Aus der Klinik und Poliklinik für Augenheilkunde
Direktor: Prof. Dr. Rudolf F. Guthoff

Clinical, radiological and histological characteristics of orbital lesions and treatment options: a study of 132 cases

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Manousaridis, Kleanthis
aus Ptolemaïda, Griechenland

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Dekan: Prof. Dr. Emil Reisinger

1. Gutachter: Prof. Dr. med. R. F. Guthoff
2. Gutachter: Prof. Dr. med. K. H. Emmerich
3. Gutachter: Prof. Dr. med. H. Busse

For my parents

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1. Introduction

1.1. Anatomy of the orbit

1.1.1. Bony Anatomy

The orbits are bony cavities situated at either sides of the nasal fossa, between the anterior compartment of the base of the skull and the superior portion of the facial bones occupied by the maxillary sinuses. The orbit displays a pyramidal and irregular shape with a square base directed anteriorly, corresponding to the facial opening of the orbit. The orbital vertex is located in the posterior extreme of the orbit. The orbit represents an anatomical unit with an approximate volume of 30 cc. In it converge complex structures such as bones, muscles, sensory and motor nerves, vascular elements as well as fat and connective tissue, while the globe occupies a volume of approximately 7cc.

The medial walls of the orbit are 2,5cm apart, roughly parallel, and 4,4cm to 5cm long. The lateral walls are 4,5cm to 5cm long and lie at right angles to each other. The distance from the inferior orbital rim anteriorly to the infraorbital groove posteriorly is 2,5cm to 3cm. The depth of the temporalis fossa laterally is 2cm.

Orbital roof: It is triangular. It is composed by the horizontal plate of the frontal bone anteriorly and the lesser wing of the sphenoid bone posteriorly.

Orbital floor: It is triangular. Anteromedialy it is composed by the orbital plate of the pyramidal process of the maxillary bone. The horizontal portion of the orbital process of the zygomatic bone contributes anterolaterally. Its vertex is composed by the orbital process of the palatine bone. The inferior orbital wall is a thin bony wall that separates the orbit from the adjacent maxillary sinus. The infraorbital sulcus is a fissure located on the orbital plate of the maxillary bone that runs the orbital floor displaying a posteroanterior direction. After a 2cm trajectory it transforms into the infraorbital canal and exits the orbit through the infraorbital foramen, located 5mm below the inferior orbital rim.

The maxillary sinus and often some of the ethmoid sinuses are immediately adjacent to the floor.

Medial wall: It is the thinnest wall (0,2mm to 0,4mm) and is made of the maxillary, lacrimal, ethmoid and lesser wing of the sphenoid. About 20mm behind the anterior medial orbital margin is the anterior ethmoid foramen and 12mm behind this the posterior ethmoid foramen, which is 5 to 8 mm from the optic canal. These foramina mark the horizontal level of the cribriform plate at the fronto-ethmoidal suture line. The ethmoid and frequently the sphenoid and maxillary sinuses form part of the medial wall.

Lateral wall: It is composed by the greater wing of the sphenoid, frontal and zygomatic bones, and is at an angle of 45 degrees to the medial wall. It is the strongest orbital wall. Posteriorly it is separated from the roof by the superior orbital fissure, which is 2,2cm long, and from the floor by the inferior orbital fissure, which is 2cm long. Laterally it forms a portion of the temporalis fossa, which is thinnest at the suture line between the greater wing of the sphenoid and the zygomatic bone (where it can be fractured easily at surgery).

Orbital apex: At the level of the orbital vertex there is a confluence of its walls. The orbital vertex is occupied by two important foramina containing all the elements that compose the orbital pedicle:

a). Optic foramen: It constitutes the anterior boundary of the optic canal, through which the orbital cavity and the middle cranial fossa communicate.

b). Sphenoidal or orbital fissure: This is the space between the lesser wing of the sphenoid bone superiorly and the medial border of the greater wing of the sphenoid inferiorly.

The periorbita is a thin fibromuscular membrane that lines the orbital walls completely from the orbital vertex to the orbital rim, where the orbital septum is attached. Posteriorly it is continuous with the dura of the optic nerve and that surrounding the superior orbital fissure and anteriorly with the periosteum of the orbital margins. Thus surgery or trauma posteriorly may result in cerebrospinal fluid leaks.

The table below indicates the anatomic structures which pass through the foramina mentioned above.

Table 1. The anatomic structures which pass through the foramina (Moreiras JVP, Prada MC Orbit: Examination, Diagnosis, Microsurgery, Pathology 2004, modified).

Superior sphenoidal fissure	Communicates with the cavernous sinus	Cranial nerves III, IV, and VI. Superior ophthalmic vein. V1 (frontal, lacrimal, and nasociliary nerves)
Optic canal	Communicates with the optic chiasm	Optic nerve. Ophthalmic artery
Inferior orbital fissure	Communicates with inferiortemporal and pterygopalatine fossae, and foramen rotundum	V2 (infraorbital nerve). Inferior ophthalmic vein.
Anterior and posterior ethmoidal foramina	Communicates with ethmoidal sinus mucosa	Arteries, veins, and anterior and posterior ethmoidal nerves (respectively)
Zygomaticofacial foramen	Communicates with tissues from the inferior and lateral orbital rim	Zygomaticofacial artery, vein, nerve.
Zygomaticotemporal foramen	Communicates with tissues of the superior and lateral orbital rim	Zygomaticotemporal artery, vein, nerve.

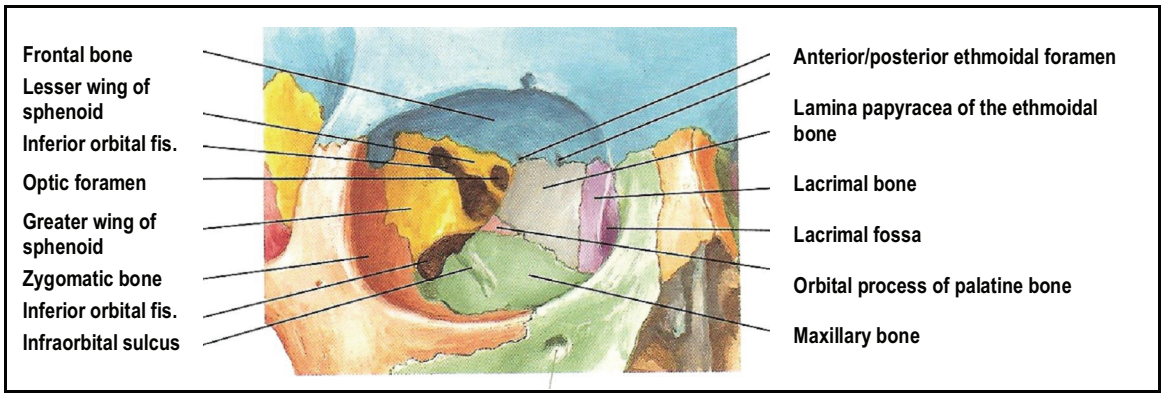

Figure 1. The bony anatomy of the orbit *(aspect 1)*. (Netter Atlas of Human Anatomy, 2nd Edition 1997).

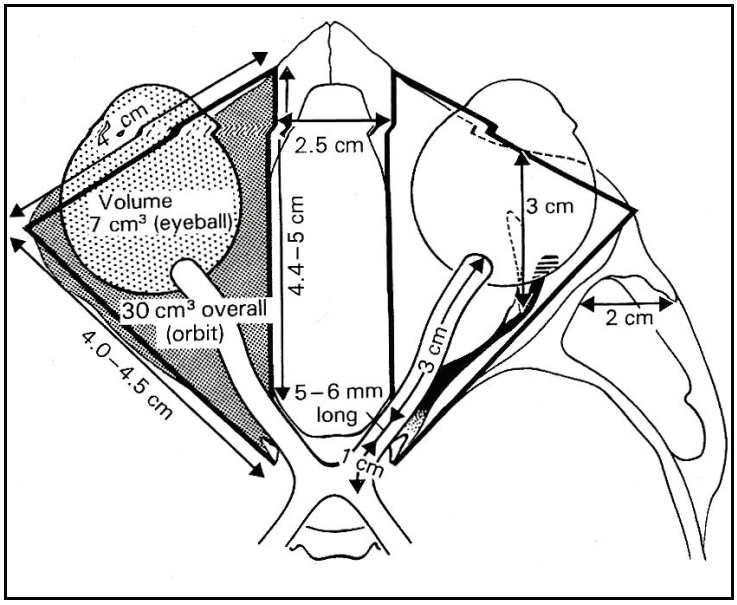

Figure 2. The bony anatomy of the orbit *(aspect 2).* (Rootman J Diseases of the orbit 1988).

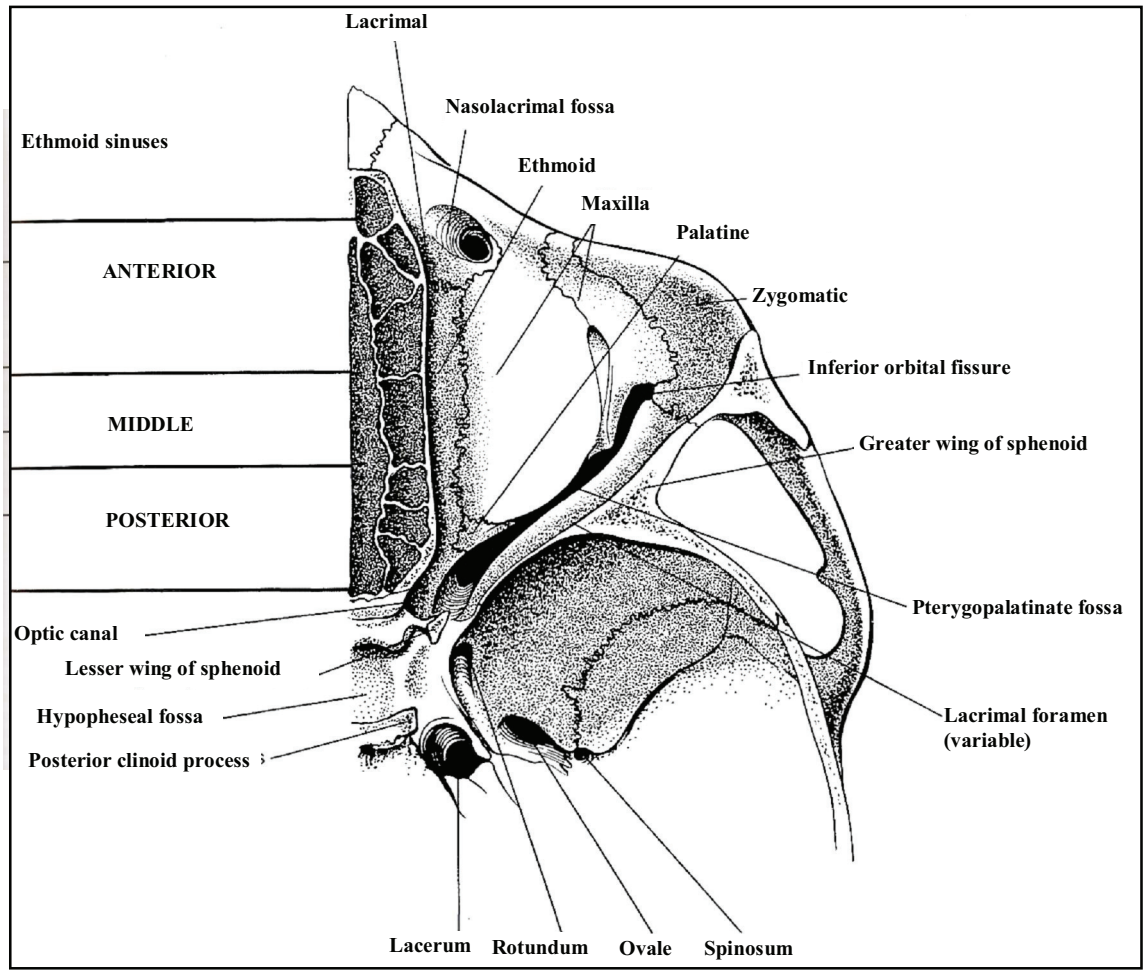

Figure 3. The bony anatomy of the orbit *(aspect 3).* (Rootman J Diseases of the orbit 1988).

