely performed. Whether the suspicion of metastatic disease has arisen because of symptoms such as weight loss, abdominal complaints, or malaise or due to the screening examinations, the patient is usually referred to a medical oncologist for evaluation of treatment.

3.8.5. Lead-time Bias

In cancer research, especially in treatment studies, overall survival is a key parameter which refers to the time from diagnosis or treatment start to death. In fast progressing cancer it is crucial when the diagnosis is made because a few months have a great effect on measured

survival. This presents a problem in treatment trials of metastatic uveal melanoma. After the primary tumor is treated the observed disease free time may be several years, but when the metastases are detected the overall survival is typically counted in months.

To obtain an accurate estimate of the effect of a particular treatment for metastases the patients should ideally be randomized or, failing that, be enrolled in similar condition or categorized in corresponding groups. The former option requires constant and frequent follow-up and the latter a way to reliably estimate the prognosis of an individual patient and to stage the patient according to this prognosis. In this way, it is possible to differentiate between the natural history of the disease and treatment effect.

3.8.6. Staging

TNM classification is a widely used staging method for various cancers. T refers to primary tumor characteristics, N to the possible involvement of regional lymph nodes, and M to systemic metastatic disease. Each of these indexes has its own numeral corresponding to the extent of the clinical findings. Based on the TNM classification patients are staged into 4 stages (I, II, III, IV). Each of these 4 stages may have subgroups e.g. (IIA, IIB, IIC). Stage IVB corresponds metastatic uveal melanoma (as of January 2003; Stage IV in the new TNM classification).[137]

Although it is uncommon to include serum factors, S-LD level considered with site(s) of metastases has such prognostic value in evaluating patients suffering from stage IV cutaneous melanoma, that they are subcategorized within the M categories into three groups by their S-LD levels (M1a, M1b, and M1c; 1-year survival 59%, 57%, and 41%, respectively).[14]

3.8.7. Growth Rate

Understanding the kinetics of tumor growth is helpful in planning optimal treatment and follow-up programs. A basic method to analyze tumor progression based on clinical data is calculation of tumor doubling times.[24;55;66;83;85;86;152] The concept of doubling times was introduced by Collins in 1956,[27] before which no quantitative measures of estimating tumor growth were available. He drew attention to the presumably long asymptomatic period and seemingly rapid growth when metastases become detectable, theorems which are still valid. He also postulated that if the growth rate of a tumor is known, then the time when micrometastasis occurred can be estimated.[27] His calculations and deductions were based, however, on the assumption of a constant exponential growth of primary tumors and their metastases.[27]

In fact, cancer cells undergo sequential mutations which often give rise to faster growing subclones.[74] Problems are created by changes in the shape of the tumor over time, apoptosis, deficient blood supply, and by loss of cells due to immune defense and other host factors.[151] Indeed, it has been definitively shown that neither primary tumors nor their metastases have constant growth rates.[74;104;151] This fact makes use of doubling times based on certain points in their progress imprecise predictors of tumor behavior. Alternatively, Gompertzian growth kinetics could be used in estimating tumor growth. It assumes that the growth rate slows as the tumors increase in size. It is more accurate but also much more complicated.[71] In spite of these problems, exponential growth kinetics - doubling times provide an estimate of the average growth rate during specified intervals, and such data can provide clinically useful estimates for planning appropriate treatment and follow-up programs.

Limited information about doubling times of primary uveal melanomas is available, mainly from small untreated tumors followed over time and from patients who refused treatment.[10;24;55] These times range from 60 to more than 4000 days, and it has been inferred from epidemiological data that small melanomas might take an average of 7 years to grow large.[92] Only theoretical doubling times for metastatic uveal melanoma have been published. These times are estimated to be comparable with the shortest doubling times of primary uveal melanoma.[85] The growth rate of detectable metastases is notably faster than that of the primary tumors. Several factors could impede the growth rate and thus the progress of the disease, such as overall health condition, age, other diseases, gender, and the treatments given. Also, the nature of the metastatic tumor itself is one of the most important factors.

3.8.8. Screening Program

In the mid 1970's, it was suggested that patients with malignant uveal melanoma should be screened for metastases.[21;44;94] Clinical examination to detect hepatomegaly, liver function tests (LFT), and chest x-ray were recommended annually, followed by liver imaging if abnormal.[21;44] It was, and still is, unclear what constitutes an adequate screening program, however.[21;114] Few papers devoted to the clinical and laboratory findings of patients with metastatic uveal melanoma have been published since,[6;21;37;38;45;94] and two major review articles on the treatment of primary and metastatic uveal melanoma, respectively, do not discuss screening at all.[4;131] Only recently some articles have again emphasized and recommended scheduled screening.[114;145]

North American centers mostly use clinical examination, LFTs, and chest x-ray for screening,[58;114;141;143] even though imaging of the liver as an additional measure has been

recommended by investigators interested in metastatic melanoma.[70;90;114] The time schedule of the program is also unclear, most centers recommend annual screening, but in some centers semiannual program is used[114] In some countries, imaging of the liver has been routine for the last decade.[75;139] In others, however, screening is thought to be of no benefit, given the limited impact on survival of current chemotherapy regimens.[4;5;17;21;44;58;70;97;110]

3.8.9. Adjuvant Therapy

The possible benefits of adjuvant therapy at the time of treatment of the primary tumors are under investigation. In 1990, the Bacillus-Calmette vaccination was used to enhance the immune system to fight cancerous cells but it did not show any effect.[90] DTIC has been tried as an adjuvant therapy but the results have not been published. EORTC has recently launched a study were cutaneous melanoma and uveal melanoma patients are administered a vaccination program where the immune system is sensitized against certain antigens common in uveal melanoma cells. The results are expected after 2 years of enrollment and 5 years of follow-up, around 2009.

3.8.10. Treatment

Recently, a shift of emphasis from palliative chemotherapy given on an individual basis[4;5] to controlled clinical trials in centers treating metastatic uveal melanoma has taken place.[75;97] Current chemoimmunotherapy regimens have provided few objective responses and no long-term cures. [4;5;17;21;44;58;70;75;97;106;110]

One of the chemoimmunotherapy regimens used in Finland is a combination of bleomycin, vincristine, lomustine, dacarbazine (BOLD) with intercycle alpha interferon-2b. It has been considered active in the treatment of metastatic uveal melanoma but recent results are not encouraging.[97;108] Among twenty evaluable patients, four objective responses were observed (RR = 20%).[97]

Surgery is pursued in some cases with solitary metastasis with good results in carefully selected patients. The median survival has reached more than 22 months.[43;113] Palliative radiotherapy is also used, more so in extrahepatic tumors.

Given the rarity of objective responses that can be imaged and measured in longer survival and the possibility of lead-time bias in median survival, tumor doubling times might provide an additional criterion for comparing systemic treatment responses in metastatic uveal melanoma.

4. AIMS OF THE PRESENT STUDY

The purpose of this study was to:

1. Enlighten the prognostic significance of factors related to the screening program of patients with uveal melanoma.

2. Present an estimate of the possible lead time bias of survival in treatment trials.

3. Develop a working formulation for staging patients into subcategories according to their predicted survival.

4. Estimate the time of dissemination based on the doubling times of the metastatic tumors.

5. Evaluate the sensitivity of various screening tests routinely used in our institution, the time schedule and overall yield of our screening program.

6. Identify delays in the chain of treatment before treatment of the primary uveal melanoma

5. PATIENTS AND METHODS

5.1. Eligibility criteria and enrolment

All enrolled patients had had unilateral melanoma of the uvea. Patients were ascertained according to regimens of each study design from the registry of the Helsinki University Central Hospital, which is a tertiary referral unit that manages over 90% of uveal melanoma patients in Finland. All four studies are retrospective cross sectional studies by design (Fig.1). They were approved by the Institutional Review Board and followed tenets of the Helsinki Declaration.
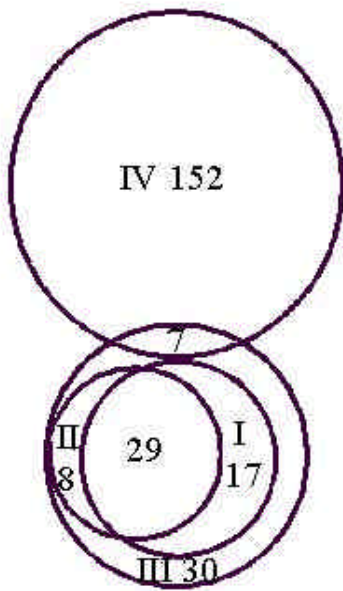
Fig.1. Diagram showing overlapping of the cohorts of the four studies. The patients in the three first studies (I; 46, II; 37, III; 91) all had metastatic disease and most of them had already died by the time of the study. Death was a prerequisite in the third study (III). The patients in the fourth publication (IV; 159) were alive without metastases. The paradoxical overlapping is due to different timing of the four studies and to the fact that they are not numbered chronologically.

5.1.1. Screening for Metastatic Malignant Melanoma of the Uvea (I)

Entry criteria were development of metastases from malignant melanoma of the uvea and regular participation in an annual screening program to detect such metastases allowing for one missed visit. A total of 62 consecutive patients who had been diagnosed to have

developed metastatic uveal melanoma between January 1985 and December 1996 were ascertained.

Of the 62 patients, 46 (74%) fulfilled both inclusion criteria. The mean age at diagnosis of metastatic malignant melanoma of the uvea in the 46 patients was 63 years (range, 23 to 86). The diagnosis of metastatic uveal melanoma was histopathologically verified in 30 of them (65%). In the remaining 16 patients (35%), the diagnosis was based on typical clinical and imaging findings, progression, and absence of any evidence of second cancer. Because many of the latter patients were not willing or ultimately eligible to receive active treatment, histopathologic confirmation had not been pursued.

In 3 of the 16 ineligible patients, the diagnosis of disseminated uveal melanoma was proved wrong, and 13 patients had not participated in the screening program.

5.1.2. Tumor Doubling Times in Metastatic Malignant Melanoma of the Uvea (II)

Entry criteria were 1.) diagnosis of metastatic malignant melanoma of the choroid and ciliary body between August 1986 and April 1998, 2.) participation in an annual screening program to detect such metastases, 3.) availability of imaging data from a prior screening examination performed within 15 months before the diagnosis of metastases, and 4.) availability of US or CT scans with measurable metastases at diagnosis of disseminated disease.

A total of 70 consecutive patients were diagnosed to have metastatic uveal melanoma. Of these 70 patients, 37 (53%) fulfilled all four inclusion criteria and were enrolled. Their mean age was 61 (range, 23 to 86). Of 33 excluded patients, 7 (10%) had not participated in the screening program, 10 (14%) had missed the previous screening examination, 11 (16%) had imaging data that did not allow accurate measurements, and 5 (7%) had been followed up with liver isotope scanning rather than with US or CT.

Diagnosis of disseminated melanoma was confirmed by histopathology in 26 patients (70%). The remaining patients (30%), many of whom were not candidates for chemoimmunotherapy, were diagnosed on the basis of clinical findings and imaging data. Of the 37 patients, 30 (81%) were treated with chemotherapy or chemoimmunotherapy, most often combination chemotherapy with bleomycin, vincristine, lomustine and dacarbazine (BOLD) with interferon[97;107] that was given to 23 of the 30 (77%) patients. Subsequent imaging data during therapy were available from 23 of the 30 treated patients (77%).

5.1.3. A Prognostic Model and Staging for Metastatic Uveal Melanoma (III)

Entry criterion was death of metastatic malignant uveal melanoma between January 1985 and December 2000. A total of 99 consecutive patients who had been suspected of dying of metastases were ascertained from the registry.

Of the 99 patients, 95 (96%) fulfilled the inclusion criteria. The diagnosis of metastatic uveal melanoma was confirmed by cytology or histology in 59 (62%) of them. The diagnosis of the remaining 36 patients (38%), most of whom were not candidates for systemic chemotherapy, was based on typical clinical and imaging findings, progression, and absence of any evidence of second cancer

The suspected metastases of the 4 ineligible patients proved to be unrelated to uveal melanoma.

One eligible patient whose metastases were first diagnosed at autopsy and 3 patients whose charts on treatment of metastases were unavailable were excluded from the analysis, leaving 91 patients in the study (inclusion ratio, 96%). Their mean age was 62 years (range, 23y to 86y).

5.1.4. Mode of Presentation and Time to Treatment of Uveal Melanoma in Finland (IV)

All consecutive patients with primary malignant melanoma of the uvea diagnosed between July 1994 and June 1999 were eligible. Of the 184 eligible patients, 10 (5%) had died of various reasons and 15 (8%) of them could not be contacted. All 159 patients contacted consented to the study and underwent a structured telephone interview (inclusion rate, 86%). Their mean age at the time of diagnosis of primary uveal melanoma was 60 years (range, 14-87).

5.2. Data Collection

5.2.1. Clinical Data Collection

The date of the diagnosis of primary uveal melanoma and the date of the diagnosis of metastatic tumor were taken from patient charts, and relapse-free interval was calculated as the difference between the two dates. In addition, the age and gender of the patient, Karnofsky index, symptoms from metastases, and the duration of these symptoms were recorded (I - III). Karnofsky index is a measure to categorize patients' overall health condition.

In addition, the time on chemotherapy was calculated as the interval from the date of the first cycle to that of the last. (III)

The dates of all visits to a dispensing optician, a physician other than an ophthalmologist, an ophthalmologist, and the ocular oncology service were determined by structured interview and verified, whenever possible, from patient charts, bills, and other legal documents. The reason for each appointment was identified. (IV) The date of diagnosis of primary tumor, the tumor height and diameter, and the date and type of treatment were obtained from patient charts. If the patient had been screened because of a presumed intraocular nevus, the charts were obtained from the practitioner in question. (IV)

5.2.2. Liver Function Tests

The levels of AST, ALT, AP, and LD at the time of diagnosis of metastases and at the two preceding screening examinations were recorded from the patient charts. (I, III) The latter had taken place one and two years before, except when metastases were diagnosed on the basis of symptoms or one screening visit had been missed.