1.1.2. Orbital spaces

1. Subperiosteal space (virtual): located between the periosteum and the orbital portions of the orbital bones.
2. Preseptal space: located outside the orbital septum, includes the eyelids, lacrimal drainage system, palpebral lobe of the lacrimal gland and preseptal fat.
3. Tenon's space (virtual): located between the Tenon capsule and the episclera.
4. Intraconal space: located inside the muscular cone, it contains the optic nerve and intrakonal fat.
5. Extraconal space: located on the outside of the muscular cone and extending to the periosteum. It contains the oblique muscles, orbital lacrimal gland and extrakonal fat.

1.1.3. Orbital extraocular muscles

The six striated extraocular muscles, including the four recti and two oblique muscles control eye movement. The recti arise from the annulus of Zinn at the apex, where it is continuous with the dural sheath of the optic nerve and periorbita. Because of this intimate relationship apical disease frequently affects all of these structures simultaneously. Anteriorly the recti insert into the globe 5mm to 7mm posterior to the limbus. The superior oblique originates just superior to the annulus, and passes forward through the trochlea (4mm to the orbital margin) from whence it extends in a slight posterolateral plane to insert on the superior aspect of the globe. The inferior oblique arises from the bone just posterolateral to the nasolacrimal fossa, then it extends in a slight posterolateral direction beneath the inferior rectus and inserts on the inferolateral aspect of the eye.

Levator palpebrae/upper lid retractor muscle

This muscle originates in the deeper portion of the orbit from the lesser wing of the sphenoid, posteriorly to the tendon of Zinn. It courses forward and is situated between the orbital roof and the rectus superior. At the level of

superior orbital rim it passes into the insertional aponeurosis that curves following a descending direction reaching the entire width of the upper lid. The insertional fibers of the levator are disposed in two superposed layers: one superficial of aponeurotic nature, and another deep layer composed by non-striated muscle fibers. The superficial layer ends inserting on the anterior portion of the tarsus. The non-striated muscle fibers of the deep layer insert on the upper border of the tarsus and the upper fornix. These non-striated fibers are known as the upper lid muscle of Müller. The striated and non-striated muscle fibres of the levator constitute the upper lid retractor muscle.

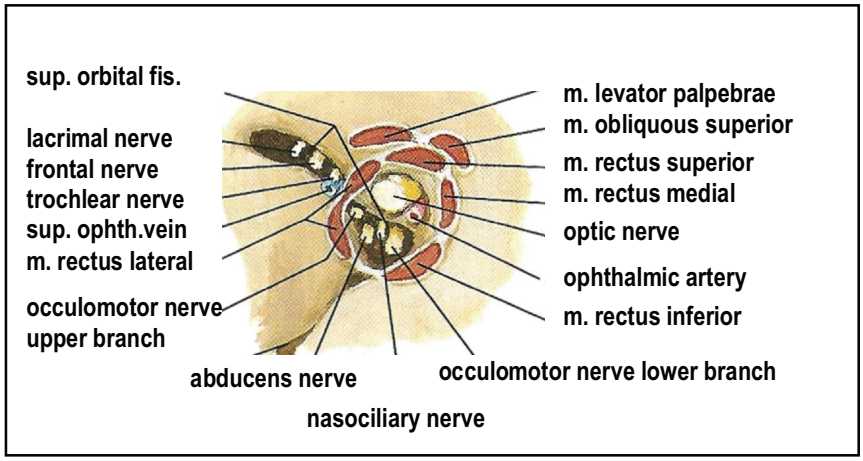

Figure 4. Apical structures. (Netter Atlas of Human Anatomy, 2nd Edition 1997).

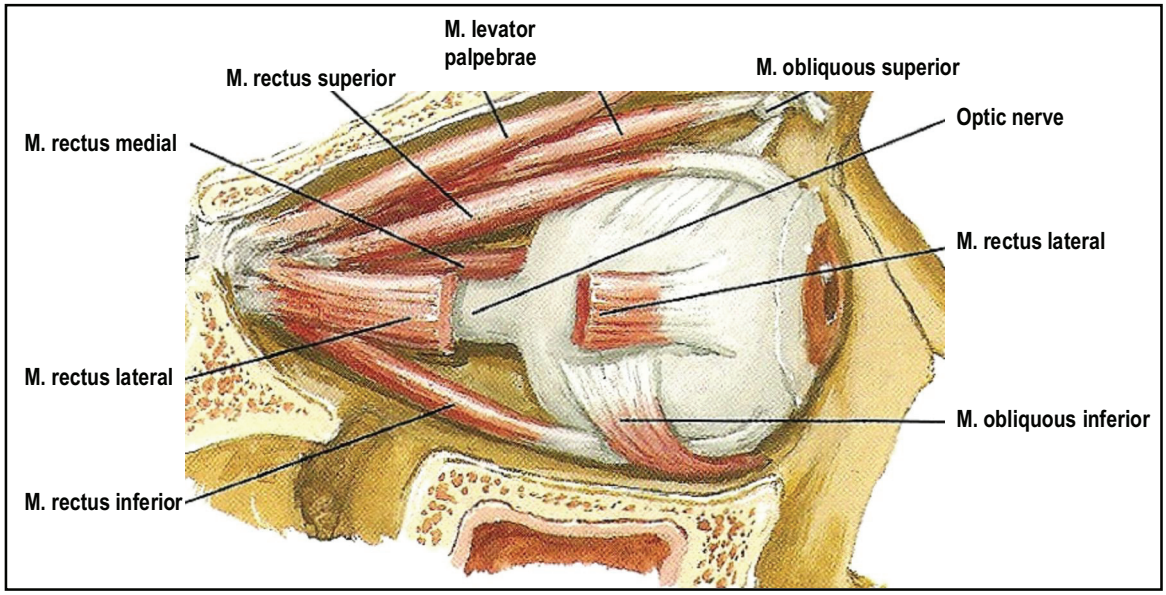

Figure 5. The muscles of the orbit *(aspect 1).* (Netter Atlas of Human Anatomy, 2nd Edition 1997).

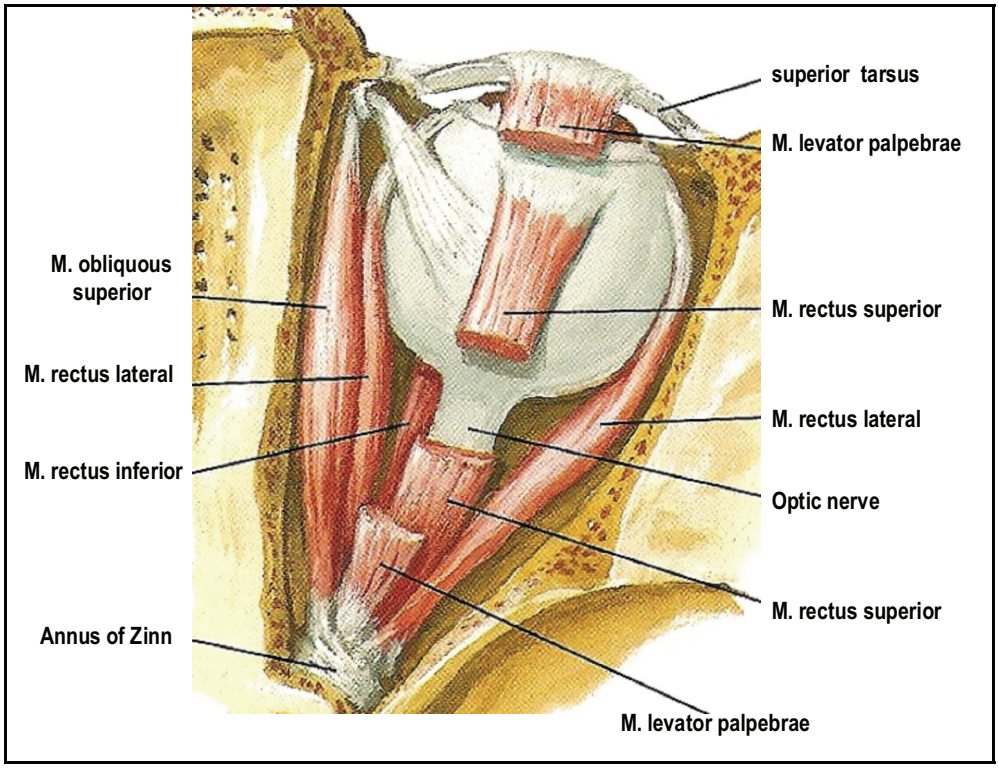

Figure 6. The muscles of the orbit *(aspect 2).* (Netter Atlas of Human Anatomy, 2nd Edition 1997).

1.1.4. Orbital arteries and orbital venous drainage

1.1.4.1. Ophthalmic artery

Orbital vascularisation depends on the ophthalmic artery system, which is a collateral branch of the internal carotid artery. The ophthalmic artery enters the orbit through the optic canal accompanying the optic nerve. The ophthalmic artery adopts a caudal position in relation to the optic nerve.

In the orbit, the ophthalmic artery initially adopts a lateral position in relation to the optic nerve (laterooptical portion); after a short distance of approximately 5mm, the artery traverses the superior side of the optic nerve (supraoptical portion), and then situates near the medial orbital wall, where it adopts an undulated trajectory while travelling forward between the superior oblique muscle above, and the medial rectus muscle below. The artery reaches the

anterior border of the orbit and perforates the broad upper lid ligament, between the trochlea of the superior oblique muscle above, and the medial check ligament, below. Finally, it reaches the base of the nose where it anastomoses with the angular artery, the terminal branch of the facial artery.

Collateral branches of the ophthalmic artery

The ophthalmic artery sends the following ten collateral branches along its intraorbital trajectory:

Central retinal artery

Initially it lies on the lateral side of the optic nerve, and then reaches its inferior side. it sends multiple branches to the optic nerve sheaths, and finally, approximately 1cm behind the eyeball, penetrates the optic nerve through its inferior portion. When it reaches the eyeball, it penetrates into it through the lamina cribrosa, traverses the optic papilla and then branches onto the retina.

Lacrimal artery

The lacrimal artery follows an anterior direction applied to the superior edge of the lateral rectus muscle, accompanied by the lacrimal nerve. Before it reaches the posterior portion of the lacrimal gland, the artery divides into several branches that irrigate the gland.

Supraorbital or frontolateral artery

This takes an ascendant direction and travels along the internal portion of the superior rectus and levator muscles. It exits the orbit through the supraorbital foramen, and ends innervating the frontal region and upper lid.

Posterior ciliary arteries

Initially they are composed of two or three branches that immediately send new branches. They follow the direction of the optic nerve, following an undulated trajectory until they reach the posterior pole of the globe. They penetrate the sclera around the optic nerve and distribute some branches on the sclera, but fundamentally into the choroid.

Long ciliary arteries

These are two arteries, one medial and the other lateral, that lie medially and laterally to the optic nerve respectively. When these arteries reach the eyeball they penetrate the sclera and reach the suprachoroidal space where they travel (without sending branches) along the nasal and temporal meridians of the globe accompanied by branches of the long ciliary nerves.

Posterior and anterior ethmoidal artery

They penetrate the anterior and posterior ethmoid foramina.

Medial Palpebral arteries

These two arteries, one the superior palpebral and the other the inferior palpebral, originate from the ophthalmic artery through a common trunk below the trochlea of the superior oblique muscle. They traverse the broad palpebral ligament and situate between the tarsus and the orbicularis muscle, parallel to the free margin of the corresponding lid.

Internal frontal artery

Originates from the ophthalmic artery in the vicinity of the trochlea of the superior oblique muscle, traverses the broad upper lid ligament and exits the orbit accompanying the internal frontal nerve

Terminal branch of the ophthalmic artery

After sending all its collateral branches, the ophthalmic artery lies in the superomedial orbital angle and traverses the broad upper lid ligament, between the internal frontal artery inwards, and the superior palpebral artery outwards. Once it exits the orbit, the ophthalmic artery displays an oblique, downward and outward trajectory following the base of the nose. It traverses the angular vein and ends anastomosing to the angular artery, the terminal branch of the facial artery.