5.2.3. Imaging Data

The original x-rays, liver isotope scans, printouts of ultrasound examinations, and CT scans were reviewed. (I - III) Largest perpendicular diameters of all metastases were measured using a lightbox and a caliper. For US examinations, measurements were also taken from the original reports.

5.2.4. Tumor volume

5.2.4.1. Primary tumor volume

The height and the largest basal diameter of the primary intraocular melanoma were taken from the patient chart and printouts of US examinations. For calculation of the volume of the primary tumor, an equation based on ellipsoidal forms was used, (II)[24;55]:

$$(1) \qquad V_{prim} = \frac{\pi}{6} * h * lbd^2$$

where h is the height and lbd is the largest basal diameter of the primary intraocular melanoma in millimeters.

5.2.4.2. Metastatic volume

The hepatic, extrahepatic and total metastatic burden was estimated as the sum of the product of the largest perpendicular dimensions, multiplied by their mean, of measurable metastases. (I – III)

5.2.5. Estimation of Doubling Times

The measurements originated from imaging studies performed at diagnosis of metastatic disease and at follow-up visits during active treatment for metastases. (II)

For calculating tumor doubling times, the equation of Schwartz was used:[116]

$$(2) \qquad\qquad DT = \frac{t}{10 * \log(D_1 / D_0)}$$

where t is the time between measurements, D_0 is the diameter of the metastasis at baseline, and D_1 the diameter after time t. Whenever possible, the doubling times were calculated as the mean for the three largest metastases to lessen the effect of variable growth rates and inception times of individual metastases.[66;66;151]

When analyzing the growth of metastases at diagnosis, t was the interval between the first positive and the last negative scan. The assumption was made that the metastasis was present but below detection threshold when the scan had been negative.[152] A liver metastasis that is 10 mm in diameter is more likely than not to be visible by routine US and CT, and is already suitable for FNAB.[93] The smallest metastases actually detected were 4 to 6 mm in diameter. In most calculations, we presumed that D_0 was 6 mm for all metastases. As a sensitivity analysis, alternative values of 4 mm and 8 mm were used.

When analyzing the growth of metastases during active treatment for metastatic uveal melanoma, the average tumor doubling times during treatment were directly calculated from the diameters of metastases measured at diagnosis and at the end of active therapy. In these calculations, t was the time between the diagnosis of metastases and the last screening scan, and D_0 and D_1 were the means of the largest perpendicular diameters of metastases at diagnosis and at last screening, respectively.

To estimate the time of initial micrometastasis the following equations were used:

$$(3) \qquad\qquad V_1 = V_0 * 2^N$$

$$(4) \qquad\qquad T = N * DT$$

where V_0 is volume of a single tumor cell, V_1 is volume of the metastasis at diagnosis, N is the number of cell divisions, T is time from micrometastasis to diagnosis of disseminated disease, and DT is the tumor doubling time. By solving for N we obtain:

$$(5) \qquad\qquad T = \frac{\log \dfrac{V_1}{V_0}}{\log 2} * DT$$

To get V_0, diameters of 35 epithelioid uveal melanoma cells were measured. Presuming them to be spherical in shape, a value of $4*10^{-6}$ mm^3 was obtained. V_1 was calculated as the product of the largest perpendicular diameters multiplied by their mean. The calculation was carried out alternatively by using the doubling time calculated for the largest metastasis and by using the mean doubling time calculated for up to three largest metastases.

These calculations are based on constant exponential growth.[27] Actually, tumors may accelerate growth before becoming clinically detectable and they may decelerate growth once metastases are bulky.[104]

5.3. Statistical Methods and Data Analysis

5.3.1. General guidelines (I - IV)

The data were collected and analyzed using the database and statistical software packages Dbase4 (Ashton-Tate Corporation, UK), BMDP PC-90 (BMDP Statistical Software, Cork, Ireland), GraphPad Prism 2.01 (3.01) (GraphPad Software, San Diego, CA, USA), Microsoft Access, SPSS for Windows 9.0.1 (SPSS Inc.), Power and Precision 2 (Biostat, Englewood, NJ), and Stata 7.0 (Stata Corporation, College Station, TX).

The mean and standard deviation are given for normally distributed variables, and median and range for other variables. The 95 % confidence intervals (CI) were calculated for main findings.[27] Normally distributed variables were compared with Student's *t*-test, other continuous variables with Mann-Whitney's *U*-test, Kruskal-Wallis test, and their interrelationships were analyzed with Spearman's rank correlation. Fisher's exact test and Pearson's χ^2 test were used to compare unordered contingency tables.

5.3.2. Analysis of doubling times (II)

To estimate the range of the doubling times, the doubling times calculated for each patient were plotted, ordering them from shortest to longest based on the default sensitivity limit of 6mm. Three different values for the sensitivity of imaging to detect metastases at screening were used. To find out if large size of primary tumors and metastases was associated with more rapidly growing metastases, the doubling times were plotted against the height, largest basal diameter, and volume of the primary tumor, and against the largest diameter of the largest metastasis. To find out whether long disease-free intervals were associated with more slowly growing metastases, the doubling times were plotted against the observed relapse-free interval. Association between the variables above was assessed using Spearman's rank correlation coefficient. To gain an insight into the time of initial micrometastasis relative to the treatment of the primary tumor, the difference between the observed relapse-free interval and the calculated estimates of the time of micrometastasis was plotted against the observed relapse-free interval. To asses the effect of treatment on growth of metastases that did not show an objective response, the mean doubling time at the time of diagnosis of disseminated disease and during treatment were plotted against each other for all patients whose metastases continued to grow.

5.3.3. Survival analysis (III)

5.3.3.1. Kaplan-Meier method

Survival analysis was based on Kaplan-Meier product limit method, and melanoma-specific survival was compared with the log-rank test that gives equal weight to the entire survival curve. Test for linear trend was used if categories analyzed were ordered. For analysis, age at diagnosis, the largest dimension of the largest metastasis, metastatic burden, and serum LFT levels were divided into tertiles. Alternatively, LFTs were categorized relative to the upper normal limit (< 1X UNL, 1-2.5X UNL, >2.5X UNL). The performance status was categorized into three groups: essentially asymptomatic patients (Karnofsky index 100 to 90 [equivalent to ECOG performance status[98] 0]), symptomatic patients (Karnofsky index 80 to 60 [ECOG 1-2]), and symptomatic patients generally not fit for chemoimmunotherapy (Karnofsky index 50 or less [ECOG 3-4]). Differences between unordered and ordered categories were assessed by the log-rank test and test for trend.

5.3.3.2. Cox multiple hazard regression

Cox proportional hazards regression was used to adjust survival time data for the effect of confounding factors[146] and to identify independent predictors of prognosis. Age at diagnosis, the largest dimension of the largest metastasis, metastatic burden, and serum levels of LFTs were modeled as continuous variables. The assumption of proportional hazards was tested by the method of Therneau and Grambsch.[146] Independent variables were allowed in the model if $P < .10$ and confounding variables were kept in the model irrespective of statistical significance.[63] Regression coefficients and hazard ratios (HR) with 95% confidence intervals (CI) were calculated. Power analysis indicated that the present study had an 80% power to detect a HR of 1.8 and 95% power to detect a HR of 2.2 as significant.

Time on chemotherapy was modeled as a confounding variable. The number of variables in the final model was restricted to four, based on a rule that at least 15 to 20 events are required per variable.[101]

5.3.3.3. Working formulation for predicted survival with metastatic uveal melanoma

The coefficients were entered into the general Cox model, and the predicted median survival time was calculated from adjusted survival curves for a variety of clinically relevant combinations of covariates. Uveal melanoma regional lymph node and systemic metastases are currently categorized as stage IVB (as of January 2003; stage IV).[136;137] Based on predicted survival, three subcategories for stage IVB were formulated: median survival in excess of 12 months (stage IVBa), median survival from 6 to 11 months (stage IVBb), and median survival less than 6 months (stage IVBc). Thereafter, patients were staged according to the working formulation, and the observed survival for each category was plotted by the Kaplan-Meier product-limit method and compared with the log-rank test for trend.

5.3.4. Analysis of delay times (IV)

To compare delay times, cumulative frequency distribution plots for time from initial presentation of the tumor to treatment planning and to treatment at the ocular oncology service were also drawn making it possible to determine by which time any specified proportion of patients was attended. The tumors were categorized as: small if they were less than 10.5 mm wide in their LBD and less than 2.5 mm in height; medium if LBD was between 10.5 mm and 15.4 mm or the height was between 2.5 mm and 8.4 mm; and large if LBD or height exceeded these figures.[31]

6. RESULTS AND DISCUSSION

6.1. SCREENING FOR METASTATIC MALIGNANT MELANOMA OF THE UVEA (I)

Because of the wish to detect patients with metastases at a sufficiently early stage to allow chemotherapy or surgery, there is now a need to critically evaluate the usefulness of noninvasive screening procedures in detecting metastases from malignant uveal melanoma. This uncertainty and lack of data are reflected in great differences in current screening programs worldwide.

6.1.1. Diagnosis of metastases

The mean age at diagnosis of metastatic malignant melanoma of the uvea in the 46 patients was 63 y (SD, 13; range, 23 to 86). Their median relapse-free interval was 2.2 y ranging from 4 months to 6 years 11 months. Altogether 27 patients were entirely asymptomatic and 19 patients had symptoms when metastases were diagnosed (Table 2). In 34 patients (74%; 95% CI, 59 to 86), metastatic uveal melanoma was diagnosed at a scheduled screening examination, irrespective of recent onset of symptoms in 7 patients (15%; 95% CI, 6-29) who had a skin nodule or abdominal complains (Table 2).In 12 patients (26%; 95% CI, 14 to 41), signs or symptoms of metastases led to the diagnosis before the next scheduled screening visit (Table 2). The median interval from the preceding visit was 10.7 months (range, 5 months to 2 years 2 months); 1 patient presented within 6 months after previous screening, 9 patients within 6 months before the next screening, and 2 patients had missed the immediately preceding screening visit. The median relapse-free intervals of patients whose metastases were diagnosed at screening and on the basis of symptoms (2.2 *v* 2.0 y; *P* = .28, Mann-Whitney *U*-test) or those of asymptomatic and all symptomatic patients (2.2 *v* 2.1 y; *P* = .26) did not differ.

Of the 46 patients in our screening program, 59% were without symptoms when metastases were detected. The diagnosis was made earlier than in the case if they had not been screened. In 74% the diagnosis was made at a scheduled screening visit. Seven patients (15%) who had symptoms but were diagnosed at screening may have waited for the forthcoming visit instead of consulting their physician, and hence may have had the diagnosis delayed. Their screening results resembled more of the asymptomatic patients' results detected at screening than those diagnosed on the basis of symptoms before the next scheduled visit.

TABLE 2. The frequency and type of symptoms at the time of diagnosis in 46 patients with metastatic uveal melanoma who participated in an annual screening program.

Symptom	Diagnosed during a screening visit (n = 34)			Diagnosed on the basis of symptoms (n = 12)			All symptomatic (n = 19)			Total (n = 46)		
	no.	%	(95% CI)	no.	%	(95% CI)	no.	%	(95% CI)	no.	%	(95% CI)
Asymptomatic	27	79	(62-91)	--	--	--	--	--	--	27	59	(43-73)
Hepatic symptoms												
Abdominal discomfort	3	9	(2-24)	8	67	(35-90)	11	58	(34-80)	11	24	(13-39)
Malaise	3	9	(2-24)	7	58	(28-85)	10	53	(29-76)	10	22	(11-36)
Weight loss	1	3	(0-15)	4	33	(10-65)	5	26	(9-51)	5	11	(4-24)
Extrahepatic symptoms												
Palpable nodule	2	6	(1-20)	6	50	(21-79)	8	42	(20-60)	8	17	(8-31)
Pulmonary	0	0	(0-10)	2	17	(2-48)	2	11	(1-33)	2	4	(1-15)
Central nervous system	1	3	(0-15)	0	0	(0-26)	1	5	(0-26)	1	2	(0-12)
Miscellaneous	0	0	(0-10)	2	17	(2-48)	2	11	(1-33)	2	4	(1-15)

6.1.2. Sites of metastases

In 37 patients (80%; 95% CI, 66 to 91), only hepatic metastases were detected; they were multiple in 22 patients. Two patients had only extrahepatic metastases, and 7 had hepatic and extrahepatic lesions (Table 3). All 34 patients (100%; 95% CI, 90 to 100) who were diagnosed at screening had hepatic metastases; 3 (9%) also had extrahepatic metastases (Table 3). In particular, all asymptomatic patients had hepatic metastases, and two had pulmonary metastases. Out of 12 patients diagnosed on the basis of symptoms, liver metastases were found in 10; 6 (50%) also had extrahepatic ones. Of 31 patients who had no weight loss or abdominal complains, 30 (97%; 95% CI, 83-100) had hepatic metastases. In 80% of 46 patients (95% CI, 66 to 91), only liver metastases were detected. Only 2 (4%, 95% CI, 1-15) of our 46 patients had pulmonary metastases at diagnosis.

These findings are in line with previous studies. Traditionally, hepatic metastases are initially present in over 40 to 60% of patients.[17;21;44;58;90;110] Eventually the liver is affected in up to 95% of patients,[5;17;58;69;70;110;139;145] even though up to 50% later also have extrahepatic metastases, most often in the lungs, bone, skin, and brain. [5;17;21;58;69;70;110;145]

6.1.3. Metastatic burden

The median size of the largest metastasis of 38 patients with measurable lesions was 4.8 cm (range; 1.0 to 30.0). The median total, hepatic, and extrahepatic burden of metastasis was 102 cm^3 (range; 1.2 to 6050), 95 cm^3 (range; 0 to 6050), and 0 cm^3 (range; 0 to 103), respectively. The median size of the largest measurable metastasis of patients diagnosed at screening and on the basis of symptoms did not differ (4.5 *v* 5.2 cm; *P* = .96, Mann-Whitney *U*-test). Their total (104 *v* 71 cm^3; *P* = 1.00) and hepatic metastatic burdens (98 *v* 39 cm^3; *P* = .82) were also comparable. These three parameters were similar also between asymptomatic and all symptomatic patients (5.0 *v* 4.0 cm, *P* = .51; 112 *v* 38 cm^3, *P* = .33; and 109 *v* 38 cm^2, *P* = .31, respectively).

The fact that the median size of largest metastasis, tumor burden, and disease-free interval of patients who did or did not have symptoms were overlapping suggests that some patients are more likely to have symptoms than others, perhaps based on the growth rate and location of the metastases.

Results and Discussion

TABLE 3. The frequency of metastases by site at the time of diagnosis in 46 patients with metastatic uveal melanoma who participated in an annual screening program.

Site	Diagnosed during a screening visit (n = 34)			Diagnosed on the basis of symptoms (n = 12)			Asymptomatic (n = 27)			All symptomatic (n = 19)		
	no.	%	(95% CI)	no.	%	(95% CI)	no.	%	(95% CI)	no.	%	(95% CI)
Liver	34	100	(90-100)	10	83	(52-98)	27	100	(87-100)	17	89	(67-99)
Liver only	31	91	(76-98)	6	50	(21-79)	25	93	(76-99)	12	63	(38-84)
Liver and other sites	3	9	(2-24)	4	33	(10-65)	2	7	(1-24)	5	26	(9-51)
Subcutaneous	0	0	(0-10)	2	17	(2-48)	0	0	(0-13)	2	11	(1-33)
Bone	0	0	(0-10)	1	8	(0-38)	0	0	(0-13)	1	5	(0-26)
Lung	2	6	(1-20)	0	0	(0-26)	2	7	(1-24)	0	0	(0-18)
Pancreas	1	3	(0-15)	0	0	(0-26)	0	0	(0-13)	1	5	(0-26)
Lymph nodes	0	0	(0-10)	1	8	(0-38)	0	0	(0-13)	1	5	(0-18)
Other sites	3	9	(2-24)	6	50	(21-79)	2	7	(1-24)	7	37	(16-62)
Other sites only	0	0	(0-10)	2	17	(2-48)	0	0	(0-13)	2	11	(1-33)
Bone	0	0	(0-10)	1	8	(0-38)	0	0	(0-13)	1	5	(0-26)
Subcutaneous	0	0	(0-10)	1	8	(0-38)	0	0	(0-13)	1	5	(0-26)

6.1.4. Liver Function Tests

   At least one LFT was abnormal in 32 patients (70%; 95% CI, 54 - 82). Such a finding was equally frequent in patients whose metastases were diagnosed at screening and on the basis of symptoms (65% *v* 83%, *P* = .29, Fisher's exact test), as well as in patients who had or did not have symptoms attributable to hepatic metastases (80% *v* 65%, *P* = .33). The overall sensitivity of AST, ALT and AP ranged from 0.27 to 0.43, whereas that of LD was 0.67 (Table 4). The specificity of all LFTs ranged from 0.90 to 0.96 (Table 4). LD had the greatest likelihood ratio for a positive and a negative test (Table 4).

Patients whose metastases were detected due to symptoms rather than at screening had more often an elevated AP level (*P* = .004, Fisher's exact test), and their median AST (*P* = .01, Mann-Whitney *U*-test) and AP (*P* = .001) was higher (Table 5; Figure 1). The sample size of LD was too small for subgroup comparison. The median LFT levels of asymptomatic patients did not differ from those of all patients diagnosed at screening (Table 5).

TABLE 4. Sensitivity (true positive rate), specificity (true negative rate), and likelihood ratios of liver function tests in detecting metastatic uveal melanoma.[*]

				Likelihood ratio	
Enzyme	Criteria	Sensitivity	Specificity	Positive test[†]	Negative test
AST					
	Above normal value	0.43	0.93	5.8	0.62
	1.2 X higher	0.63	0.73	2.3	0.52
ALT					
	Above normal value	0.38	0.90	3.8	0.68
	1.2 X higher	0.66	0.65	1.9	0.52
AP					
	Above normal value	0.27	0.95	5.0	0.77
	1.2 X higher	0.49	0.92	6.3	0.55
LD					
	Above normal value	0.67	0.96	14.7	0.35
	1.2 X higher	0.65	0.71	2.3	0.49

[*] Based on data from 46 patients with and 325 patients without metastatic uveal melanoma.
[†] The false positive rate can be calculated as 1-specificity.

The sensitivity of observing a 20% increase in LFT levels ranged from 0.49 to 0.65, and the specificity of these tests ranged from 0.65 to 0.92 (Table 4). Increase in the level of AST ($P = .025$, Mann-Whitney *U*-test), ALT ($P = .016$), and AP ($P = .006$), as compared with the level at the preceding screening examination, was greater in patients whose metastases were diagnosed on the basis of symptoms rather than at screening (Table 5). This difference was smaller when asymptomatic patients were compared with all symptomatic patients (Table 5).

LFTs are used for screening of hepatic metastases of skin and uveal melanoma.[6;17;21;37;38;45;47;58;90;94;114] A set of four liver enzymes identified 70% of our patients with metastases, including 2 patients who had a falsely negative abdominal US. The specificity of all four LFTs among the selected, predominantly elderly patients screened was high, translating to a false positive rate of 10% or less. In line with other studies, LD was the most efficient LFT.[16;22;38] As estimated from our data set, the post-test likelihood of a patient having hepatic metastases is more than 14 times higher if LD is elevated. Thus, liver function tests may provide useful additional evidence to supplement US findings when the latter are unclear. Elevated LD may and AP seems to have prognostic significance in metastatic uveal melanoma.(III)[16;75] Gamma glutamyl transpeptidase (GGT) is probably similar to LD in sensitivity and prognostic value.[75]

AST and ALT performed less well as individual tests, as expected on account of previous studies.[16;22;38] Nevertheless, some of our patients with hepatic metastases had only an elevated AST, ALT, or both. They cannot be completely dismissed as screening tests.

This study also evaluated whether observing a specified increase compared with preceding enzyme levels might be a sensitive test to identify hepatic metastases. The optimal cutpoints were determined by plotting ROC curves.[112] Even though the sensitivity of noting a specified increase was higher for AST, ALT, and AP, the difference was not marked, and the specificity and likelihood ratios were worse, except for AP.

TABLE 5. The frequency of an abnormal liver function test, its median value (relative to the upper normal limit), and the median increase in a liver function test (from preceding screening visit) in 46 patients with metastatic uveal melanoma who participated in an annual screening program.

	Diagnosed during a screening visit (n = 34)		Diagnosed on the basis of symptoms (n = 12)		P	Asymptomatic (n = 27)		All symptomatic (n = 19)		P
Above Upper Normal Level, % (95% CI)										
AST	36	(18-57)	60	(26-88)	.27†	43	(22-66)	43	(18-71)	.99
ALT	31	(15-51)	60	(26-88)	.14†	29	(13-51)	53	(27-79)	.27†
AP	15	(5-32)	64	(31-89)	.004†	19	(7-39)	39	(17-64)	.31†
LD*	67	(45-84)	67	(9-99)		68	(43-87)	63	(24-91)	
Median level, X times upper normal limit, (95% CI)										
AST	0.84	(0.50-1.9)	1.6	(0.78-3.5)	.01‡	0.86	(0.72-1.2)	1.0	(0.68-2.0)	.027‡
ALT	0.86	(0.26-1.7)	1.1	(0.49-2.0)	.067‡	0.83	(0.60-1.1)	1.1	(0.86-1.7)	.025‡
AP	0.67	(0.40-2.5)	1.4	(0.67-2.7)	.001‡	0.69	(0.59-0.86)	0.9	(0.65-1.6)	.10‡
LD*	1.1	(0.50-7.2)	3.1	(0.75-7.1)		1.1	(0.98-1.7)	1.2	(0.50-7.2)	
Median increase, X times higher than preceding level, (95% CI)										
AST	1.4	(0.51-3.2)	3.7	(0.97-6.4)	.025‡	1.8	(0.79-2.2)	2.0	(1.1-4.7)	.13‡
ALT	1.6	(0.45-7.3)	2.7	(1.2-8.8)	.016‡	1.4	(1.1-2.2)	2.4	(1.4-4.0)	.038‡
AP	1.2	(0.81-4.2)	2.5	(1.0-5.8)	.006‡	1.2	(1.1-1.3)	1.4	(1.1-2.6)	.074‡
LD*	1.5	(0.69-7.4)	6.1	(0.96-11)		1.7	(1.1-2.7)	1.3	(0.69-11)	

* Sample size too small for subgroup comparison,   † Fisher's exact test,   ‡ Mann-Whitney *U*-test

6.1.5. Imaging Studies

Abdominal US revealed unequivocal hepatic metastases in 36 patients (78%; 95% CI, 64 - 89). In 12 of them (33%; 95% CI, 19 - 51), all LFTs done were within normal limits. US was suggestive of metastases in 5 additional patients (11%; 95% CI, 4 - 24), all of whom were confirmed to have hepatic metastases by FNAB, CT, or both. US was negative in 2 patients (4%; 95% CI, 1 - 15), both of whom had liver metastases and at least one abnormal LFT. Three patients (7%) were not imaged. Only one patient (2%; 95% CI, 0-12) had a metastasis in lung that was diagnosed in a screening chest x-ray; she had concurrent positive abdominal US. Chest x-ray was negative in 39 patients (85%; 95% CI, 71-94), and suggestive of metastasis in 5 patients (11%; 95% CI, 4 - 24). Pulmonary metastases were confirmed by CT scan in only one of the latter five patients; this patient also had coexisting liver metastases by abdominal US. CT scans were used in 24 patients (52%) to confirm metastases suspected at screening, and as an additional staging examination when metastases had already been diagnosed by other methods. In 17 of 19 patients (89%; 95% CI, 67 - 99), CT scan and US were in agreement, but in two patients (11%; 95% CI, 1 - 33) either CT or US failed to show hepatic metastases seen by the other method.

Abdominal US revealed definite metastases or led to a diagnostic CT, FNAB, or both in 89% of patients. In 33% of these 46 patients, all LFTs done were normal. Conversely, in 4% of patients with liver metastases, US was normal whereas at least one LFT was elevated.

CT and MRI scans, not used primarily in our screening program, may be even more sensitive than US in detecting hepatic metastases from uveal melanoma. In a previous study, of 30 metastases identified in 4 patients at surgery, US detected 37%, MRI 67%, and CT 77%.[75] The most sensitive imaging method was CT combined with arterial portography. Obviously, it can only be used in staging and it is not ideal for screening.

These figures compare favorably with screening programs which used liver imaging only if symptoms, abnormal physical examination, or LFTs indicated them. In a large study by Gragoudas,[58] 30% of 145 patients (95% CI, 23 - 39) were asymptomatic, metastases involved only the liver in 56% of them (95% CI, 47 - 67), and the frequency of a positive chest x-ray was 24% (95% CI, 17 - 32). The frequency of pulmonary metastases in earlier smaller series likewise ranged from 17% to 28%.[17;37;110]

Not counting the initial work-up radiograms, a total of 143 negative screening chest x-rays had been performed to the 46 present patients who developed metastases. During the study period, those 344 patients who did not develop metastases were subjected to more than 900

chest x-rays, and some of them were screened for more than a decade. This study concludes that the yield of a chest x-ray, widely used as the primary imaging test, is very low if abdominal imaging is part of the screening program. At HUCH we have abandoned chest x-ray as a screening examination in spite of rare cases of pulmonary metastases from uveal melanoma.[64;111;145;147] We still consider chest x-ray obligatory in the initial work-up to exclude the possibility that the uveal tumor is a metastasis since both lung cancer and pulmonary metastases are common in patients with cancer metastatic to the eye.[46] It is also useful in examining patients who develop pulmonary symptoms, and as a staging examination when metastases are detected elsewhere.

6.1.6. Limitations

The main limitations of the first study (I) were retrospective collection of data and small sample size. However, most data collected were dates and laboratory results from patient charts, which leave little chance for error. Measurements of metastatic tumors could have been more precise in a prospective study and recording of symptoms would have been more accurate.

6.2. TUMOR DOUBLING TIMES IN METASTATIC MALIGNANT MELANOMA OF THE UVEA (II)

6.2.1. Tumor Doubling Times of Metastatic Uveal Melanoma at Diagnosis

The median interval from preceding negative screening imaging to detection of metastasis was 12 months (range, 4 - 14).

The tumor doubling times based on three different assumptions about the sensitivity of imaging to detect small metastases and on up to three largest metastases detected at screening ranged from 34 to 220 days (Fig.2). The corresponding median doubling times calculated for the single largest metastasis and for up to three largest metastases are summarized in Table 6. Irrespective of the sensitivity limit used in calculation, the fastest growing third of metastases gave doubling times between 30 and 70 days, and the intermediate third gave doubling times between 40 and 120 days. Among the remaining third, the doubling times heavily depended on the presumed sensitivity limit used in calculation, due to the fact that the smallest metastases were of the same size range (or even smaller) than the limit used. Based on the default limit of 6 mm of this study, two thirds of metastases had a doubling time between 30 and 80 days.

In 1980, Manschot claimed that doubling times of metastatic uveal melanoma tumors would resemble those of fastest growing primaries, which range from 60 to 120 days.[85;86] These figures are in the same range as was calculated in this study, but somewhat longer.