1.1.4.2. Orbital venous drainage

The orbital veins are valveless, the superior ophthalmic draining into the cavernous sinus by the superior orbital fissure, and the inferior into the superior ophthalmic vein and the pterygoid plexus. The superior is larger, and is formed by the confluence of the angular, nasofrontal and supraorbital veins. It has three sections, the first extending posterolaterally to the medial border of the superior rectus in the anterior third of the orbit. The second section of the superior ophthalmic vein enters the muscle cone, passing to the lateral orbit beneath the superior rectus muscle. The third section extends posteromedially along the lateral border of the superior rectus into the superior orbital fissure, where it drains into the cavernous sinus. The more variable inferior ophthalmic vein forms inferolaterally as a plexus, and passes posteriorly

adjacent to the inferior rectus muscle. It anastomoses with the superior ophthalmic vein, and has a similar branch that connects with the pterygoid plexus through the inferior orbital fissure. The tributaries are muscular, medial collateral, vortex, and lateral collateral.

Anterior venous drainage may be through the facial by means of the angular vein medially, and a plexus from the inferior ophthalmic to the facial vein laterally.

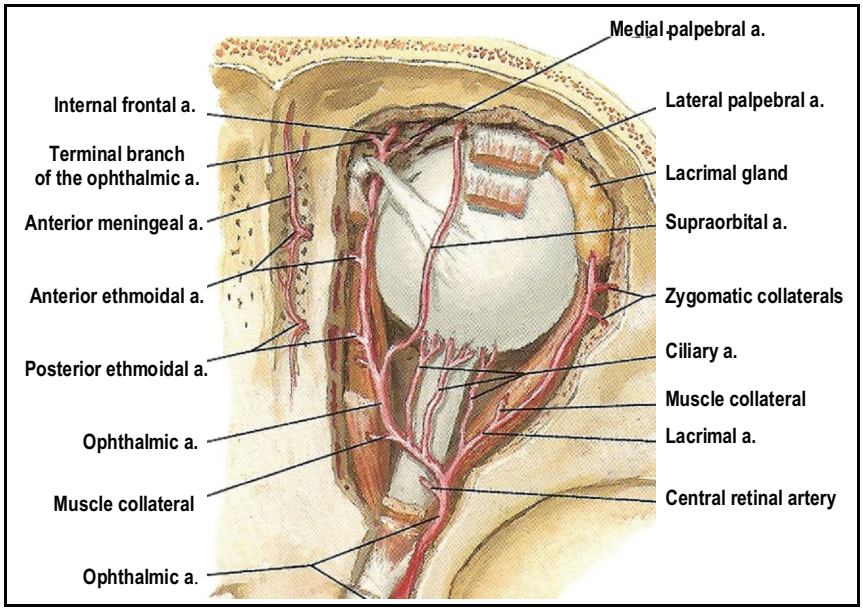

Figure 7. The arteries of the orbit *(aspect 1).* (Netter Atlas of Human Anatomy, 2nd Edition 1997).

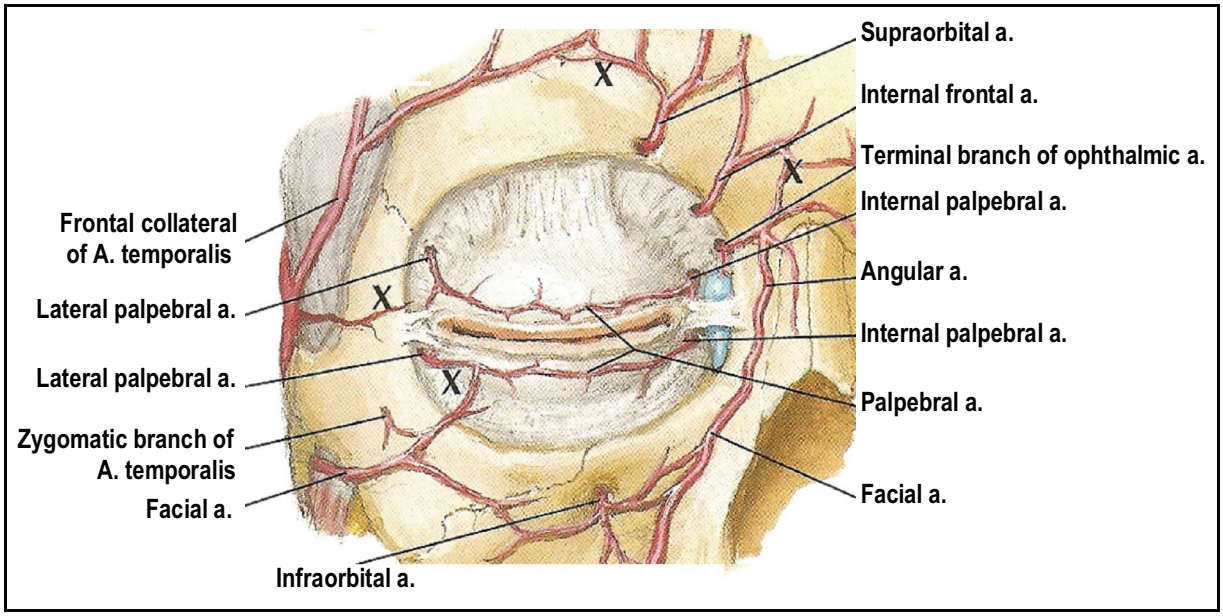

Figure 8. The arteries of the orbit *(aspect 2).* (Netter Atlas of Human Anatomy, 2nd Edition 1997).

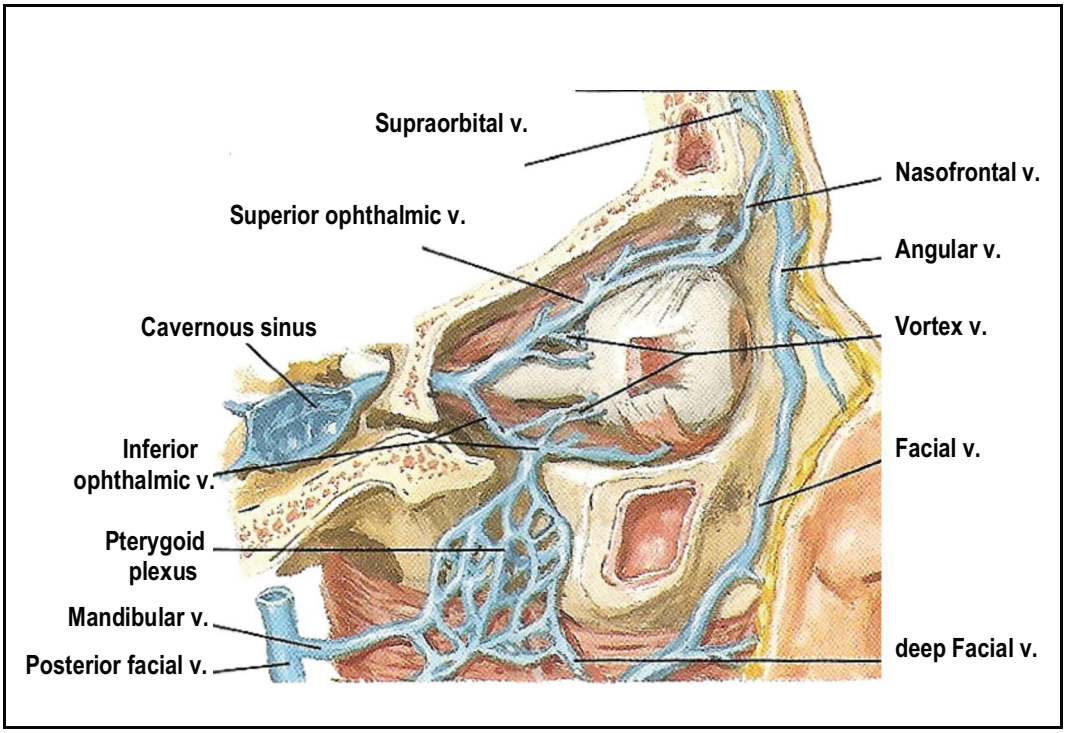

Figure 9. Orbital vein drainage. (Netter Atlas of Human Anatomy, 2nd Edition 1997).

1.1.5. Orbital nerves

Optic Nerve

The optic nerve is a nerve fiber tract, 4,5cm to 5 cm long and about 4mm in diameter, that extends from the globe to the chiasm. It is divided into four portions: intraocular (1mm), intraorbital (3cm), intracanalicular (5mm to 6mm) and intracranial (1cm). Because the distance from the globe to the apex is 20mm the intraorbital portion has an S-shaped configuration. The subarachnoid space and meningeal linings sheathe the nerve and extend from the canal forward to the globe.

Peripheral nerves

The sensory nerves of the orbit are branches of the ophthalmic and maxillary nerves which are the first 2 terminal branches of the trigeminal nerve. The ophthalmic nerve through its three terminal branches (frontal, nasal and lacrimal nerve) innervates the skin of the frontal region, upper lid, interciliar

region, the root of the nose, the lacrimal gland and it also contains postganglionic fibres for pupil dilatation. The sensory innervation of the lacrimal gland is provided by the lacrimal nerve but the secretory innervation (parasympathetic) is provided by an anastomotic branch of the zygomatic nerve, which is a branch of the maxillary nerve. The maxillary nerve has also three terminal branches (infraorbital, zygomatic and sphenopalatine nerve). From these only the first two have an intraorbital trajectory. These provide sensory innervation to the lower lid, superior lip, nose, lacrimal drainage system, skin of the zygomatic region and secretory innervation (as mentioned above) to the lacrimal gland. The ciliary ganglion constitutes a neural ganglion of parasympathetic importance and it is located at the lateral side of the optic nerve. It receives afferent branches from the long or sensory nerve (sensory branches for the eyeball and sympathetic fibres for iris dilatation), short or motor branch (ciliary muscle and pupillary sphincter muscle) and sympathetic branch (vasomotor function). The efferent branches are represented by the short ciliary nerves, which are variable in number and run along the optic nerve until reaching the dorsal extremity of the eyeball.