The calculated mean tumor doubling times did not differ between asymptomatic and symptomatic patients (P = .43, Mann-Whitney U-test) or between patients who had or had not symptoms of liver metastasis (P = .51). Tumor doubling times were statistically significantly shorter in women as compared with men (median 50 vs. 72 days, P = .016).

The calculated mean doubling time and the largest basal diameter (P=.37, Spearman's rank correlation), height (P=.59), and estimated volume (P=.22, Fig.3A) of the primary intraocular melanoma were not statistically significantly correlated with each other. Regardless of the volume of the primary tumor, estimated mean doubling times clustered between 40 and 100 days (Fig.3A).

As compared with reported doubling times of primary uveal melanoma, which ranged from 71 to 540 days (median, 292) for spindle cell tumors and from 23 to 288 days (median, 128) for mixed cell tumors,[10] the data of this study (II) support the view that many uveal melanomas accelerate growth with progression.[85;86]

Fig.2. Sensitivity analysis of tumor doubling times calculated as a mean for up to three largest metastases quantitating uncertainty in the estimates. The calculations were based on three hypothetical sizes of metastases at latest negative imaging, 8 mm (downward pointing triangle), 6 mm (solid circle), and 4 mm (upward pointing triangle). The patients were arranged in ascending order of doubling times calculated using the default limit of 6 mm. For an individual patient, the three estimates may change order because some of their metastases were smaller than the limit used in a particular calculation.
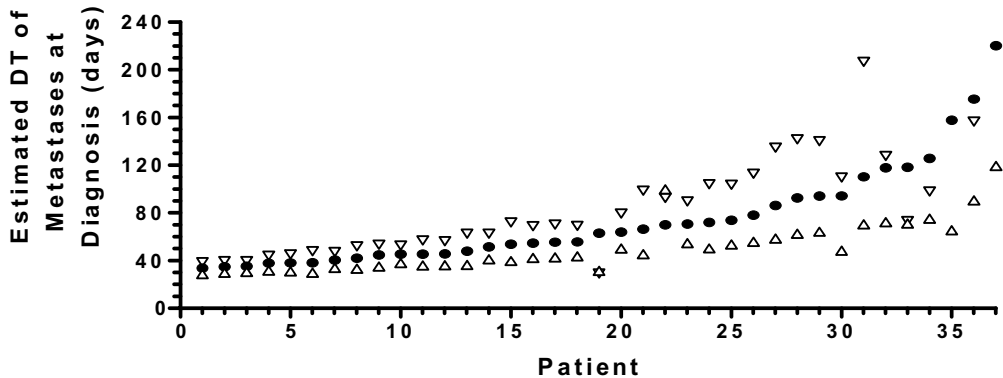
Because previous estimates are based predominantly on patients who had small tumors, they are not directly comparable with the range of primary tumors in our series. The fact that the disease-free interval did not correlate with the doubling times of metastases would be consistent with accelerated growth rates. Neither did we observe correlation between the size of the primary tumor and doubling times of their metastases, even though the doubling time of primary tumors has been shown to correlate with tumor size.[27]

The calculated mean doubling times were inversely related to the size of the largest metastasis. When considering the asymptomatic patients, this is directly due to the data collection method. When the diameter of the largest metastasis was 50 mm or more, the doubling time was in each case 50 days or less.

A plot of the mean doubling time against the observed disease-free interval did not reveal any obvious relationship between them (Fig.3B). Regardless of the length of the disease-free interval, most doubling times clustered between 40 and 80 days, and surprisingly the longest doubling times were associated with short and intermediate disease-free intervals rather than long ones (Fig.3B).

The calculated doubling times were used to roughly extrapolate the behavior of the metastases in the period prior to diagnosis.[24;27;66;152] A plot of the observed disease-free interval against the calculated time of micrometastasis relative to the time of treatment of the

primary tumor showed that most of the primary tumors, assuming a constant growth rate, would have disseminated within five years before primary treatment (Fig.4). The median interval between the calculated dissemination and the treatment of the primary tumor according to the doubling time of the largest metastasis was 1.9 years (range, 15.5 years before treatment to 4.5 years after). The median interval according to the mean doubling time of up to three largest metastases was 2.9 years (range, 15.5 years before treatment to 2.9 years after).

Table 6. Tumor doubling times of metastatic uveal melanoma calculated on the basis of the single largest metastasis and up to three largest metastases

| Sensitivity level of imaging (mm) | Tumor Doubling Time (days) | | | | | | | |
| | Largest Metastasis | | | | Three Largest Metastases | | | |
	Median	(range)	Mean	(SD)	Median	(range)	Mean	(SD)
4	41	(17-110)	41	(16)	44	(29-120)	51	(21)
6	53	(23-220)	57	(37)	63	(34-220)	74	(42)
8	61	(27-123)	61	(26)	70	(29-207)	81	(41)

This information of growth can be used to position point A relative to the time of diagnosis of the primary in following figure 5 (Fig.5). Moreover, the growth of metastases should continue 2.2 years beyond the time of diagnosis, which was our observed median interval from diagnosis of the primary tumor to diagnosis of metastases (range, 0.33-9.1). Adding these two figures together we get an estimate of 5.1 years for AC, time to clinical metastasis (Fig.5).

These data support the idea, which is also supported by similar survival after enucleation and radiotherapy of uveal melanoma, that in majority of cases dissemination has already taken place before treatment of the primary tumor, rather than at the time of or after treatment.[7;33;62;86;129] This is consistent with the theorem of Collins who suggested that half of the whole life span of a malignant tumor occurs in a period of undetected growth prior to the earliest possible sign or symptom.[27] Because most patients were treated for their metastases, it was not possible to study the association of initial tumor doubling times and eventual survival.

Fig.3. Association between tumor characteristics and mean tumor doubling time calculated for up to three largest metastases. A) The volume of the primary intraocular melanoma did not significantly correlate with doubling time of metastases. The line shows a linear regression fit with 95% confidence intervals. (B) The observed disease-free interval did not correlate with doubling time of metastases.
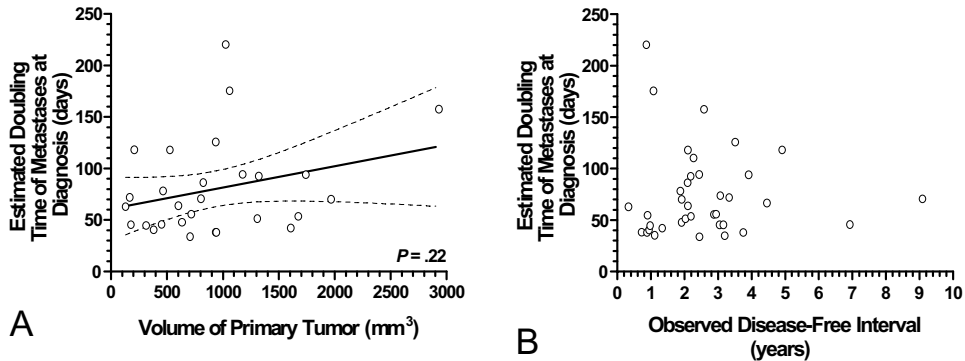

In figure 5, we have plotted the time lines for primary and metastatic tumors separately. The latter line extends from point A to the observed median volume of clinically diagnosed metastasis at point C, which was 17 000 mm^3 (Fig.5). Incidentally, this is equivalent to 32 tumor doublings and corresponds to a slightly shorter doubling time than the median. The graph predicts that the volume of a metastasis at the time of diagnosis of the primary tumor would be on average 0.5 mm^3. Such tiny metastases would not be found by current diagnostic methods, which is in line with the clinical experience that detectable metastases at baseline are rare in uveal melanoma. It can now be estimated that at micrometastasis the primary tumor would be on average 7 mm^3 in size, which roughly corresponds to a dome-shaped tumor 3.0 mm in diameter and 1.5 mm in height. This would still be a small tumor, but one that should easily be detected by ophthalmoscopy.

We estimated that tumor doubling times of metastases are more likely to be biased towards too long than too short times. If the median would be shorter than here estimated, the interval AC would be shorter and the primary tumor even bigger at the time of micrometastasis.

The tumor doubling times of three patients whose metastases were diagnosed as late as 4 to 9 years after treatment of the primary tumor ranged from 45 to 70 days. Their observed disease-free interval was longer than the extrapolated time from metastasis. These tumors had been treated with brachytherapy, and hence it is possible that they metastasized 1 to 4 years

Fig.4. The predicted time of initial micrometastasis relative to the time of treatment (dashed line) of the primary intraocular tumor plotted against the observed disease-free interval. Doubling times were based on the single largest metastasis (triangles) and on up to three largest metastases (circles). Patients who were treated for local recurrence of primary tumor (solid circles and triangles) and those who had no such recurrence (open circles and triangles) are shown separately. In two thirds of patients the primary tumor had predictably disseminated between 1 and 5 years before conservative treatment.
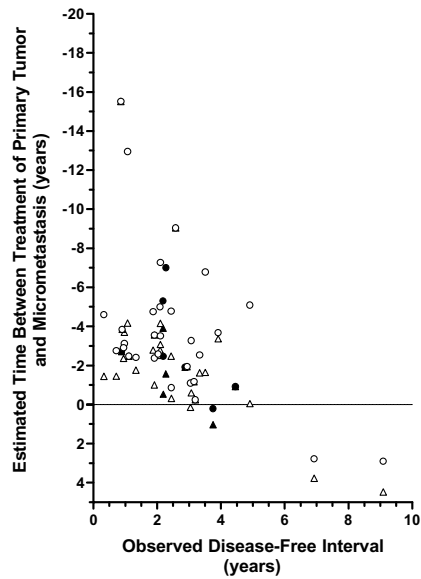

after treatment, especially the one that relapsed locally. Alternatively, these metastases could have been initially slowly growing or latent and later accelerated growth, just like those of patients who have metastasis diagnosed 10 to 20 years after enucleation.[26;54;80;91;92;117]

6.2.2. Tumor Doubling Times of Metastatic Uveal Melanoma During Treatment

The mean tumor doubling times averaged for the entire period of active treatment of the 18 patients who showed either stable disease (SD) or progressive disease (PD) ranged from 25 to 2619 days (median, 255). Five patients showed a partial response (PR) and thus would have given negative doubling times. A scatterplot of calculated doubling times during treatment against pretreatment doubling times did not suggest any correlation between them (Fig.6).

Current chemoimmunotherapy regimens for disseminated uveal melanoma have provided few objective responses and no long term cures.[4;5;17;21;44;58;70;75;97;106;110] Our findings, however, reveal that the treatment likely had an effect on tumor doubling times. The median doubling times during active treatment were generally considerably longer than at the diagnosis of metastases. This may have been due in part to the fact that growth of metastases may slow down when they become large, however.[104;151] Given the rarity of objective responses and the possibility of lead-time bias in median survival, tumor doubling times might provide an additional criterion for comparing systemic treatment responses in metastatic uveal melanoma.

Fig.5. Inferred growth of primary and metastatic uveal melanoma, based on tumor doubling time of 154 days for primary tumor and empiric clinical data for metastasis. The time of micrometastasis, point A, is estimated to be 2.9 years earlier than the diagnosis of the primary tumor, point B, and 5.1 years earlier than clinical diagnosis of metastases, point C; points B and C are plotted at 800 mm^3 and 17000 mm^3, respectively, based on observed median sizes of primary and metastatic tumors. At the time of micrometastasis, the primary tumor is estimated to be 7 mm^3 in size, and at the time of diagnosis of primary tumor, the metastases are estimated to be 0.5 mm^3 in size.
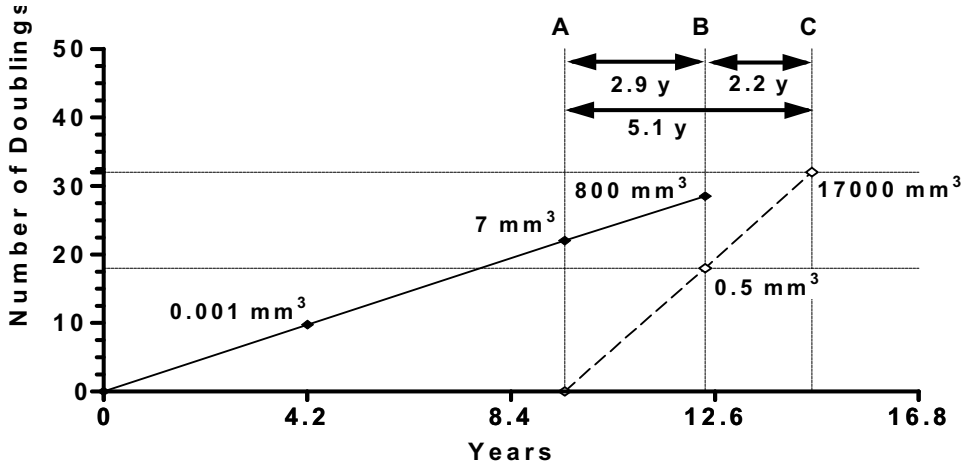
6.2.3. Limitations

Our study is the first one that uses clinical data to estimate doubling times of metastatic uveal melanoma, but it is important to note its limitations. Firstly, the calculated doubling times are based on estimates of the size of undetectable metastases.[152] The resulting values may be biased by the fact that some metastases probably were smaller than the sensitivity limit of imaging in calculations at the time when the screening US was negative. If so, we have underestimated their growth rate. This applies especially to the smallest third of metastases, which possibly had simply disseminated later instead of growing more slowly. It is therefore necessary to view the long doubling times in this study with great caution, even though some of them may well be genuine. It is also possible that an occasional tumor may have escaped detection at screening even if it was actually larger than the sensitivity limit used in calculations. In that case, we have overestimated their growth rate, but this should be less likely. To cover for both sources for bias, a sensitivity analysis using two additional sensitivity limits was performed. Our curves converge towards a doubling time of 30 to 40 days, suggesting that this estimate can be used in planning of screening program.
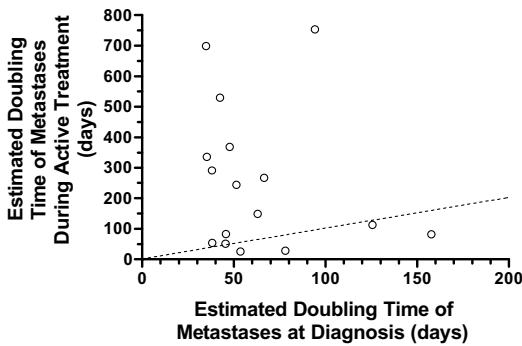
Fig.6. Scatterplot of mean tumor doubling times calculated for up to three largest metastases before and during treatment of metastatic uveal melanoma. The diagonal indicates equal doubling time before and during treatment. No correlation was present between these two variables. Five patients with partial response and two patients with stable disease and consequently extremely long doubling times during treatment were excluded.