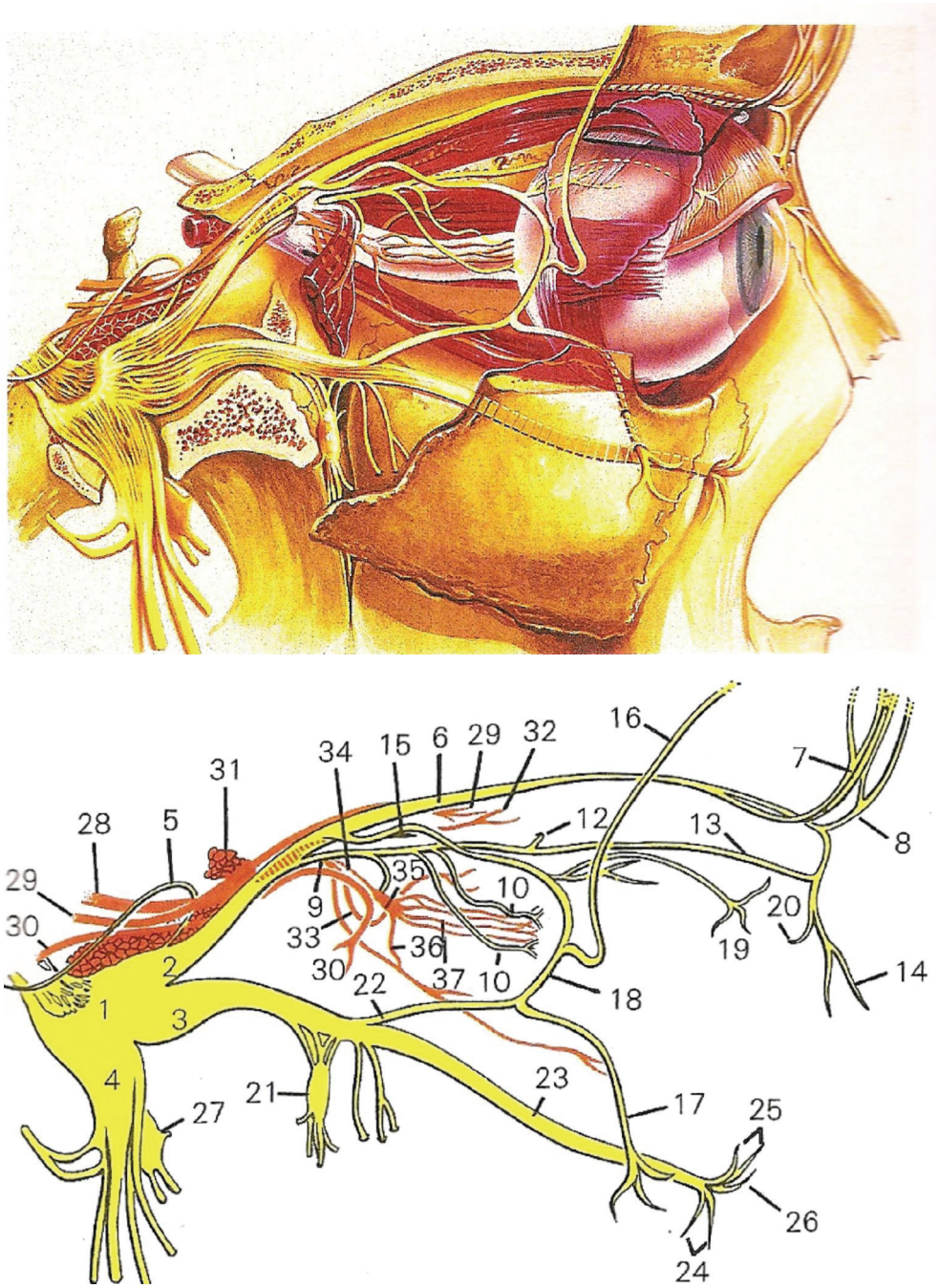

Figure 10. The nerves of the orbit *(also see Table 2.).* (Rootman J Diseases of the Orbit 1988)

Table 2. The nerves of the orbit. (Rootman J Diseases of the Orbit 1988)

Sensory nerves	Motor nerves
1. Trigeminal (Gasserian) ganglion 2. Ophthalmic (first) division 3. Maxillary (second) division 4. Mandibular (third) division 5. Meningeal branch 6. Frontal 7. Supraorbital 8. Supratrochlear 9. Nasociliary 10. Sensory (long) posterior ciliary 11. Posterior ethmoidal 12. Anterior ethmoidal 13. Infratrochlear 14. External nasal 15. Lacrimal 16. Zygomaticotemporal 17. Zygomaticofacial 18. Anastomosis with lacrimal 19. Lateral palpebral 20. Medial palpebral 21. Pterygopalatine ganglion 22. Zygomatic 23. Infraorbital 24. Superior labial branches 25. Iferior palpebral branches 26. Lateral nasal branch 27. Otic ganglion	28. Oculomotor (III) 29. Trochlear (IV) 30. Abducent (VI) 31. Carotid plexus (sympathetic) 32. Oculomotor, upper division 33. Oculomotor, lower division Ciliary ganglion 34. Sympathetic root from carotid plexus 35. Ciliary ganglion 36. Parasympathetic root to inferior division of oculomotor nerve 37. Short posterior ciliary

1.2. Classification of orbital disease

The orbital diseases account for approximately 1% of all ophthalmic diseases. Five types of processes can occur in the orbit: **inflammation**, including endocrine orbitopathy and other inflammations, **neoplasia**, **structural abnormality**, **vascular lesions** and **degenerative conditions**. The frequency of each process is different in different age groups. In the first two decades of life neoplasia and structural lesions are the most common pathology (Rootmann 2002, Deconcilis 1996). The adult middle life is dominated by the endocrine orbitopathy which is responsible for 42% of all pathology in the age group of 17 to 64 years (Rootman 2002). In the late adult life thyroid orbitopathy is still the most common process accounting for 39,3% and neoplasia is the second accounting for 31,4% of the pathology in the age group of >64 years (Rootman 2002), while according to other authors

(Perez Moreiras 1986) neoplasia dominates in this age group with 50 % of all cases, carotid cavernous fistulas are the second most common process with 12,1% of all cases and the thyroid orbitopathy is seen in 4,8% of patients of this group. De Concilis (De Concilis 1996) estimates that in this age group neoplasia is responsible for 38,4% of the pathology, endocrine orbitopathy accounts for 10,4% and vascular lesions for 5,3% of the pathology.
The neoplastic disease can be classified on the basis of the tissue of origin as follows (Rootman 1988, Jacobiec, Font 1986):

- **Neurogenic:**
  a) Tumors of the optic nerve: pilocytic(juvenile) astrocytoma, malignant optic glioma (glioblastoma) of the adulthood
  b) Menigioma: Optic nerve, sphenoid wing, other location.
  c) Tumors of the peripheral nerve sheath: Neurofibroma, Schwannoma
  d) Other secondary and metastatic optic nerve tumors: Retinoblastoma, melanoma, leukaemia, primary neoplasia of the central nervous system.

- **Lymphoproliferative, leukaemic and histiocytoses:** reactive lymphoid hyperplasia, atypical lymphoid hyperplasia, non-Hodgkin Lymphoma, plasma-cell tumors, leukaemia, Hodgkin disease, histiocytosis-X.

- **Vascular:** capillary haemangioma, cavernous haemangioma, lymphangioma, hemangiopericytoma.

- **Mesenchymal**:
  a) Osseous and cartilagous lesions: osteoma, osteosarcoma, chondroma, Ewing's sarcoma, reactive tumors of bone like aneurismal bone cyst.
  b) Fibro-osteoid lesions: fibrous dysplasia
  c) Tumors of adipose tissue: lipoma, liposarcoma
  d) Tumors of muscular tissue: rhabdomyoma, rhabdomyosarcoma, leioma, leiomyosarcoma

- **Lacrimal:** pleomorphic adenoma, adenoid-cystical carcinoma, adenocarcinoma

- **Metastatic:** carcinomas (breast, prostate, gastrointestinal, lung, others), sarcomas

- **Secondary tumors:** From neighbouring structures like lid, nasopharynx, globe, conjuctiva.

The structural lesions include congenital or acquired lesions like mucocele, microphthalmos with cyst, orbital cephalocele, bony anomalies, mucocele, orbital trauma.

The inflammatory disease includes:

- Infectious inflammation

- Non/specific Inflammation:

a) Acute and subacute idiopathic inflammation
b) Sclerosing inflammation
c) Granulomatous inflammation

- Specific inflammation: sarcoidose, vasculitis in connective tissue disorders like SLE, Wegener's granulomatosis, orbital vasculitis, Cogan's syndrome, Sjögren's syndrome.

The vascular pathology except for the vascular tumors which belong to the neoplastic category includes arteriovenous shunts like arteriovenous malformations and carotid-sinous cavernous fistulas and venous anomalies like orbital varix.

1.3. Pathophysiological and anatomical patterns of orbital disease

Apart from endocrine orbitopathy the symptomatic of orbital disease is not specific. From the clinical point of view the effect of orbital disease is influenced by the primary nature of the process (pathophysiology) and the anatomic pattern of involvement.
A pathopysiological categorization, which is very helpful in the clinical praxis, was proposed by Guthoff (1999):

- Expansive lesions: they are well circumscribed and produce mainly a mass effect in the form of axial exophthalmos, globe displacement or both, with or without signs of involvement of sensory and oculomotor structures. A typical example of this category is the cavernous haemangioma of the orbit. This type of lesions can be surgically excised and a total healing can be achieved.

- Infiltrative lesions: they cause destruction, entrapement or both, resulting in disturbance of ocular movement or neurosensory dysfunction (diplopia, optic neuropathy, pain, parasthesia). These lesions cannot be totally removed by surgery. The therapeutical procedure includes biopsy and (where applicable) surgical debulking. After the establishment of the definite diagnosis the therapeutical alternatives are generally planned on a multidisciplinary basis. The differential diagnosis includes cellulitis, non-specific or specific inflammation, neoplasia such as lymphoma or metastasis.

- Vascular lesions: an underlying vascular pathology is responsible for orbital manifestations. To this category belong arteriovenous fistulas, orbital varices, thrombosis of the ophthalmic superior vein and/or cavernous sinus involvement.

- Myopathic: The involvement of the orbital muscles is the dominant feature. The main symptom is painful or painless ocular motility disorders with

diplopia. The differential diagnosis includes endocrine orbitopathy, idiopathic non-specific myositis, metastasis, arteriovenous fistulas, and neoplasia.

The anatomic pattern of involvement is the second major factor affecting the clinical presentation of the disease. Rootman (1988) and Moreiras (2003) proposed the following categorization on the basis of the anatomical location of orbital lesions:

- Anterior: the process is situated in the anterior orbit adjacent to and affecting the globe. Typical symptoms are proptosis, lid swelling, lid injection, injection of conjuctiva, possible retinal venous dilatation or uveitis.

- Diffuse: It is similar to anterior but more severe. It is more frequently associated with optic neuropathy or motor and sensory deficits. The process occupies the preseptal, extraconal and intraconal spaces.

- Apical: It causes less proptosis but is associated with early optic neuropathy or motor and sensory symptoms. In the superior orbital fissure vascular congestion can be caused by obstruction of the ophthalmic veins. The typical symptoms include pain, limitation of movement and visual deficits named as orbital apex syndrome.

- Lacrimal: Typical symptoms are localized pain, injection of the temporal lid and fornix, palpable lacrimal gland, S-shaped lid deformity, conjuctival injection.

- Intraconal: These lesions produce axial displacement, optic neuropathy, oculomotor disorders.

- Optic nerve: The symptoms depend on whether or not the lesion is intrinsic to the nerve or affects the nerve sheath.

- Periorbital: Diseases originating from the sinuses, face and intracranial cavity may extend into and affect the orbit.

The categorization on the basis of the anatomical pattern was originally proposed for inflammatory disease. However it can be useful for the evaluation of non-inflammatory orbital lesions, as well.

1.4. Examination

1.4.1 Clinical examination of the orbital patient

The clinical examination of the orbital patient includes the recording of following parameters:

1. Visual acuity/Refraction
2. Pupil reactions/Relative afferent papillary deficit
3. Analysis of the ocular motility and exact recording of ductions
4. Cover tests & Maddox rod testing in the presence of manifest deviations
5. Visual field
6. Color vision
7. Orbital palpation
8. Measuring of the lid fissure width and function of the levator
9. Corneal sensibility
10. Exophthalmometry/Recording of vertical or horizontal displacement
11. Tonometry
12. Biomicroscopy/ Fundus examination

The evaluation of these clinical parameters additionally to a careful medical history helps the clinician proceed to the management of the patient. The application of modern diagnostic imaging methods (CT/MRI) can further contribute to the elucidation of distinct questions arising from the clinical examination.

1.4.2. Orbital imaging techniques

1.4.2.1. Ultrasonography

Computer tomography and magnetic resonance imaging have gained a privileged place in orbital exploration over the past years relegating the orbital sonography in a second place. The B-mode-sonography is most commonly used in the clinical praxis and an examination performed by a trained specialist can provide useful information regarding the pathological process (Guthoff 1991, Moreiras 2004, Dibernardo 2006), including:

1. Topographical anatomy: distinction between intraconal and extraconal lesions, relationship to adjacent tissues such as globe, optic nerve, lacrimal gland, muscles.
2. Pathophysiology: expansive, infiltrative, myogenic and vascular lesions
3. Internal structure: homogenous-heterogenous, hyporeflectivity-hyperferlectivity, cystic-solid pathology.

A synopsis of the sonographic characteristics of orbital lesions is shown in the following table.

Table 3. Sonographic characteristics of orbital lesions (Moreiras JVP, Prada MC Orbit: Examination, Diagnosis, Microsurgery, Pathology 2004, modified).