Secondly, the mathematical model used is based on constant exponential growth and the estimates can only reflect average growth rates during the period between last negative screening and diagnosis of metastases. The model used is not quite as accurate as the model based on complex Gompertzian growth kinetics but is well accepted as first approximation.[71] Serial imaging of metastases in patients who do not receive active therapy would be needed to confirm our estimates. Our method of extrapolation to earlier stages of metastatic growth is adventurous, because it is likely that growth rates were variable and potentially slower at the time of micrometastasis.[74;104;151] The finding that estimated doubling times did not correlate directly with observed disease-free interval lends support to this idea. For these reasons, it is possible that we have underestimated the time from micrometastasis to treatment of the primary tumor.

Thirdly, for technical reasons, the analysis was based on a nonrandom subset of all patients with metastatic melanoma during the study period. For example, patients who had not participated in annual screening or had not attended a screening visit may have differed from those who did.

6.3. A PROGNOSTIC MODEL AND STAGING FOR METASTATIC UVEAL MELANOMA (III)

As it is well established, the prognosis of metastatic uveal melanoma is poor with a median overall survival from 2 to 9 months.[16;58;70;110] In our study, many of the enrolled patients participated in regular screening and were asymptomatic, since lead-time bias must be taken into account. No tools have yet been available, however, to adjust for differences in case mix between trials.

6.3.1. Patients

The mean age of the 91 patients (male:female, 47:44) at diagnosis of metastatic uveal melanoma was 62 years (SD, 12; range, 23-86). The relapse-free interval ranged from 3 months to 9 years 8 months (median, 2 years 9 months; Fig.7A).

6.3.2. Symptoms and Participation in Annual Screening

Of 74 patients whose symptoms were recorded in detail, 31 (42%) were asymptomatic and 43 (58%) had symptoms from metastases. Of the 91 patients, 77 (85%) participated in annual screening. Dissemination was diagnosed at a scheduled screening in 57 of these patients (74%; 95% CI, 63-83), but 9 of them had recently developed symptoms. Signs or symptoms led to diagnosis in 34 of the 91 patients (37%; 95% CI 27-48), including 20 of the 77 patients (26%; 95% CI 17-37) who participated in annual screening.

6.3.3. Karnofsky Index

Karnofsky index was known for 82 patients, of whom 55 (67%) scored 100-90 (equivalent to ECOG 0), 24 (29%) scored 80-60 (ECOG 1-2), and 3 (4%) scored 50 or less (ECOG 3–4).

6.3.4. Sites of Metastasis

Of the 91 patients, 73 (80%; 95% CI 71-88) had only hepatic metastases at diagnosis, 7 (8%) had only extrahepatic metastases, and 11 (12%) had both hepatic and extrahepatic dissemination. Abdominal US was diagnostic in 75 of 84 patients (89%; 95% CI, 81-95) and suggestive in 5 patients, all of whom were confirmed to have hepatic metastases.

A chest radiogram was negative in 70 of 79 patients (89%; 95% CI 79-95) and suggestive of metastasis in 9 patients (11%; 95% CI, 5-21), all of whom had concurrent metastases in

Fig.7. Cumulative frequency distribution plot for (A) disease-free interval, (B) the largest dimension of the largest metastasis, and (C) serum lactate dehydrogenase, alkaline phosphatase and (D) transaminase levels at diagnosis of metastases for 91 patients who had stage IVB uveal melanoma.
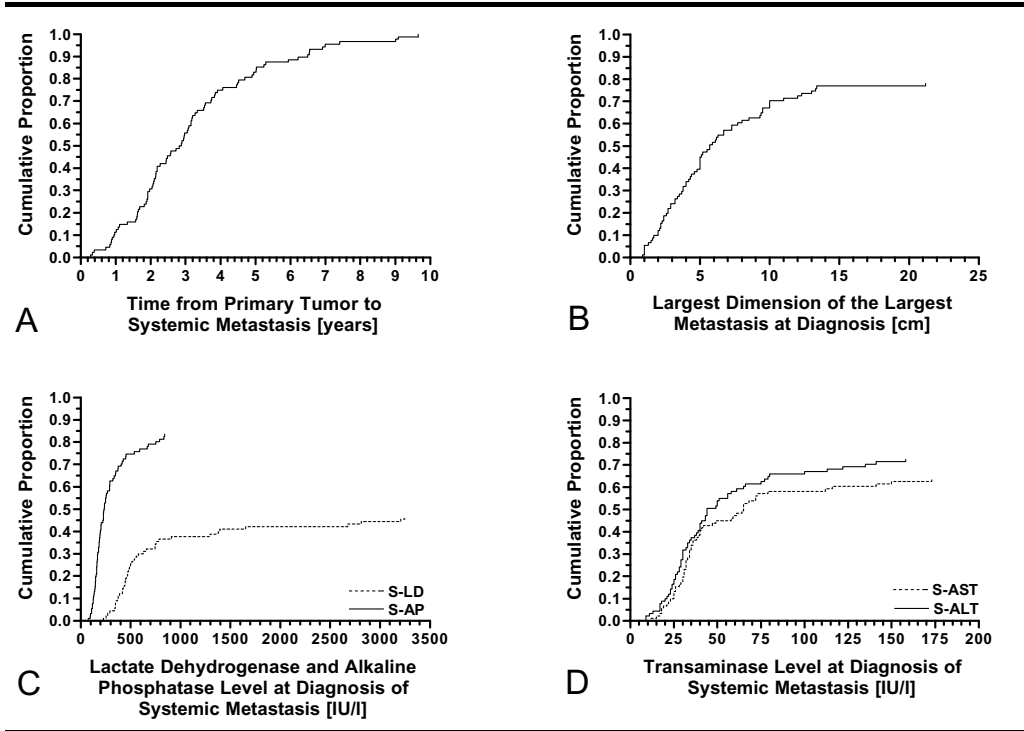
other organs diagnosed clinically or by abdominal US. Pulmonary metastases were confirmed in 5 of the 9 patients.

6.3.5. Size of Metastases

The median largest dimension of the largest metastasis of 71 patients with measurable lesions was 48 mm (range, 9-212; Fig.7B). This dimension tended to be smaller for patients who participated in annual screening than for those who did not (median, 44 v 88 cm; $P =$ .057, Mann-Whitney U test).

The estimated median total, hepatic, and extrahepatic burdens of metastasis were 95 cm^3 (range, 0.5-5434), 87 cm^3 (range, 0.5-5434) and 32 cm^3 (range, 0.5-375), respectively. The estimated total (82 v 791 cm^3; $P =$ .045) and hepatic metastatic burden (78 v 791 cm^3; $P =$ .012) were higher if the patient did not participate in annual screening.

6.3.6. Liver Function Tests

The serum AP level was over the upper normal limit in 23 of 76 patients (30%; 95% CI 20-42; Fig.7C), LD in 27 of 43 patients (63%; 95% CI 47-77; Fig.7C), AST in 21 of 58 patients (36%; 95% CI 24-50; Fig.7D), and ALT in 24 of 66 patients (36%; 95% CI 25-49; Fig.7D).

6.3.7. Treatment

Of the 91 patients, 13 (14%) received chemotherapy and 53 (58%) received chemoimmunotherapy, usually bleomycin, vincristine, lomustine and dacarbazine (BOLD) with human leukocyte or recombinant alpha interferon[97;107] that was given to 50 (76%) of the 66 patients who got systemic therapy. In addition, 9 patients underwent surgical resection and 11 patients palliative radiotherapy at some point.
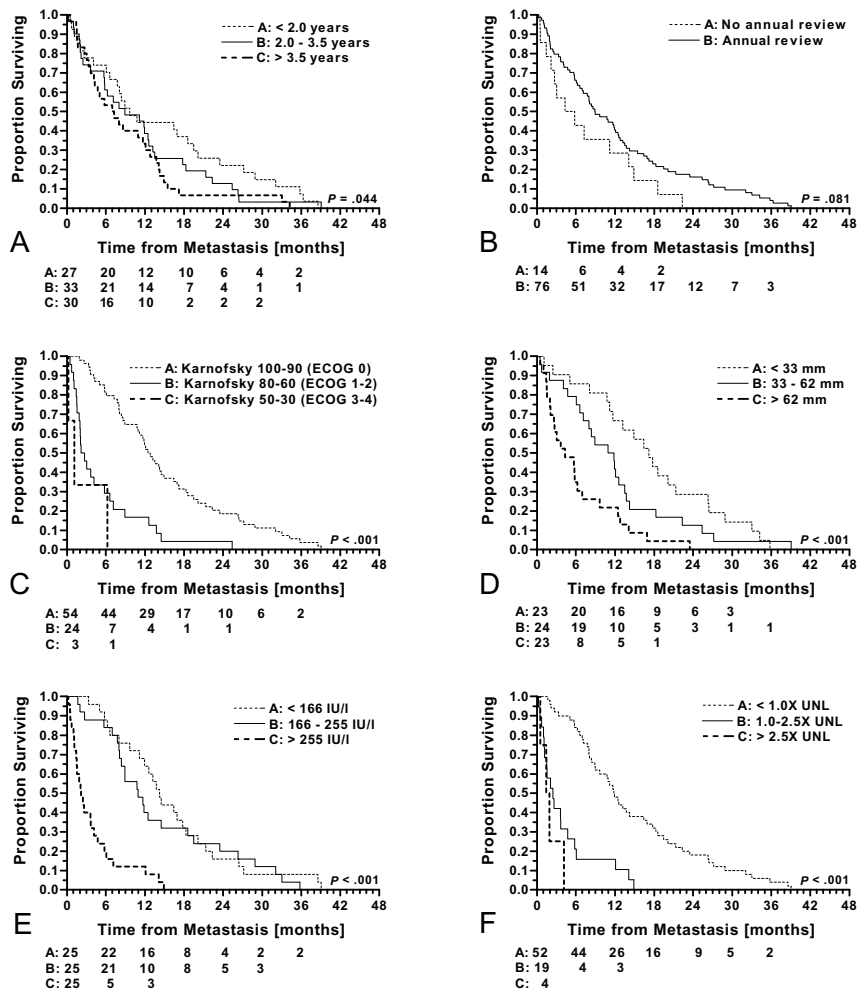
6.3.8. Overall Survival

Although recent nonrandomized, prospective, single institution phase II trials report median survival of even up to 24 months,[43;75;113] the factors contributing to improved prognosis have not been analyzed.

The patients in our series died of disseminated disease after a median interval of 8.4 months (95% CI 6.3-11.8; range 1 week to 73 months); 36 (40%; 95% CI 29-50) survived 1 year, 12 (13%; 95% CI 7-22) patients 2 years, and 4 (4%; 95% CI 1-11) patients 3 years (36, 38, 39 and 73 months). The survival was 12.0 months for those who received systemic therapy. The one who survived 73 months was excluded from survival analysis as an outlier.

In our study, the design did not enable us to discriminate whether rapid progress was due to ineffective therapy or aggressive disease. Not only are patients with smaller metastases more probable candidates for chemotherapy, but they also may have less aggressive disease. Consequently, they are more likely to stay on chemotherapy. If the disease is developing rapidly despite therapy, it is most likely discontinued. Distinguishing between these two possibilities is not mandatory, when time on chemotherapy is modeled as a confounding factor. Whether long time on therapy is due to efficacy or less aggressive disease, it will adjust for the confounding and help to quantitate contribution to prognosis of other factors of interest. An alternative approach would be to stratify according to therapy, but that would ignore variation in the length of treatment.

Fig.8. Observed overall survival for 91 patients with stage IVB uveal melanoma according to (A) disease-free interval, (B) participation in annual screening, (C) Karnofsky index, (D) the largest dimension of the largest metastasis and (E, F) serum alkaline phosphatase level at diagnosis of metastases.

6.3.9. Overall Survival in Relation to Patient Characteristics

By Kaplan-Meier analysis, the gender (P = .46 log-rank test) and age of the patient (P= .61) were not associated with overall survival.

If the relapse-free interval was shorter, overall survival was longer (Fig.8A; P = .044 log-rank test for trend). Asymptomatic patients survived longer than those who had symptoms from metastases (median, 12.1 v 5.7; P = .029). Patients who participated in annual screening

tended to survive longer than those who did not (Fig.8B; median, 8.9 v 4.3; P = .081 log-rank test), but survival from diagnosis of the primary tumor was comparable (P = .25).

Gragoudas and others agree that the asymptomatic patients have better overall survival compared with symptomatic ones.[58] Our study shows that the survival from the diagnosis of the primary tumor does not differ between these categories and suggests that lead-time bias could be responsible for these results. As regards lead-time bias, our analysis also showed that patients who participated in the annual screening tended to survive longer after detection of metastases. Patients who attended annual screening that included liver imaging were expected to survive a median of 9 months, adjusting for time on chemotherapy, whereas patients who were not screened survived a median of 4 months. None of our patients were screened only with chest radiograms and LFTs, but such patients could be expected to survive somewhat longer than those who are not screened.

Overall survival was strongly associated with Karnofsky index (Fig.8C; median, 13.2 v 2.7 v 1.2 months; P < .001 log-rank test for trend). Large dimension of the largest metastasis (Fig.8D; P < .001) and, to a lesser extent, high total metastatic burden (P = .007) were significantly associated with short survival.

High serum level of AP was significantly associated with short survival, whether evaluated by the measured level or relative to the UNL (Fig.8E, F; P < .001). Median survival was 11.9 months if AP was within UNL, 2.5 months if it was less than 2.5 times the UNL, and 1.4 months if the level was higher than 2.5 times UNL.

The median overall survival was 12.0 months for those who received systemic therapy and 4.2 months for those who did not receive it.

6.3.10. Multivariate Analysis of Survival

In our study, the survival was analyzed with Cox regression. By univariate Cox regression, Karnofsky index, the largest dimension of the largest metastasis, total metastatic burden, serum AP, AST, ALT and LD levels, and time on chemotherapy were strongly associated with survival (*P* < .001; Table 7). Presence of symptoms was also associated with survival (*P* = .031). Adjusting for time on chemotherapy by bivariate regression strengthened the association between survival, presence of symptoms (HR 2.57 *v* 1.69; *P* <.001) and regular screening (HR 2.14 *v* 1.67; *P* = .012), but decreased the association with Karnofsky index, size of largest metastasis, total metastatic burden, and LFTs (Table 7).

A multivariate model, based on 54 patients with complete data, which adjusted for time on chemotherapy and evaluated presence of symptoms (which had a higher bivariate Wald chi-

square value than participation in annual screening), Karnofsky index, the largest dimension of the largest metastasis (higher bivariate Wald chi-square than total metastatic burden), and serum AP level (highest bivariate Wald chi-square of all LFTs) as independent variables was considered first (Table 8). Karnofsky index (*P*= .037) and the largest dimension of the largest metastasis (*P* = .020) retained independent prognostic significance in the starting model (Table 8).

The two least significant variables were dropped one at a time to reduce the number of covariates to four. Of the two competing models, the one that included presence of symptoms (*P* = .060) had stronger association with overall survival than the one which included AP level (Table 8; –2 log likelihood, 247.75 *v* 274.82, *P* < .001 Chi-square test, 1 degree of freedom). The latter model, however, lended itself better for categorization. In this model, the Karnofsky index (HR 2.24 for each category change; *P* = .013), the largest dimension of the largest metastasis (HR 1.22 for each 10 mm increase; *P* = .003) and the serum AP level (HR 1.25 for each 100 IU/l change; *P* = .042) retained independent prognostic significance (Table 8).

We tried to consider different aspects relevant to the clinical situation in building of the regression model. Karnofsky index as a measure of general health and the largest dimension of the largest metastasis as a measure of gross disease entered the multivariate model. An advantage is that measuring the largest diameter of one metastasis is very easy for the clinician, compared to calculating tumor burden as the total volume of all measurable metastases.

The choice of the third independent variable had to be based both on practical and statistical considerations. Although dropping serum AP from the model gave a statistically stronger association with overall survival than dropping presence of symptoms, both models identified each included variable as a statistically significant, independent predictor of prognosis. The latter model is probably more suitable for clinical and research practice. Whether a patient has symptoms is a matter of interpretation. Consequently, the effect quantitated from our retrospective data set may be biased, and two clinicians may not agree even if they query symptoms prospectively. Instead, serum AP is measured accurately, and this also applies to retrospective data collection. Also, because it is possible to build a multivariate model which fits well in a small sample but is not generalizable, the evidence does not justify assigning priority purely on statistical grounds.

As uveal melanoma is likely to metastasize into the liver, LFTs are routinely performed. They may reflect the combined effect of deranged liver function and overall metastatic burden, because serum LD is a prognostic marker also for metastatic cutaneous melanoma,[134]

which less frequently metastasizes to the liver. Our finding that serum AP level is an independent predictor of survival even when controlling for measurable metastases suggests that LFTs also may reflect unmeasurable disease. This is a further reason why it is appealing to allow AP in the model.

In our series AP is the LFT most often performed to detect metastatic uveal melanoma. However, AST, ALT, LD, and GGT are likewise associated with survival by univariate analysis.[16;75] We chose AP, because it showed the strongest association with survival in our dataset. An advantage is that the model can be retrospectively applied to the largest possible number of patients with stage IVB uveal melanoma. However, because serum LD level was known for less than half of our patients, which might have affected our statistics, and because LD is a recognized prognostic factor in stage IV cutaneous melanoma, the validity of choosing AP instead of LD must be confirmed by analyzing representative independent datasets.

6.3.11. Working Formulation for Staging Metastatic Uveal Melanoma

Recently The American Joint Committee on Cancer revised the staging of cutaneous melanoma.[13] No categorization was proposed for stage IV. We feel that, as regards stage IVB uveal melanoma (as of January 2003; Stage IV), an effort to categorize is warranted because a prognostic model would be a useful aid to assess prognosis in clinical practice, to decide which patients to enroll and how to stratify them, and to interpret clinical trials.

In this study patients who would normally be eligible for chemotherapy were categorized into three groups based on predicted median overall survival. The coefficients of the final model were entered into the general Cox equation, adjusting for time on chemotherapy using the population mean (5 months). A table of predicted median survival was compiled for clinically relevant combinations of Karnofsky index, serum AP level and the largest dimension of the largest metastasis (Table 9). Based on the predicted survival, the table was divided in three to categorize stage IVB uveal melanoma. The 53 patients who had complete data and whose Karnofsky index was over 50 were staged in the three categories. Kaplan-Meier analysis (Fig.9A) indicated that observed median survival for stage IVBa was 14.4 (95% CI 11.7-21.3), for stage IVBb 8.9 (95% CI 2.7-13.7), and for stage IVBc 2.0 (95% CI 1.0-3.7) months. Scatterplot of predicted median against observed overall survival indicated that the model differentiated survival between stages IVBa and IVBc (Fig.9B).

Table 7. Cox proportional hazards regression of overall survival after diagnosis of metastatic uveal melanoma.

Variable	Regression coefficient (standard error)	Wald χ^2	P	Hazard ratio (95% CI)
UNIVARIATE ANALYSIS				
Gender[*]	–0.157 (0.214)	0.53	0.463	0.85 (0.56-1.29)
Age[†]	0.032 (0.005)	0.41	0.157	1.03 (0.93-1.14)
Largest basal diameter of primary tumor[‡]	–0.016 (0.027)	0.38	0.54	0.98 (0.97-1.04)
Mode of diagnosis[§]	0.748 (0.225)	11.10	<0.001	2.11 (1.36-3.28)
Karnofsky index[¶]	1.223 (0.215)	32.49	<0.001	3.40 (2.23-5.18)
Presence of symptoms[**]	0.526 (0.244)	4.67	0.031	1.69 (1.05-2.73)
Largest dimension of largest metastasis[††]	0.152 (0.030)	25.10	<0.001	1.16 (1.10-1.24)
Estimated total metastatic burden[‡‡]	0.427 (0.119)	12.88	<0.001	1.53 (1.21-1.93)
S-AST[§§]	0.247 (0.045)	30.03	<0.001	1.28 (1.17-1.40)
S-AST >2.5 UNL[¶¶]	2.468 (0.692)	14.29	<0.001	11.80 (3.28-42.4)
S-ALT[§§]	0.172 (0.047)	15.54	<0.001	1.19 (1.08-1.30)
S-ALT >2.5 UNL[¶¶]	1.328 (0.526)	6.92	0.009	3.98 (1.42-11.2)
S-AP[***]	0.397 (0.070)	32.04	<0.001	1.49 (1.30-1.71)
S-AP >2.5 UNL[¶¶]	2.037 (0.552)	13.61	<0.001	7.67 (2.60-22.6)
S-LD[***]	0.054 (0.013)	16.97	<0.001	1.06 (1.03-1.08)
S-LD >2.5 UNL[***]	2.130 (0.406)	27.46	<0.001	8.42 (3.80-18.7)
Time on chemotherapy[†††]	–0.122 (0.022)	29.59	<0.001	0.88 (0.85-0.92)

BIVARIATE ANALYSIS – Adjusted for time on chemotherapy

Mode of diagnosis[§]	1.072 (0.238)	20.34	<0.001	2.92	(1.83-4.65)
Karnofsky index[¶]	0.859 (0.227)	14.29	<0.001	2.36	(1.51-3.69)
Presence of symptoms[**]	0.944 (0.264)	12.82	<0.001	2.57	(1.53-4.31)
Largest dimension of largest metastasis[††]	0.156 (0.064)	25.81	<0.001	1.17	(1.10-1.24)
Estimated total metastatic burden[‡‡]	0.454 (0.117)	14.98	<0.001	1.57	(1.25-1.98)
S-AST[§§]	0.219 (0.046)	22.94	<0.001	1.25	(1.14-1.36)
S-AST >2.5 UNL[¶¶]	2.058 (0.654)	9.92	0.002	7.84	(2.18-28.2)
S-ALT[§§]	0.204 (0.042)	23.91	<0.001	1.23	(1.13-1.33)
S-ALT >2.5 UNL[¶¶]	1.222 (0.528)	5.38	0.021	3.39	(1.21-9.55)
S-AP[***]	0.356 (0.072)	24.60	<0.001	1.43	(1.24-1.64)
S-AP >2.5 UNL[¶¶]	1.607 (0.552)	8.47	0.004	5.00	(1.69-14.7)
S-LD[***]	0.049 (0.013)	13.99	<0.001	1.05	(1.02-1.08)
S-LD >2.5 UNL[¶¶]	1.861 (0.409)	20.70	<0.001	6.42	(2.88-14.3)

[*]	Coding: Male = 0; Female = 1
[†]	Continuous variable, per 5 years
[‡]	Continuous variable, per millimeter (mm)
[§]	Coding: Diagnosed at screening = 0; Diagnosed because of symptoms = 1
[¶]	Coding: 100-90 = 1; 80-60 = 2; 50-0 = 3
[**]	Coding: Asymptomatic = 0; Symptomatic = 1
[††]	Continuous variable, per cm
[‡‡]	Continuous variable, per 1000 cm^3
[§§]	Continuous variable, per 10 International Units (UI)
[¶¶]	Coding: 2.5 x the upper normal limit = 0; 2.5 x the upper normal limit = 1 (Upper normal limits: S-AST and S-ALT: males = 50 UI, females = 35 UI; S-AP = 275 UI; S-LD = 450 UI)
[***]	Continuous variable, per 100 International Units (UI)
[†††]	Continuous variable, per months

Table 8. Cox proportional hazards regression of survival after diagnosis of metastatic uveal melanoma. Time on chemotherapy included as a confounding factor.

Variable	Regression coefficient (standard error)	Wald χ^2	P	Hazard ratio (95% CI)	
MULTIVARIATE ANALYSIS					
Model 1 (Likelihood ratio, −136.3)					
Time on chemotherapy[†††]	*−0.130 (0.033)*	*15.05*	*<0.001*	*0.88*	*(0.82-0.94)*
Mode of diagnosis[§]	0.582 (0.386)	2.28	0.132	1.78	(0.84-3.81)
Karnofsky index[¶]	0.795 (0.329)	5.86	0.016	2.21	(1.16-4.22)
Largest dimension of largest metastasis[††]	0.194 (0.066)	8.76	0.003	1.21	(1.07-1.38)
S-AP[***]	0.147 (0.120)	1.51	0.219	1.16	(0.92-1.47)
Model 2 (Likelihood ratio, −176.4)					
Time on chemotherapy[†††]	*−0.100 (0.027)*	*13.99*	*<0.001*	*0.90*	*(0.86-0.95)*
Mode of diagnosis[§]	0.649 (0.345)	3.53	0.060	1.91	(0.97-3.76)
Karnofsky index[¶]	0.515 (0.284)	3.28	0.070	1.67	(0.96-2.92)
Largest dimension of largest metastasis[††]	0.152 (0.051)	9.00	0.003	1.16	(1.05-1.29)
Model 3 (Likelihood ratio, −137.4) – **Final Model**					
Time on chemotherapy[*]	*−0.118 (0.031)*	*14.14*	*<0.001*	*0.89*	*(0.84-0.95)*
Karnofsky index[¶]	0.807 (0.325)	6.15	0.013	2.24	(1.18-4.24)
Largest dimension of largest metastasis[††]	0.197 (0.066)	8.88	0.003	1.22	(1.07-1.39)
S-AP[***]	0.221 (0.109)	4.16	0.042	1.25	(1.01-1.54)

For categories and coding, see Table 7.

Our working formulation can be tested as a guide in estimating overall survival in clinical practice and in comparing risk between given sets of covariates. For example, a patient whose Karnofsky index is 100, largest metastasis is 40 mm and AP level is 350 U/l would be predicted to live twice as long as one whose Karnofsky index is 80, largest metastasis is 60 mm and AP level is 250 IU/l (median survival 12 *v* 6 months).

As this far no randomized trials have been launched due to the rarity of metastatic uveal melanoma, we recommend reporting working formulation categories in the future to enable more meaningful evaluation of results. For example, if all patients who were enrolled participated in liver imaging and were asymptomatic they should represent stage IVBa, and a median survival of 14 months would be expected and suggestive of limited treatment effect. Had all enrolled patients been of stage IVBb, a median survival of 14 months would be unexpected and suggestive of a survival gain of about 5 months. Finally, we reiterate that the working formulation is provisional and subject to change until verified with independent datasets, and we encourage studies to that effect.