Well-defined, regular lesion			
Homogenous		**Heterogenous**	
Medium-low reflectivity	***Low reflectivity***	***Medium-high reflectivity***	***Medium reflectivity***
Lymphoma (lympoid lesions) Schwannoma Glioma (optic nerve)	Hemorrhage Subperiosteal cyst Varix (Valsava's maneuver)	Cavernous hemangioma (intraconal, orbital floor) Hemangiopericytoma	Lacrimal gland mixed tumor Dermoid cyst (high lipid content)

Meningioma (optic nerve) Metastasis Myositis (non-specific inflammation)	Mucocele Dermoid cyst Abscess (cellulitis)	Cavernous lymphangioma Lacrimal gland adenoma Dermoid cyst	Cholesterol grannuloma

Ill-defined, irregular lesion	
Homogenous	**Heterogenous**
Infiltrating tumors (rhabdomyosarcoma, metastases, diffuse pseudotumor)	Sclerosing non-specific inflammation Diffuse capillary hemangioma Cellulitis (increased volume) Carcinoma

1.4.2.2. Computed tomography (CT)

This examination has become an extremely useful diagnostic tool offering a wide range of information regarding the anatomy and pathophysiology of the orbital lesions. The main advantage of this method (in comparison to the MRI) is that it can be used for the evaluation of the bony pathology and it has a very good resolution for lesions affecting or arising from bone. It is also helpful for the evaluation of tumor limits and extension before surgery. The morphology of the orbital structures tissues depends on the plane of the section. A complete study requires two orthogonal incidences: axial and coronal. The axial view is superior for demonstrating the lateral and medial bony margins, the superior orbital fissure and the optic canal. Coronal views are best for assessing the floor and roof. The lacrimal sac and nasolacrimal duct as well as the inferior orbital fissure and infraorbital canal are equally well seen on axial and coronal images. The majority of cases are studied using a plane of section including lens, optic nerve and optic canal. If this plane is correctly attained, the orbits will appear symmetrical, and structures, such as medial and lateral rectus muscles, optic canal and bony walls will also be visualized.

1.4.2.3. Magnetic Resonance Imaging (MRI)

Magnetic resonance imaging (MRI) is a technique that provides high resolution images of orbital disorders. Although CT scan is more useful for evaluation of bone structures, MRI is superior to CT in a number of other cases (Atlas Scott 1988), such as:

- Lesions of the orbital apex, sphenoidal fissure, optic canal.
- Differentiation between optic nerve and periorbital lesions.
- Differentiation between inflammatory pseudotumor and other malignant neoplastic processes with similar clinical presentation.
- Detection of neoplastic lesions with hemorrhagic foci or other paramagnetic materials (melanin).
- Evaluation of posterior extension in optic gliomas.
- Detection of anomalous flow in vascular structures.

Every patient must be carefully studied and prepared for this examination. The examination is absolutely contraindicated in the presence of magnetic foreign bodies in the orbit or periorbital soft tissues, in patients with pacemakers and magnetic vascular clips or other magnetic prostheses.

Proton density, T1- and T2-relaxation times are characteristic and different for each tissue. Rapid sequences, such as “turbo spin-echo” or “fast spin-echo”, although similar to conventional techniques, have remarkably reduced the examination time and improved the image quality by reducing movement artifacts. T1- weighed spin-echo sequences are useful for estimation of the volume and extension of lesions, whereas T2-weighed turbo spin-echo sequences obtain a better lesion characterization by signal intensity. Fat suppression techniques, also called STIR and FAT SAT, increase the ability to visualize lesions with similar behavior to fat. The use of paramagnetic contrast injection of gadolinium-dimeglumine-gadopentate (DTPA) in T1-weighed sequences with fat suppression can be very useful in distinguishing neoplastic tissues capturing contrast, which may be otherwise confused with fat. Some authors (Link TM et al 1995) suggest that the fat-suppression technique is superior to the conventional technique in respect to the visualisation of extraocular muscles and the optic nerve. Moreover pathological conditions of the orbit (optic glioma and neuritis, spread of local

tumors to the orbit) were better visualised using the fat suppression technique. The appearance of orbital tissues in different MRI sequences is shown on the following table.

Table 4. Appearance of orbital tissues in MRI sequences (Moreiras JVP, Prada MC Orbit: Examination, Diagnosis, Microsurgery, Pathology 2004).

Sequences	*T1*	*Proton density*	*T2*
Cortical bone	No signal	No signal	No signal
Retroorbital fat	Hypersignal	Hypersignal	Hypersignal
Extraocular muscles	Isosignal	Isosignal	Isosignal
Vitreous	Hyposignal	Hypersignal	Hypersignal
Anterior chamber	Hyposignal	Hypersignal	Hypersignal
Lens	Hypersignal	Hypersignal	Hyposignal

1.5. Orbital surgery

The development of modern imaging techniques has allowed for a more targeted and less invasive surgical approach, which has reduced postoperative complications. Dependent on the nature and the anatomic and pathophysiological patterns of the lesion following surgical procedures can be performed:

1. Incisional biopsy for infiltrative disease to establish a histological diagnosis.
2. Total excision of an expansive/ well circumscribed lesion.
3. Exenteration, when malignant disease processes originate within the orbit and threaten to extend beyond it.

The routes used in orbitotomy are:

- Anterior: It can be carried out through an anterior incision in skin or conjuctiva. There is no opening of the periosteum or bony structures of the

orbit. This approach is used for incisional biopsy or removal of well defined anteriorly located or even some deeper intraconal lesions.

- Lateral: The removal of the lateral wall allows for a clear access to the orbital contents. The amount of bony excision can be customised to include more of the superolateral rim and if necessary even the zygomatic arch, depending on the size and location of the lesion. Most retrobulbar or parabulbar lesions can be handled by an anterior or lateral orbitotomy alone ore in combination.
- Superior: This approach is conducted either by a transfrontal or by temporofrontal (panoramic) incision. The cooperation of ophthalmologists and neurosurgeons is needed. This approach is conducted in case of compound trauma of the orbit or intracranial cavity, as well as for decompression of the optic canal or removal of apical or combined apical and intracranial lesions.
- Medial: This approach facilitates the intraoperative palpation of the lesion, which was of high significance before the development of modern orbital imaging techniques. Due to the possible development of convergent strabismus resulting from manipulation of the medial rectus muscle, this approach is nowadays rarely used.

All of the approaches mentioned above can be used in combinations or with variations in order to gain access to any of the surgical spaces of the orbit.
The total removal of the orbital contents (exenteration) is indicated when malignant procedures originate within the orbit and have reached the bone or threaten to extend beyond it. The operation includes removal of the orbit and periorbital contents. The exenteration can be either total or subtotal when the lids are not included. Depending on the process soft tissue can be left in the orbital apex, which serves as starting point of the granulomatous procedure. The cosmetic result is usually satisfactory and a flat cavity forms, which can be covered with a bone-anchored epithesis.

2. Material and methods

2.1. Patients

This retrospective study includes 132 cases of patients with orbital disease who were treated from the year 1993 to the year 2008 in the University Clinic of Ophthalmology Rostock. All individuals were inpatients. The vast majority of the patients came from northern Germany and was referred to our clinic from private ophthalmology practices. A minority of patients were referred to our clinic from other German ophthalmology clinics.

2.2. Exclusion criteria

Patients with endocrine orbitopathy were excluded from this study. Also patients with orbital cellulitis were excluded. These patients are treated in-patiently or operated in the University Clinic of Otolaryngology Rostock and are examined by ophthalmology consultants only on an outpatient basis. There were no exclusion criteria regarding age, race, sex or presence of systemic disease.

2.3. Data

The data of this study was obtained from patient's archives of the University Clinic of Ophthalmology Rostock. Postoperative follow-up examinations have taken place mainly in the University Clinic of Ophthalmology Rostock. The rest of the patients were examined postoperatively by ophthalmologists in private practices. Information about the postoperative course for these patients was collected by questionnaires which were sent to and filled out by private ophthalmologists.

Aim

Purpose of this study is to propose a practical pathophysiological and anatomical categorization of orbital disease, excluding endocrine orbitopathy, on the basis of clinical manifestations and characteristics in orbital imaging techniques, and to discuss treatment options. This sort of categorization could serve as a guideline in the management of orbital patients for clinical ophthalmologists.

3. Results

3.1. Epidemiologic characteristics

3.1.1. Distribution of lesions by age and histological correlations

The patients were distributed to the following age groups: 0-20 years (10 patients, 8%), 20-60 years (70 patients, 53%) , > 60 years (52 patients, 39%).

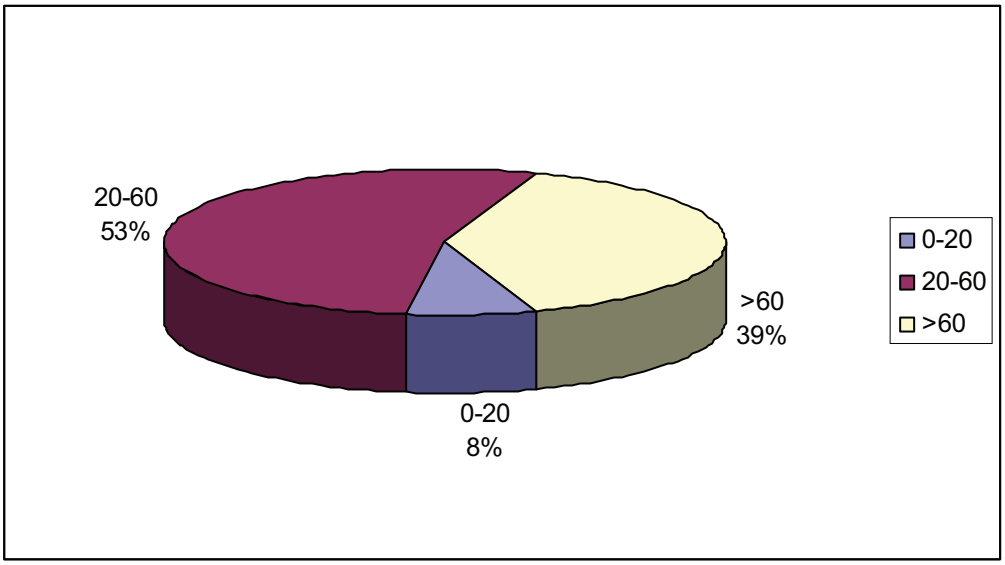

Figure 11. Distribution by age.

Out of the 132 patients, 98 (74,2%) had benign disease and 34 (25,8%) had malignant disease. Histologically our series comprised 48 (36%) cases of inflammatory disease, 59 (45%) cases of neoplastic disease, 19 (14 %) cases of vascular pathology (tumors excluded) and 6 (5%) cases of structural and degenerative lesions. The inflammatory disease included 44 cases of non-specific inflammation and 4 cases of specific inflammation (2 sarcoidose, 2 Wegener granulomatosis).

In the age group of 0-20 years 8 patients (80%) had inflammatory disease, 1 patient (10%) had neoplasia and 1 patient (10%) had a structural lesion. In the age group of 20-60 years 28 patients (39%) had inflammatory disease, 27 patients (39%) had neoplasia, 11 patients (16%) had vascular disease and 4

patients (6%) had a structural lesion. In the age group of > 60 years 12 patients (23%) had inflammatory disease, 31 patients (60%) had neoplasia, 8 patients (15%) had vascular disease and 1 patient (2%) had structural lesion.