Table 9. Categorization of Stage IV metastatic uveal melanoma into three subgroups according to the predicted median survival, in months, based on Karnofsky index, serum alkaline phosphatase (S-AP) and largest dimension of the largest metastasis[*]

Karnofsky Index	S-AP Level (U/l)	Largest Dimension of Largest Metastasis (mm)				
		20	40	60	80	100
100-90	250	A 14	12	11	8	7
	350	13	12	8	8	6
	450	12	11	8	6	5
	550	B 11	8	7	6	4
80-60	250	11	8	6	6	4
	350	8	8	6	4	3
	450	8	6	C 5	4	2
	550	7	6	4	3	2

[*] Data express predicted median survival in months. Stage IVA corresponds to predicted survival of 12 months or more, Stage IVB to predicted survival of 6-11 months, and Stage IVC to predicted survival of less than 6 months. Calculated from the final Cox proportional hazards regression model given in Table 8.

Fig.9. Observed overall survival for 53 patients with stage IVB uveal melanoma by subcategory (stage IVBa, IVBb, IVBc). (A) Patients were assigned to the subcategories based on predicted median survival calculated from Karnofsky index, serum alkaline phosphatase level and largest dimension of the largest metastasis at diagnosis. (B) Scatterplot of predicted median against observed overall survival by subcategory.
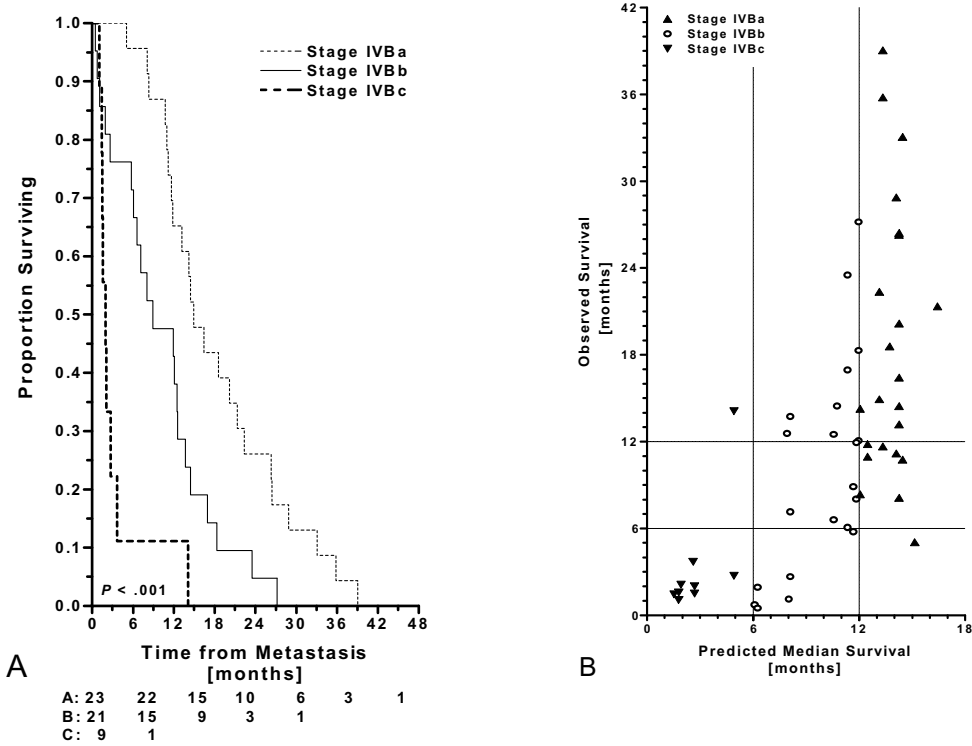
6.3.12. Limitations

A distinctive strength of this study is that the series is essentially population-based and consecutive. As in study II the main limitations of this study are retrospective collection of data and small sample size. However, most data consist of dates and laboratory results from patient charts, which leave little scope for error. Measurements taken from images might have been more precise in a prospective study and recording of symptoms would certainly have been more accurate. Given the small sample, number of variables in the Cox multivariate model was limited, but it was not feasible to set aside a validation sample. In spite of these limitations, we believe that the results can be generalized to other Caucasian patients with metastatic uveal melanoma.

6.4. MODE OF PRESENTATION AND TIME TO TREATMENT OF UVEAL MELANOMA IN FINLAND (IV)

This retrospective survey of referral to treatment of patients with primary uveal melanoma identified several differences as compared with a previous prospective analysis conducted in the United Kingdom.[3;30;31;67]

6.4.1. Symptoms

Out of 159 patients, 139 (87%; 95% CI 81-92) had symptoms prior to their first contact with health care, most commonly blurred vision and a visual field defect (Table 10). The symptoms appeared a median of 84 days previously (range, 0 days-5 years 11 months), and 119 patients (86%; 95% CI 79-91) sought help because of the symptoms. The other 20 patients (13%; 95% CI 8-19) made or kept an appointment made for other reasons, most commonly to change spectacles and to attend a scheduled screening examination for a presumed nevus (Table 11).

Intraocular tumor was diagnosed or suspected in 20 entirely asymptomatic patients (13%; 95% CI 8-19) during an appointment made for various reasons, again most often to change spectacles and to attend a scheduled nevus screening examination (Table 11).

In our series, the tumor was diagnosed in one eighth (13%; 95% CI 8-19) of patients during a routine visit without symptoms. The proportion of asymptomatic patients was one third of that in the British studies, in which 30-45% of patients were asymptomatic.[30;67] This difference suggests that ophthalmic opticians in United Kingdom who perform ophthalmoscopy, may be better accessible than ophthalmologists in Finland. The British might also be better informed about the advantages of routine ocular check-ups, or presence of symptoms may have been coded differently.

As regards the mean age of the patients (59.7 vs. 60.6 years), mean LBD of the tumor (11.6 vs. 11.3 mm), and mean duration of symptoms before first contact (2.2 vs. 3.1 months) the British and Finnish series were comparable[31;67] and do not suggest a systematic difference in accessibility to treatment. The larger mean tumor thickness of Finnish patients (4.9 vs. 6.4 mm) remains unexplained because both values were based on basically identical ultrasonographic measurements.

6.4.2. Initial presentation

The first health care professional contacted was a dispensing optician in 24 cases (15%, 95% CI 10-22), a nonophthalmologist in 30 cases (19%, 95% CI 13-26) and an ophthalmologist in 104 cases (65%, 95% CI 58-73). Prior to the first visit related to the tumor, 39 patients (25%, 95% CI 18-32) had seen a dispensing optician a median of 24 months earlier (range, 3 weeks-15 years 11 months), and 104 patients (65%; 95% CI 58-73) had seen an ophthalmologist for unrelated reasons a median of 26 months previously (range, 3 months–19 years 11 months) (Fig.10).

Of Finnish patients, 45 (28%) had seen an ophthalmologist for reasons unrelated to the tumor less than two years before the initial presentation. In some of such cases it may be that an examination had not been carried out thoroughly. The British studies did not include comparable information.

Table 10. Symptoms before diagnosis of primary uveal melanoma in 159 Finnish patients.

Symptom	N	%*	95% Confidence Interval
Blurred vision	78	49	41-57
Visual field defect	51	32	25-40
Photopsia	29	18	13-25
Irritation and pain	26	16	11-23
Metamorphopsia	10	6	3-11
Floaters	9	6	3-10
Redness	9	6	3-10
Pressure	8	5	2-10
Change in appearance	4	3	1-6
Other symptoms[†]	17	11	6-17
Asymptomatic	20	13	8-19

* Patients typically had more than one symptom
[†] Headache (5), change in color perception (3), tearing and discharge (3), diplopia (1), convergence insufficiency (1), oscillating vision (1), photophobia (1), tic (1), subconjunctival hemorrhage (1).

6.4.3. Diagnosis and referral

The diagnosis made during the first visit was mentioned in 111 of the 159 (70%) patient charts. A tumor was mentioned in 77 (69%) of them.

The dispensing optician referred 21 of 24 patients (88%; CI 95% 68-97) to a private ophthalmologist. Two patients were referred to a nonophthalmologist. The only patient who was not referred had seen floaters for three months and received a prescription for spectacles. Dispensing opticians do not make diagnoses.

The nonophthalmologist referred 26 of 30 patients (87%) to an ophthalmologist. An intraocular tumor was mentioned in two referral letters. Of 25 patients who sought help because of tumor symptoms, 4 (16%) were not referred but were treated for presumed tension neck syndrome, conjunctivitis, blepharitis, and floaters interpreted to be a symptom of concurrent high blood pressure. All four contacted an ophthalmologist within 3 months. Of the 5 patients who made contact for unrelated reasons, 4 had ocular symptoms and 1 had tumor diagnosed when fundi were examined for diabetic retinopathy. All five were referred. Of 104 patients seen first by an ophthalmologist, 23 (22%) were though to have findings typical of uveal melanoma, and 44 (42%) were diagnosed to have an unspecified intraocular

Table 11. The reason for making appointment for 40 patients with primary uveal melanoma who did not seek help because of symptoms

Reason for appointment	Recently symptomatic*			Entirely asymptomatic			Total		
	N	%	(95% CI)	N	%	(95% CI)	N	%	(95% CI)
Spectacle prescription	8	5%	(2-10)	7	4%	(2-9)	15	9%	(5-15)
Nevus screening	4	3%	(1-6)	5	3%	(1-7)	9	6%	(3-10
Health check-up	3	2%	(0-5)	1	1%	(0-3)	4	3%	(1-6)
Unrelated surgery	1	1%	(0-3)	2	1%	(0-4)	3	2%	(0-5)
Diabetic retinopathy	1	1%	(0-3)	1	1%	(0-3)	2	1%	(0-4)
Glaucoma	0	0%	(0-2)	2	1%	(0-4)	2	1%	(0-4)
Other cause[†]	3	2%	(0-5)	2	1%	(0-4)	5	3%	(1-7)

*   The symptoms developed after the appointment was made
[†]   Screening because of cataract (2), systemic medication (2), and congenital toxoplasmosis (1)

tumor. A suspicious nevus was diagnosed in 7 patients (7%) of whom 3 were referred and the rest scheduled for follow-up. Thus, 74 patients (71%; 95% CI 61-80) were diagnosed to have a tumor during the first appointment. However, only retinal detachment was diagnosed in 7 patients (7%) and five patients were referred because of acute glaucoma, uveitis, cataract, vitreous hemorrhage, and an unidentified fundus lesion, one case of each. In 3 of them the tumor was not visible before the secondary problem had been treated. In 10 instances (10%), the reason for referral was not specified.

Of the other 7 patients (7%) who were not referred, 4 were diagnosed to have a refractive error and received spectacles, and the reason for floaters and visual field defect was not identified in 3 patients. All made a new appointment (one saw a dispensing optician who referred him back to the ophthalmologist). During the second visit, 4 of them were diagnosed to have a tumor, one a retinal detachment, and one an unidentified fundus lesion. One tumor still remained undiagnosed and the patient was referred with headache and blurring of vision to a family physician, who suspected a tumor a year later.

Based on our data on uveal melanoma patients in Finland, two out of three seek help from an ophthalmologist whether they have symptoms or not. The probability for them to be immediately referred and correctly diagnosed at first visit was 88% and 71%, respectively. One fifth consulted family practitioners and other nonophthalmologists, and one sixth saw a dispensing optician. They had 88% and 87% chance of being immediately referred, respectively, and 13% of those referred by a nonophthalmologist were diagnosed correctly.

Fig.10. Cumulative frequency plot of the time span between the last visit unrelated to the tumor to an ophthalmologist and to a dispensing optician and initial presentation with the tumor.
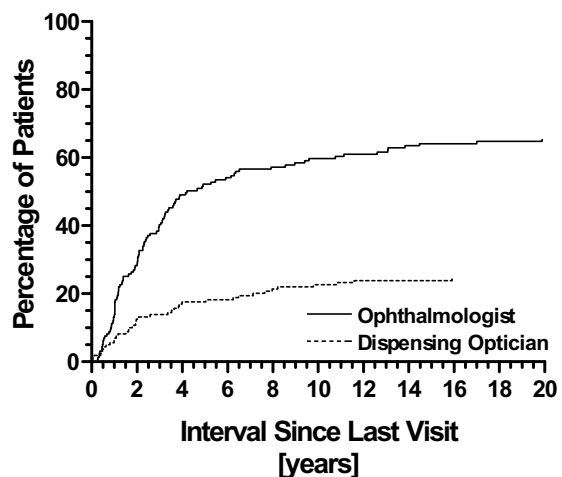
In Finland, the dispensing opticians do not give diagnoses. In Britain, 59% of patients saw first an ophthalmic optician, and only 14% an ophthalmologist.[67] We had an impression that the choice of a health care professional was dictated by availability and personal preference rather than concern related to symptoms (Table 1). Uveal melanomas are relatively rare and it is likely that the patients did not know that the symptoms might be serious.

It is disappointing, but also a sign of sometimes so difficult diagnosis making, that an intraocular tumor apparently was missed by an ophthalmologist in 29% (95% CI 20-39) of patients during the first visit. What is even more important is that most of them were nevertheless referred because of secondary effects of the tumor. Moreover, some of our patients had seen an ophthalmologist for unrelated reasons during previous month(s) without the tumor being diagnosed. The proportion was comparable in the British study, in which misdiagnosis occurred in 4 of 16 patients (25%; 95% CI 7-52) seen by an ophthalmologist.[67] Misdiagnosis rate was 15% when patients presented first to an ophthalmic optician in U.K.[30] This implies a need for further education as regards signs and symptoms of intraocular tumors and emphasizes the importance of dilated fundus examination by indirect ophthalmoscopy, which may not have been carried out in every instance.

6.4.4. Melanomas developing from nevi

The question of following up choroidal nevi is a constant topic of debate. Various views of screening have been presented and several high-risk characteristics have been identified as a useful aid to predict growth of small choroidal melanocytic tumors; such as presence of symptoms and subretinal fluid, tumor thickness greater than 2 mm, orange lipofuscin pigment over the tumor, and tumor margin touching the optic disc.[123;127] The Collaborative Ocular Melanoma Study Group reported three additional features associated with growth: larger basal diameter, absence of drusen, and absence of retinal pigment epithelial change adjacent to the tumor.[144] Of 11 choroidal nevi, 10 (91%) had at least 1 risk factor for growth. Seven nevi (36%) were associated with 3-4 of the 8 known high-risk characteristics for growth.

Table 12. Nine presumed nevi that were regularly screened and later evolved into a uveal melanoma

Gender	Age (years)	Follow-up Length (years)	Follow-up Interval (months)	Location	At first visit Diameter (mm)	At first visit Height (mm)	At diagnosis of melanoma Diameter (mm)	At diagnosis of melanoma Height (mm)
Female	51	35	24	Iris*	5 x 3	1	7.0 x 5.0	3.0
Male	68	6	12	Iridociliary†	N/A	N/A	N/A	N/A
Female	52	2	3	Choroid	5.2 x 4.7	2	9.9 x 7.6	3.6
Female	53	6	12	Choroid	7 x 6	3	11.6 x 11.6	5.2
Male	54	3	12	Choroid	13 x 8	1	13.0 x 9.0	3.2
Female	61	10	12	Choroid	6 x 5	1	12.0 x 9.5	5.5
Female	69	2	12	Choroid	4 x 4	1	6.0 x 5.8	1.9
Female	72	2	12	Choroid	7 x 5	1	7.3 x 6.2	4.3
Female	73	3	12	Choroid	8 x 6	1	12.0 x 8.0	3.5

* Very slowly growing iris tumor finally removed at cataract surgery

† A presumed iris nevus that evolved into a ring melanoma, not applicable

In Finland, of the 159 patients, 13 (8%) developed a melanoma from a previously identified presumed nevus. In 9 of them the melanomas were diagnosed in a scheduled screening (69%; Table 12), the others were not followed up systematically. The median follow-up time before diagnosis of uveal melanoma was 3 years (range, 1–35 years) and the screening interval 12 months (range, 3 months - 2 years). Despite screening, in 8 of the 13 (62%) eyes, symptoms developed before diagnosis.

The median LBD of the presumed nevus at first examination was 6.0 mm, height 1.0 mm, and volume 19 mm^3. When uveal melanoma was diagnosed, the median LBD had increased by 1.7 times to 10 mm, the height by 3.5 times to 3.5 mm, and the volume by 7.5 times to 142 mm^3.

Roughly one out of ten uveal melanomas in this population-based study developed from a known presumed nevus. The proportion who had a previous nevus was roughly the same, 3 of 50 patients in the British study.[3] This is likely to be an underestimate, because a third of our patients had not seen an ophthalmologist before and because nevi in the peripheral fundus may escape attention. It is of note that 10 of the 11 presumed nevi that developed a melanoma were initially associated with at least one of the eight known high-risk characteristics for growth. In particular, 8 had developed symptoms since last screening. We suggest that follow-up of presumed nevi would be ideally based on fundus photographs and, when the nevus is elevated, on ultrasonographic measurements. The smaller the nevus is, the more difficult it is to observe growth only by ophthalmoscopy, and this applies particularly to change in tumor height. Thus, the tumors in our study were on average almost twice as large by LBD at diagnosis of uveal melanoma than initially, but their median volume was seven times bigger. Prior growth was thus probably missed or overlooked which emphasizes the importance of referring small suspicious tumors for second opinion at an early stage and of following them with photography and ultrasonography, especially as tumor doubling times suggest that micrometastasis may take place one to five years before diagnosis of primary tumor in two thirds of patients with metastases. Patients with nevi should also be told to return immediately if any visual symptoms develop.

6.4.5. Number of visits and delay times

The median number of visits before treatment was 4 (range, 2-23) including a visit to a regional hospital to rule out other malignancies and metastases and treatment planning visit to the ocular oncology service.

The median time from initial presentation to treatment planning was 35 days (range, 0-1426). When the first contact was a dispensing optician the median was 22 days (range, 1-1156), when a nonophthalmologist was contacted it was 68 days (range, 0-1283), and when an ophthalmologist was consulted, the median delay was 34 days (range, 1-1426). The differences in delays were not statistically significant ($P = 0.16$, Kruskal-Wallis test).

Whether the tumor was suspected during the first visit or not did not statistically significantly affect the delay before treatment planning (Fig.11A; 77 patients vs. 82 patients, median, 34 days vs. 49 days, $P = 0.15$ Mann-Whitney *U*-test).

In our dataset, 25 patients (16%; 95% CI 10-22) were recognized to have been misdiagnosed or to have had administrative problems related to their referral. The delay before treatment planning for these 25 patients was statistically significantly longer than that of patients who had not experienced such a problem (Fig.11B; median, 101 days *vs.* 34 days, $P = 0.001$).

The British study identified avoidable delay in referral in 42% (95% CI 28-57) of 50 patients.[3] Based on the same categorization, 16% (95% CI 10-22) of our patients encountered a similar delay in referral. In Finland the specialist at the receiving unit decides the urgency of the referred patient based on the information in the letter. The British study speculated that reassurance that symptoms are not serious leads to late diagnosis,[3] but the Finnish patients usually searched rapidly a new consultation when symptoms persisted.

One cause of delay in our study was the waiting time to imaging of the liver in regional hospitals which are financial gatekeepers as regards referral to the ocular oncology service. Waiting for special investigations also caused delay in Britain, where the most important delay was referral to an ophthalmologist via a general practitioner,[31;67] also a financial gatekeeper. We did not find difference in delays whether or not the patient was seen first by an ophthalmologist or other health care professional, and whether or not a tumor was immediately suspected.

Even if the delay might not affect survival, patients feel most distressed during the interval from suspicion of a tumor to eventual treatment after which the stress diminishes.[29]

Because micrometastasis may take place between 1 and 5 years before diagnosis,[84;86] a median delay of less than 4 months from the onset of symptoms to treatment may not always represent a serious hazard to life, but a shorter delay could potentially salvage more useful vision and perhaps prevent some metastases from developing. These findings also seem to indicate that an earlier diagnosis in several instances might be possible if routine dilated

fundus examinations were performed without exception. Routine referral of patients with suspicious nevi for second opinion could also reduce delay in a subgroup of patients.

6.4.6. Tumor dimensions and treatment

The median time from initial presentation to the treatment was 57 days (mean, 126 days; range, 6-1435). Of the 159 patients, 8 (5%) were treated within 2 weeks from the initial presentation and the delay was longer than 20 weeks in 33 (21%) instances.

None of the patients had clinical metastases at diagnosis. The median height of the melanoma was 6.0 mm (mean, 6.4 mm; range, 1.0-17.0), LBD was 11.0 mm (mean, 11.3 mm; range, 2.5-22.0), and volume 286 mm^3 (mean, 484 mm^3; range, 5-3686). The presence of tumor symptoms ($P = 0.16$; Mann-Whitney U-test) and tumor volume ($r = - 0.89$; $P = 0.29$; Spearman's rank correlation) were not statistically associated with the delay but a tendency of large and medium-sized melanomas being diagnosed earlier than small ones was present when compared according to categorized tumor sizes (Fig.11C, $P= 0.068$; Kruskal-Wallis test).

The median time from treatment planning to treatment was 11 days (mean 16 days; range, 0-126). Of the 159 patients, 100 (63%) were treated within 2 weeks and 126 (79%) within 3 weeks time. Delays less than 3 weeks were related to waiting for the appropriate plaque to be ready from previous treatment. Delays longer than 3 weeks occurred when an indeterminate tumor was first observed for growth, vitreous hemorrhage initially made the diagnosis uncertain, further investigations to rule out metastasis were needed, and when required by the patient because of intercurrent disease, personal reasons, or need for second opinion.

Brachytherapy with ruthenium and iodine plaques was given to 81 (51%) and 63 (40%) patients, respectively. The involved eye was enucleated from 11 (7%) patients and 4 tumors were treated with local resection. A statistically significant association was found between the delay and type of brachytherapy. The median delay was 59 days (range, 4 days-3 years 6 months) for patients who underwent ruthenium plaque therapy and 33 days (range, 0 days-2 years 10 months) for those who underwent iodine brachytherapy (Fig.11D; $P = 0.009$; Mann-Whitney U-test).

In Britain, patients who were promptly referred were more likely to be treated with eye- and vision-conserving methods.[3] In Finland, no such difference emerged partly because of much more common use of iodine plaque radiotherapy instead of enucleation for large tumors. However, an unforeseen difference was noticed between the two modes of brachytherapy. Ruthenium brachytherapy, used for smaller melanomas, was paradoxically

Fig. 11. Cumulative frequency plots of time from the initial presentation to treatment planning in the national ocular oncology service according to (A) the health care professional seen. One patient referred by a school nurse is omitted, (B) whether or not misdiagnoses or administrative problems occurred in the referral process. (C) categorized tumor size (Kruskal-Wallis test), and (D) the type of brachytherapy (Mann-Whitney *U*-test).
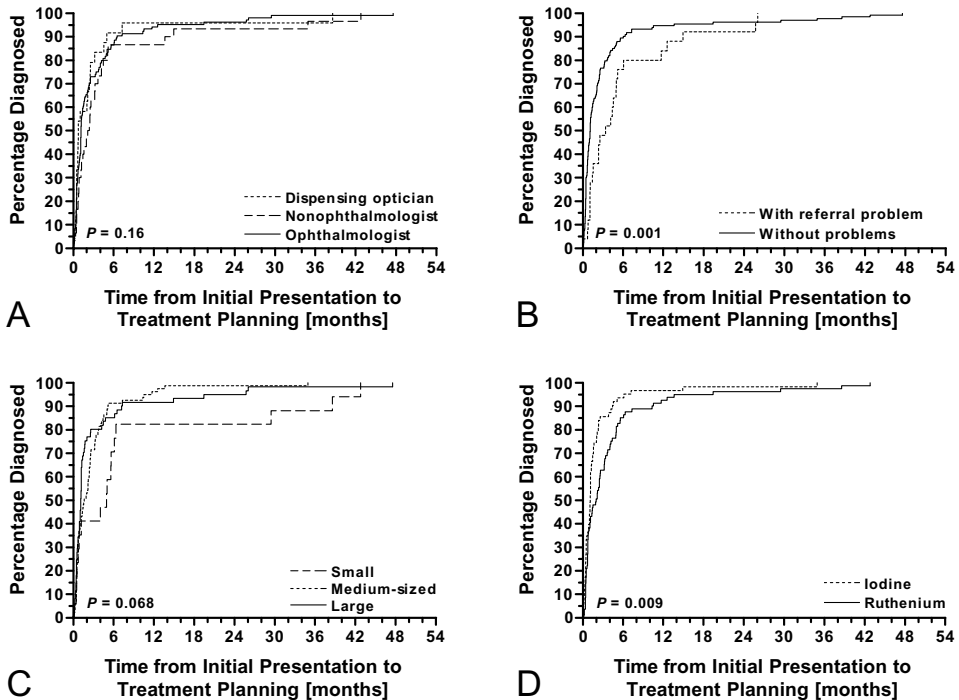
associated with longer delays than iodine brachytherapy, given to patients who have larger tumors. Even though we did not find statistically significant differences in delay according to tumor size this finding suggests that larger melanomas caused more symptoms and were easier to diagnose and were thus also treated faster.

6.4.7. Limitations

Because of its retrospective nature, this study was liable to missing and erroneously recalled data. Checking the data against patient charts and other legal documents have minimized this problem. The number of patients was small, but this is compensated for by the fact that the present series was population-based, consecutive, and had a high inclusion rate. We believe that the results reflect the current referral for uveal melanoma in Finland reasonably well.

6.5. FUTURE DIRECTIONS

This study was planned and carried out to help physicians to detect primary and metastatic uveal melanoma as early as possible and to understand the clinical course of disseminated disease. By earlier diagnosis, better survival and quality of life might be achieved, although the diagnostic delay, when present, was generally found to be relatively short with regard to the predicted time of micrometastasis. One may predict that efforts to combat micrometastasis are likely to prove more successful in improving prognosis than pursuing an earlier diagnosis of the primary tumor, which nevertheless remains a desirable goal.

Regarding management of disseminated uveal melanoma, the new information presented in this thesis will help clinicians to:

1. Plan and organize screening programs for metastatic disease based on sensitivities and specificities of various examinations available at the moment and schedule them accordingly based on tumor doubling times. In the future one would like to have more sensitive means of imaging hepatic and extrahepatic metastases, so that patients who have metastases in either or both of these compartments can receive appropriately targeted therapy. Neither computed tomography, magnetic resonance imaging nor ultrasonography are perfect for this purpose.

2. Stratify patients who are enrolled into treatment trials for metastatic disease according to predicted survival so as to obtain more valid data on the effect of therapy even when randomization is not possible. The HUCH working formulation will also be an important tool in evaluating survival results of different trials, but it still needs to be validated by external data and it may need adjustments in the future if significant development in diagnostic strategies and prognostication takes place. The advent of adjuvant treatments may also require changes in the formulation.

3. Recognize procedures in their clinical practice that are inefficient and not evidence-based as regards detecting, identifying and referring patients with intraocular melanoma and suspicious nevi.

Future research must identify factors which influence the time that micrometastases need to grow into clinical metastasis. If this time can be controlled and prolonged, it may be possible to improve the prognosis of patients with uveal melanoma even if the metastases cannot be totally cured.

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