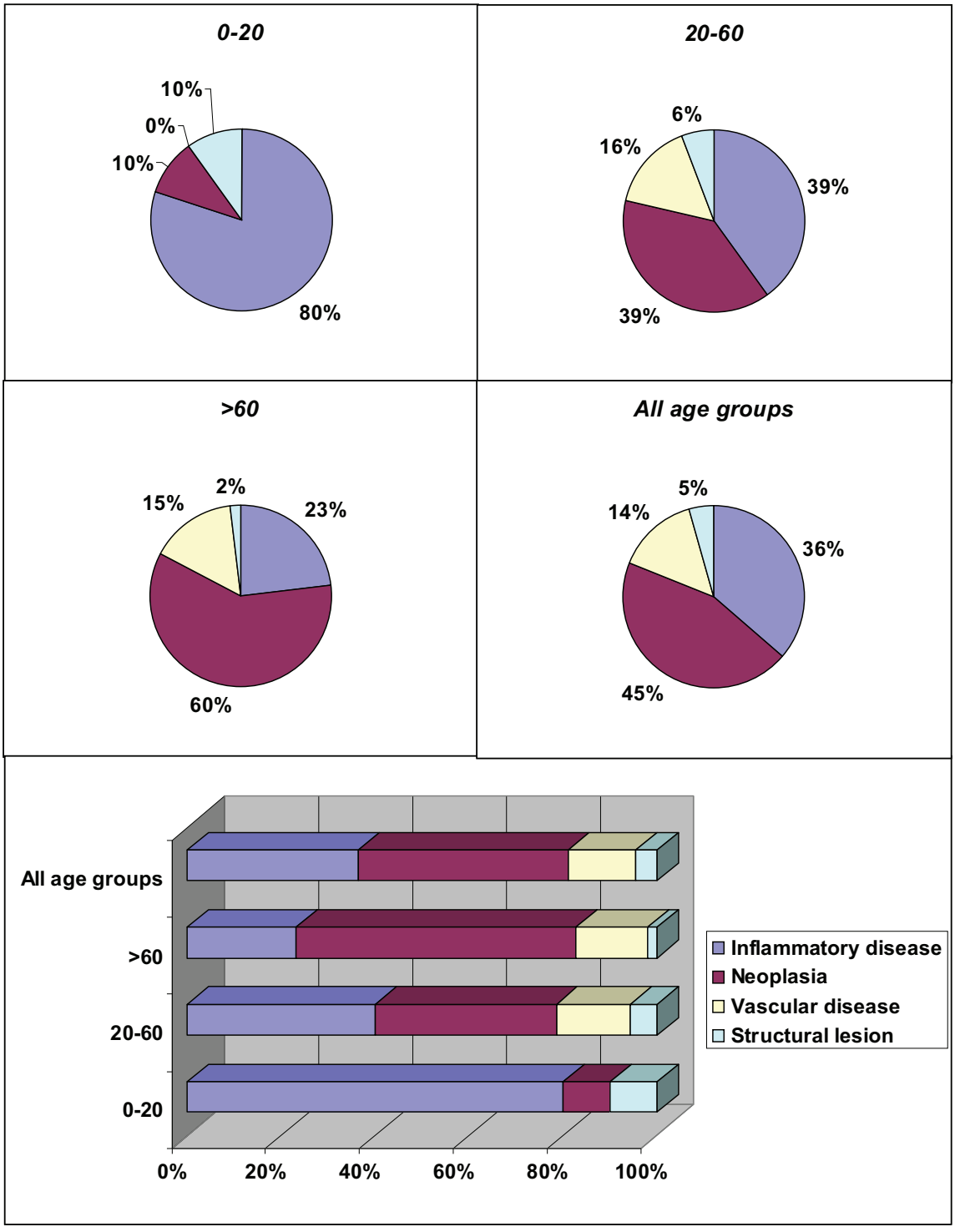

Figure 12. Distribution by histological group and age group.

3.1.2. Distribution of lesions by pathophysiological mechanism

We observed 43 expansive, 60 infiltrative, 10 myopathic and 19 vascular lesions (vascular tumors excluded).

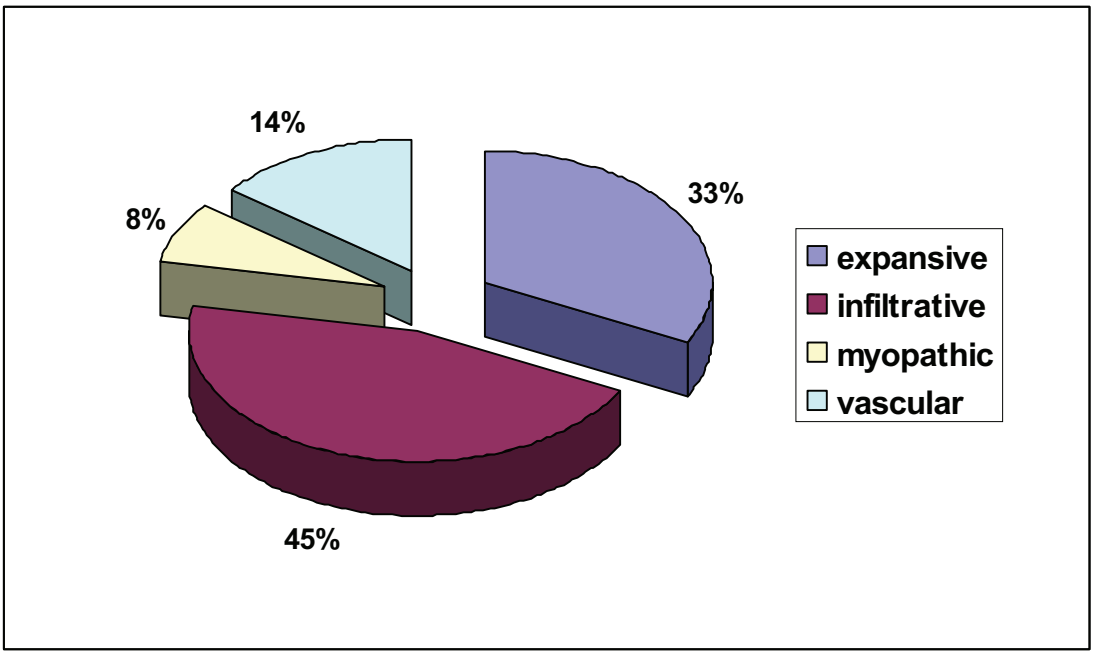

Figure 13. Distribution by pathophysiological mechanism.

3.1.3. Distribution of lesions by anatomical pattern

The anatomical pattern of involvement for the expansive and infiltrative lesions (103 patients) was the following: 32 (31%) intraconal, 32 (31%) lacrimal, 27 (26%) anterior, 7 (7%) diffuse, 3 (3%) periorbital and 2 (2 %) apical.

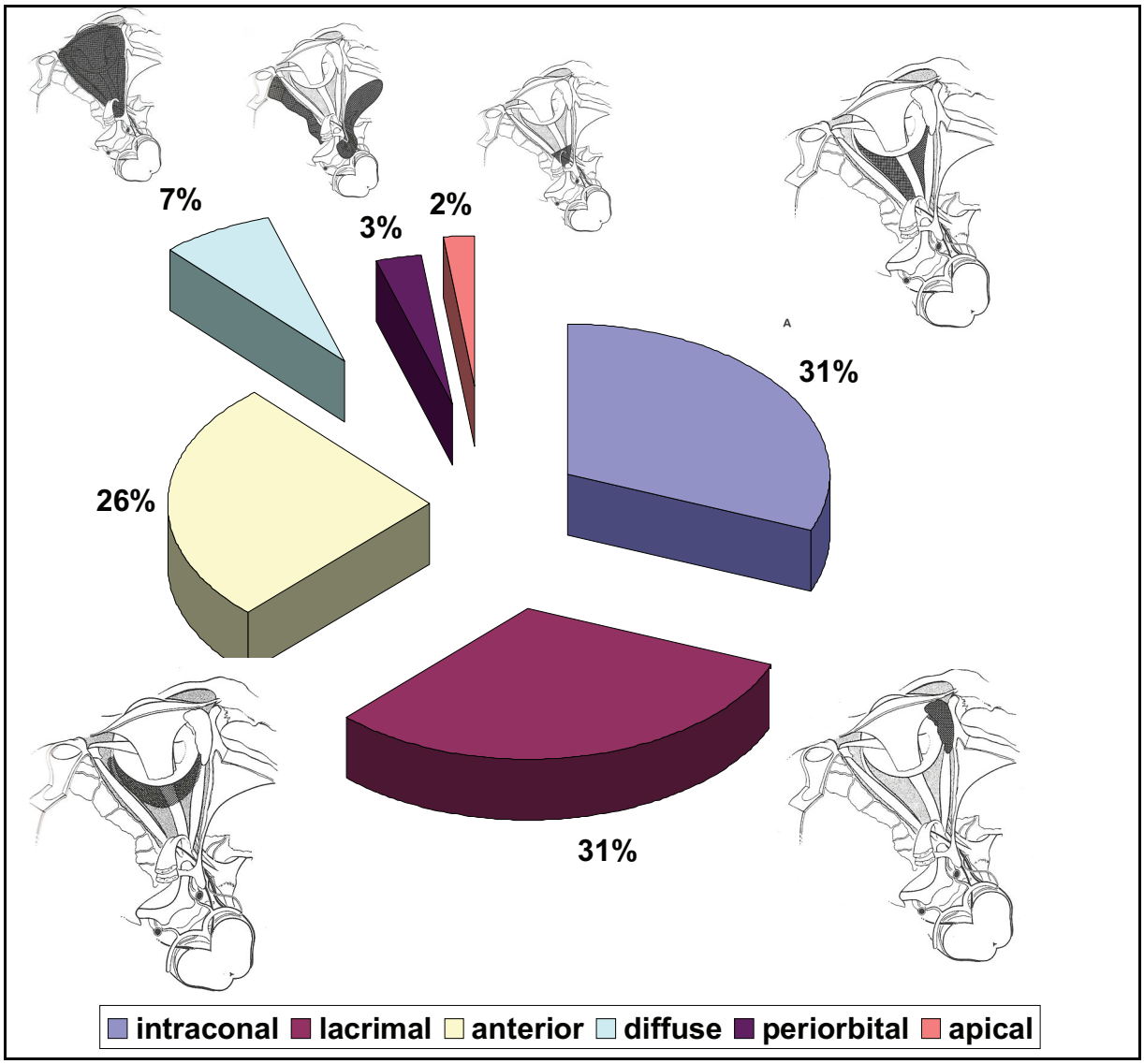

Figure 14. Anatomic site of involvement for expansive and infiltrative lesions.

3.1.4. Histology of neoplastic lesions

The neoplastic category included 25 (42%) benign and 34 malignant tumors (58%). The benign tumors comprised:

- 16 vascular tumors: 14 cavernous haemangiomas, 1 lymphangioma and 1 angiomyoma.
- 6 lacrimal tumors: all of them were pleomorphic adenomas.
- 3 neurogenic tumors: 2 neurinomas, and 1 neurofibroma.

The malignant tumors comprised:

- 22 tumors of haemopoietic system: 18 lymphomas, 2 cases of Langerhans-cell Histiocytosis (LCH), 1 chloroma, 1 case of Erdheim-Chester-Disease (ECD)
- 3 lacrimal tumors: all of them were adenoid cystic carcinomas.
- 5 mesenchymal tumors: 2 liposarcomas, 1 malignant fibrous histiocytoma, 1 malignant fibrous solitary tumor, 1 rhabdomyosarcoma.
- 3 metastatic tumors: 1 neuroendocrine tumor, 1 prostate adenocarcinoma, 1 mammal carcinoma.
- 1 case of basosquamous carcinoma of the canaliculi.

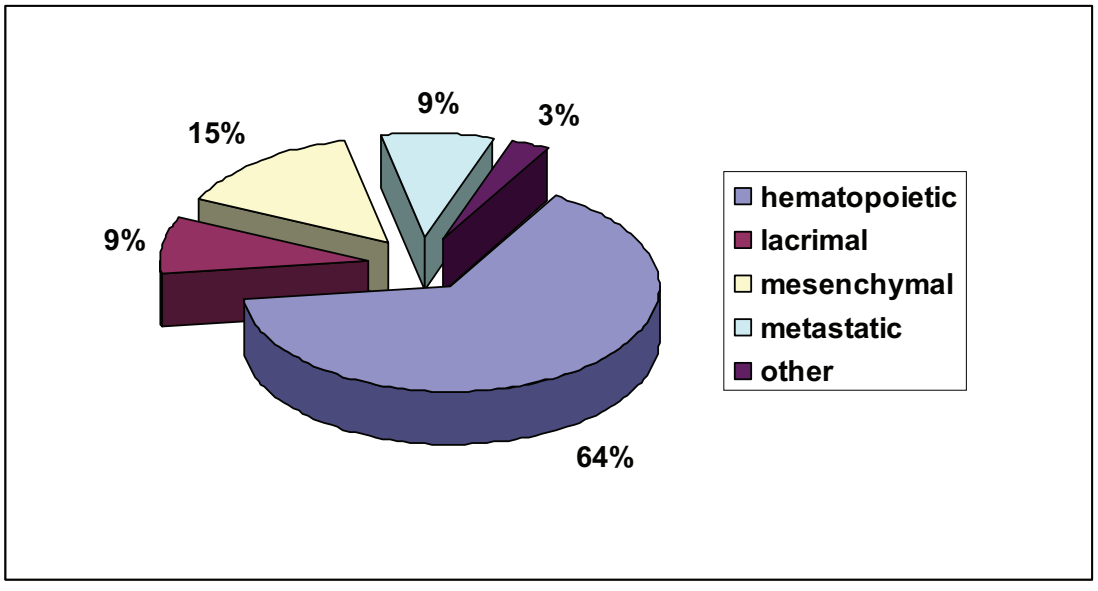

Figure 15. Malignant tumors by origin.

3.1.5. Histology of lacrimal gland lesions

The lacrimal gland along with the intraconal space was found to be the most common anatomical site of disease. We examined 32 patients with lacrimal gland disease. 20 of these cases were non-specific inflammations (NSI), 10 cases were neoplastic (6 benign and 4 malignant) and 2 cases were sarcoidose with bilateral involvement of the lacrimal gland.

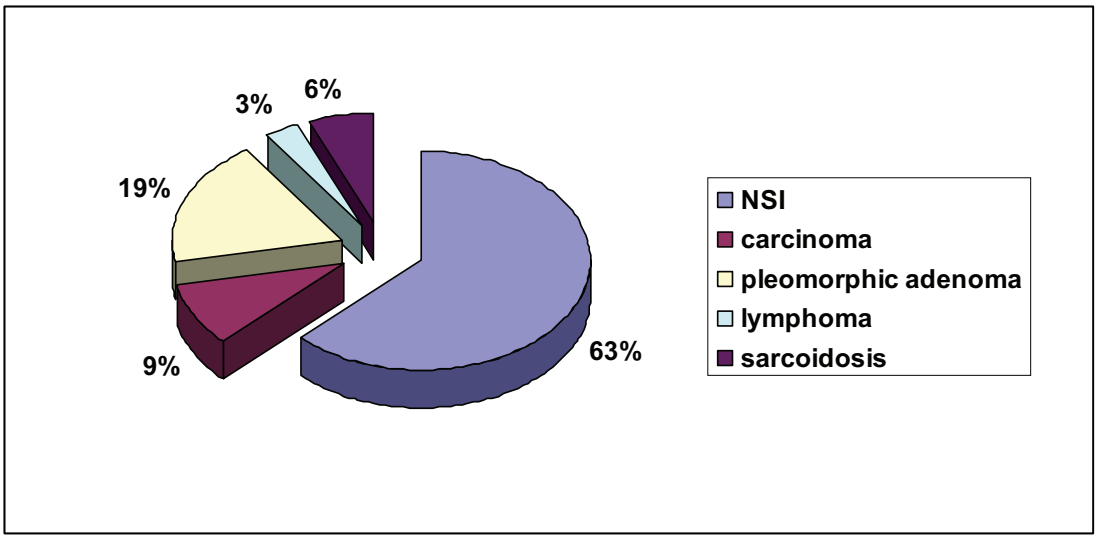

Figure 16. Distribution of lacrimal lesions by histology.

3.2. Clinical presentation and treatment of disease on the basis of histology and pathophysiology

The major symptoms and the therapeutical procedures are presented seperately for inflammatory, neoplastic, vascular (tumors excluded) and structural/ degenerative lesions.

3.2.1 Inflammatory disease

Our series included 48 patients with inflammatory disease. 44 of these patients had non-specific orbital inflammation (orbital pseudotumor) and 4 patients had a specific inflammatory infiltrate (2 with sarcoidose and 2 with Wegener granulomatosis). In all of these patients the anatomic pattern of involvement was studied by means of orbital CT or MRI scans and the diagnosis was confirmed by biopsy of the lesion.
As to the group of non-specific inflammation the following anatomical patterns were observed:

- Anterior (7 patients): lesion situated in the anterior 1/3 of the orbit, parabulbar or retrobulbar, with or without involvement of the eyelids and the anterior portion of the external muscles.
- Intraconal (5 patients): lesion situated within the muscle cone.
- Diffuse (1 patient): lesion extending from the extraconal space to the intraconal space and from the anterior to the posterior orbit.
- Apical (2 patients): lesion situated in the orbital apex.
- Lacrimal (20 patients): the inflammatory process affects primarily the lacrimal gland and can extend to the surrounding extraconal space, periorbital skin with or without involvement of the lateral rectus muscle or the superior rectus muscle.
- Myositis (9 patients): the inflammatory process affects primarily one external muscle.

8 patients were 0-20 years of age, 25 patients were 20-40 years of age and 11 patients were older than 60 years of age.

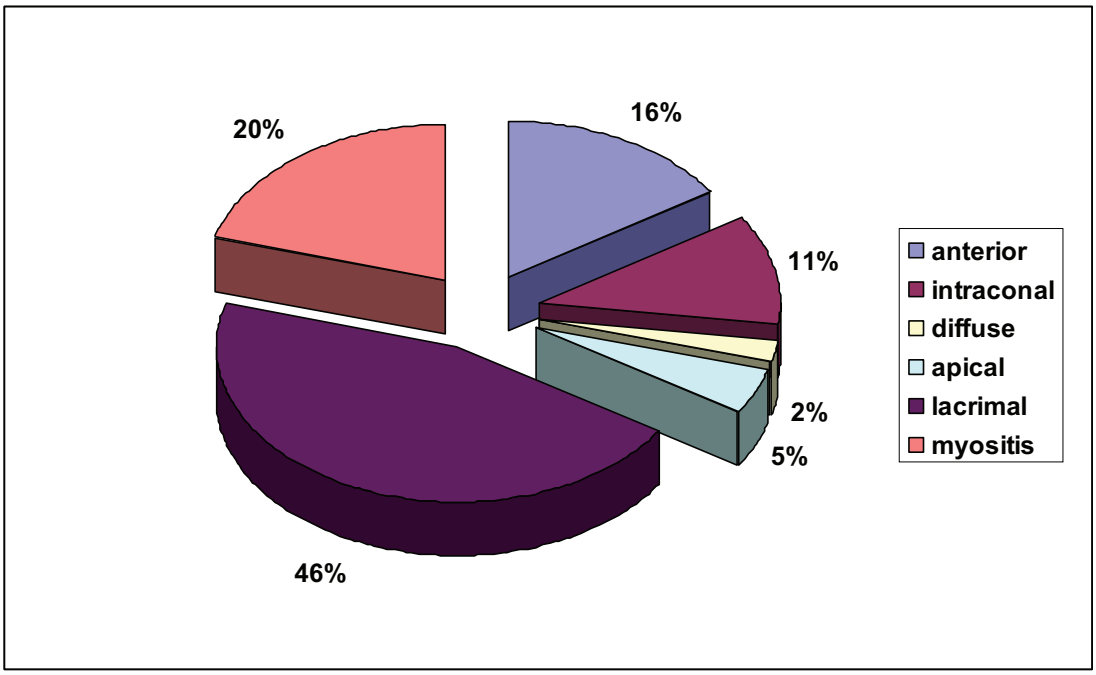

Figure 17. Anatomical site of involvement in non-specific inflammation.

Anterior: All the patients with anterior inflammation had lid swelling and moderate to severe lid injection. In one patient exophthalmos (8 mm difference in Hertel exophthalmometry) was the main symptom as the inflammatory process was situated in the anterior 1/3 of the orbit directly retrobulbar with additional involvement of the lacrimal gland and the anterior portion of the rectus superior and rectus lateral muscle. The other patients had no or minimal exophthalmos (up to 3 mm difference in Hertel exophthalmometry). The ocular motility was normal in 3 patients, 4 patients had restriction in ocular motility in at least one direction of gaze. No patient had an optic nerve compression.

Orbital biopsy was performed in all of the patients. Histologically 4 patients had a florid inflammatory infiltrate (inflammatory pseudotumor) and 3 patients had a chronic inflammatory infiltrate with less cellular component and variable degree of fibrosis. 5 patients were treated with systemic prednisolon (3 with inflammatory pseudotumor) and a complete remission was observed in 4 of them. In one patient with florid inflammation and exophthalmos of 8 mm the

systemic prednisolon resulted in a complete regression of lid injection and lid swelling but the exophthalmos was persistent 2 years after initial diagnosis. A deficit in down gaze was also present with subsequent diplopia in the same patient but no further treatment occurred, as the patient was not severely disturbed in daily life. In one patient corticosteroids were contraindicated and this patient was treated with systemic ibuprofen with complete regression. In one female patient after histological exclusion of malignity no further treatment occurred and the clinical course is unknown to us.

Intraconal: In the group with intraconal involvement exophthalmos was the main symptom in all of the 5 patients. All patients had restriction in ocular motility in at least one direction of gaze with subsequent diplopia. No patient had clinically or radiographically compression of the optic nerve. Biopsy of the lesion was performed in each patient. 3 patients had histologically no or minimal amount of fibrosis and were initially treated with systemic prednisolon. In one patient even if a clinical improvement was observed the therapy was stopped due to side effects. The other two patients had no clinical improvement and subsequently each of these three patients underwent orbital radiotherapy with complete regression of the inflammatory process. However, one patient had persistent diplopia in abduction, which nevertheless was not disturbing in daily life. 2 patients had a chronic inflammatory infiltrate with severe amount of fibrosis (sclerosing pseudotumor). In one of them prednisolon and methotrexate had been systemically administered ex domo without any success. At the time of first examination in our clinic this patient had an exophthalmos (5 mm difference in Hertel exophthalmometry) and restriction of abduction with subsequent diplopia. The inflammatory process was in the intraconal space with extension in the ethmoid cells and infiltration of the medial rectus muscle. Medial orbitotomy with evacuation of the ethmoid cells was performed and 3 months postoperatively this patient had no exophthalmos, but only a minimal restriction in adduction without diplopia was observed. The second patient received no therapy after initial diagnosis because of mild exophthalmos and minimal restriction in ocular motility; one year after surgery no progression was observed.

Diffuse: 1 patient presented with bilateral exophthalmos. The patient had no diplopia, but ocular motility was restricted in all directions of gaze on both eyes. Visual acuity was normal and there were no signs of optic nerve compression. As previous steroid therapy had been without any success, we performed bilateral lateral orbital decompression with surgical dekulking. We achieved reduction of exophthalmos (7 mm on the right side and 8 mm on the left side), but postoperative diplopia occurred and strabismus surgery followed.

Apical: Two patients in our series had an apical involvement. One of them reported severe decrease in visual acuity; on first presentation he was only able to perceive hand movements. This patient had mild exophthalmos (3 mm difference in Hertel exophthalmometry) with paresis of the III and VI cranial nerves. In MRI scan optic nerve compression in the apex was observed. Despite immediate orbital decompression no improvement of visual acuity was achieved and no further therapy occurred. Histologically, a sclerosing orbital inflammation was observed. The second patient had restriction of ocular motility without any exophthalmos or optic compression. After treatment with systemic prednisolon complete regression was observed, ocular motility returned to normal and no diplopia was present any more.

Lacrimal: The lacrimal gland was the most common site of involvement in our series. All of the 20 patients underwent an orbital biopsy. Histologically, non-specific inflammatory infiltrates (lymphocytes, plasmocytes, granulocytes, epitheloid cells) with variable amount of fibrosis were observed. 7 patients had severe fibrosis in terms of a sclerosing inflammation. Clinically lid swelling with variable amount of lid injection was present in 18 patients, 5 patients had indolent palpable mass, 4 patients had ptosis, 4 patients had restriction in up gaze with subsequent diplopia and 10 patients had exophthalmos.

5 patients had a well circumscribed process (3 out of them with sclerosing inflammation). All lesions were treated as expansive with en-block resection of the lacrimal gland region. In three of these patients no further treatment was necessary as they were free of symptoms after surgery. One patient had persistent diplopia in abduction and strabismus surgery was subsequently performed. In one patient the clinical course is not known.

Among the remaining 15 patients there were 4 patients with sclerosing inflammation. 8 patients out of them (3 with sclerosing inflammation) were treated with systemic prednisolon. In 5 patients, all of them without sclerosing inflammation, complete or partial clinical improvement was observed. 1 of the patients with sclerosing inflammation had only partial improvement and 1 patient had no improvement. Orbital radiotherapy was recommended to this patient; the further clinical course is not known to us. The other patient with sclerosing inflammation had initially a very good response to therapy, but reported severe loss of visual acuity 1 month after initial regression of disease. The visual acuity was hand movement perception; the patient had mild exophthalmos with restriction in ocular motility. In MRI-scan an inflammatory process located in the apex and causing optic nerve compression, was shown. Despite immediate endonasal and lateral decompression the visual acuity failed to improve. The clinical course in the remaining 7 patients is not known.

Myositis: All the patients with myositis had acute painful restriction in ocular motility. 6 out of them had lid swelling. The rectus superior muscle was the muscle most frequently involved. Diagnosis was established by clinical examination and sonography, which showed enlargement of muscle with involvement of the tendon. The inflammation responded rapidly to corticosteroid treatment. 3 patients (33%) had a recurrence of the myositis, which also responded to corticosteroids.

The group with specific inflammation included 2 patients who presented with a dacryoadenitis due to sarcoidose. The first patient was female, 40 years of age and presented with a unilateral palpable mass of the temporal upper lid. Visual acuity and ocular motility were normal. In CT scans an enlarged lacrimal gland was seen. Biopsy and further diagnostic evaluation through the internists confirmed the diagnosis of sarcoidose without any lung involvement. Under steroid therapy there was a complete regression of ocular symptoms. The second patient was female, 50 years of age and presented with a bilateral lid swelling with normal visual acuity and ocular motility. This patient had a known systemic sarcoidose. In CT scans bilateral enlargement of the lacrimal gland was seen. Therapy with corticosteroids was recommended.

2 of our patients had Wegener granulomatosis of the orbit. The first patient was female, 74 years of age and presented with subacute exophthalmos (8 mm difference in Hertel exophthalmometry) and motility restriction in all directions of gaze. Visual acuity was 40/100 on both eyes due to cataract formation. In MRI scans we saw an infiltrative process with an intraconal and an extraconal component. The lesion was in contact with the medial orbital wall and caused downward and lateral globe displacement. The lesion had an intense gadolinium uptake. In the contralateral inflammatory infiltrates taking up gadolinium were seen, as well. There was a great deformity of nasal sinus and the paranasal sinuses; the ethmoid cells and sphenoid sinus were not definable from the nasal sinus. Orbital biopsy confirmed the diagnosis of orbital Wegener granulomatosis. The disease was limited to the orbit and paranasal sinuses without any other systemic involvement. cANCA antibodies were negative. A systemic therapy with cyclophosphamide followed and a complete regression of the exophthalmos was achieved.

The second patient was female, 38 years of age, and had a known systemic Wegener granulomatosis with kidney and lung involvement. Over the past 8 years she had been suffering bilateral vision loss due to optic atrophy caused by a pituitary adenoma. The patient was referred to us due to unilateral subacute painful exophthalmos with lid swelling, lid and conjuctival injection. At first presentation the visual acuity was no light perception on both eyes. In funduscopy bilateral optic nerve atrophy was seen. There were restrictions in ocular motility on both eyes. MRI scans showed a bilateral diffuse infiltrative orbital process (on the left more pronounced) with intracranial extension. Biopsy confirmed the diagnosis. Therapy with cyclophosphamide followed; however, only minimal reduction of the exophthalmos was achieved.

3.2.2. Neoplasia

Our series included 59 cases of neoplastic disease (34 malignant, 25 benign). These cases were categorized according to the tissue of origin.

3.2.2.1. Malignant tumors

1). Neoplasia of haemopoietic system (22 cases): 18 patients with orbital lymphoma, 3 patients with histiocytosis (2 Langerhans cell histiocytosis, 1 Erdheim-Chester disease) and 1 patient with a myeloblastoma (chloroma).

Lymphoma

3 patients (16%) had bilateral disease. 4 patients (22%) had systemic stadium IV disease with involvement of the bone marrow in 3 patients, the lymph nodes in 2 patients, tonsils in 1 patient, bones in 1 patient and of lungs in 2 patients. In all of these patients the ocular symptoms were the first symptoms of the disease. In one patient the orbital lymphoma was a relapse of a systemic lymphoma treated with chemotherapy seven years before. Histologically, 12 (66,7%) were MALT-lymphomas of low malignity, 2 were follicular (centroblastic-centrocytic) of low malignity, 2 were lymphoplasmocytic immunocytomas of low malignity, 1 was chronic lymphoid leucaemia, and 1 was diffuse lymphoma of large B-cells (centroblastic-immunoblastic) of high malignity.

Out of the 18 cases of orbital lymphomas, 11 lesions were situated exclusively in the anterior orbit forming 61% of all observed lymphomas. Pathophysiologically, 2 cases presented as expansive, 1 case as myogenic, and 15 cases as infiltrative lesions.

In both cases which presented as expansive, the lesions were situated in the anterior orbit extraconally and were well circumscribed. Both of them had lid swelling and a palpable orbital mass. The histological examination showed a low malignant orbital lymphoma of MALT-Type in both cases.

In the case with the myogenic pattern the superior rectus muscle was the only anatomical site of involvent. This patient presented with progressive ptosis as unique symptom. Biopsy showed a low-malignity MALT-Lymphoma.
The remaining 15 lesions which presented as infiltrative, exhibited following anatomic patterns:

- Anterior: The anterior orbit was the most common site of anatomical involvement (9 patients). Lid swelling was the most common symptom and was found in 6 patients. 4 patients had restriction of ocular motility with subsequent diplopia, 5 patients had moderate exophthalmos (4 monolateral up to 4 mm difference in Hertel exophthalmometry, one bilateral) and one patient had a palpable indolent orbital mass. One patient had visual acuity deterioration with choroidal folds in funduscopy.
- Diffuse: All 4 patients had slow progressive moderate to severe exophthalmos (5 to 11 mm difference in Hertel exophthalmometry) with restriction in ocular motility and diplopia. No patient had bone destruction in orbital imaging. One patient had visual acuity deterioration because of optic nerve compression and one patient had a palpable indolent orbital mass.
- Intraconal: 2 patients with intraconal lymphoma were treated. Both of them had exophthalmos (11 mm and 7 mm difference in Hertel exophthalmometry) and motility restriction in more than one direction of gaze with diplopia. No patient had lid swelling. One patient had visual acuity deterioration due to optic nerve compression.
- Lacrimal: One patient with lymphoma had exclusively a bilateral infiltration of the lacrimal gland with lid swelling. A diagnosis of dacryoadenitis had been made ex domo and the patient had been treated with systemic corticosteroids without any success. Orbital biopsy established the diagnosis of a bilateral low malignity MALT-lymphoma.

The patients were treated as follows:

9 patients were initially treated exclusively with orbital radiotherapy (3 patients with bilateral lymphoma/ bilateral dose 36 Gy and 6 patients with unilateral lymphoma/ dose 40 Gy). 7 patients had a low malignity MALT-Lymphoma, one of them bilateral, 1 patient had a bilateral low malignity

lymphoplasmocytic immunocytoma and 1 patient had a bilateral relapse of a low malignity systemic follicular (centroblastic-centrocytic) lymphoma treated with chemotherapy 7 years before. 8 of them had localized disease; one patient with a low malignity MALT-lymphoma had an involvement of bone marrow and lungs, as well. 1 to 2 years after initial treatment, 7 patients were completely free of disease clinically and in orbital MRI scans. However, occlusive radiation retinopathy with cystoid macular oedema developed in one patient. Final visual acuity was 1/15 despite panretinal laser coagulation and intravitreal injection of triamcinolon. The patient with the bilateral relapse of the centroblastic-centrocytic lymphoma had a distinct decrease of tumor mass in orbital MRI scans; tumor rest was however present 6 months after initial treatment. The further clinical course in this patient is not known. In one patient with a unilateral MALT-lymphoma an increase in tumor mass was diagnosed 3 months after radiotherapy. This patient was therefore additionally treated with chemotherapeutical schema in an oncology centre (CHOP/ Rituximab/ Bendamustin/ Interferon) and was completely free of disease clinically and in orbital MRI scans 2 years after chemotherapy.

One patient with a low malignity MALT-lymphoma stadium IV and involvement of bone marrow, lymph nodes and tonsils, was initially treated with a combination of orbital radiotherapy with a dose of 36 Gy and chemotherapy schema in an oncology centre (MCP/Interferon). This patient was clinically free of orbital disease one year after treatment, but the systemic clinical status is not known to us.

One patient with a high malignity centroblastic- immunoblastic lymphoma stadium IV and bone marrow involvement was exclusively treated with a chemotherapy schema (Prednisolon/Vincristin) in an oncology centre. This patient was clinically free of orbital disease 1 year after treatment; the further clinical course is not known.

Two patients with well-circumscribed tumor without systemic involvement were initially treated with surgical tumor excision alone. Both of them had a low malignity MALT-lymphoma. In one of them a recurrence of the lymphoma was observed 2 years after surgery. An orbital radiotherapy with a dose of 36 Gy was subsequently performed and the patient was free of disease clinically

and in MRI scans 2 years after treatment. The clinical course of the second patient is not known to us.

One patient with a MALT-lymphoma with involvement of lymph nodes, bones and lungs, died 4 months after diagnosis before completion of the planned treatment.

In the rest of the patients the treatment and clinical course are not known to us.

The following table summarizes the therapeutical steps chosen for each of our patients with lymphoma.

Table 5. Therapeutical strategy in patients with lymphoma.

Patient	***Histology***	***Systemic involvement***	***Initial treatment***	***Clinical course***
1	Lympho-plasmocytic-immuncytoma (bilateral)	no	radiotherapy 36 Gy (bilateral)	in 1 year complete regression (clinical, MRI)
2	MALT	no	radiotherapy 40 Gy	in one year complete regression (clinical, MRI)
3	MALT	no	radiotherapy 40 Gy	in two years complete regression (clinical, MRI)
4	MALT (bilateral, lacrimal gland)	no	radiotherapy 36 Gy (bilateral)	in one year complete regression (clinical, MRI)
5	MALT	bones, lungs, mediastinal lymph nodes Stadium IV)		died 4 months after diagnosis
6	relapse of a follicular systemic lymphoma (bilateral)	no	radiotherapy 36 Gy (bilateral)	distinct decrease in tumor mass 6 months after radiotherapy (MRI)
7	MALT	no	radiotherapy 40 Gy	in two years complete regression (clinical, MRI)
8	MALT	bone marrow, lungs (Stadium IV)	radiotherapy 40 Gy	in two years complete regression (clinical, MRI) occlusive radiation retinopathy

				systemic status unknown
9	MALT	no	radiotherapy 40 Gy	increase of tumor 3 months after initial treatment. chemotherapy (CHOP, Rituximab, Bendamustin, INF) : in two years complete regression (clinical, MRI)
10	Diffuse lymphoma of large B-cells (centroblastic-Immuno-blastic)	bone marrow (Stadium IV)	chemotherapy (Prednisolon, Vincristin)	in one year clinically free of orbital disease, systemic status not known
11	chronic lymphoid leucaemia	No	Not known	Not known
12	MALT	bone marrow, tonsils, lymph nodes (Stadium IV)	radiotherapy 36 Gy chemotherapy (MCP, INF)	in one year clinically free of orbital disease, systemic status not known
13	MALT (expansive)	no	surgical excision	relapse two years after initial treatment radiotherapy 36 Gy : in two years complete regression (clinical, MRI)
14	MALT	no	radiotherapy 40 Gy	in one year complete regression (clinical, MRI)
15	MALT	no	not known	not known
16	follicular	no	not known	not known
17	Lymphoplasmocytic immuno-cytoma	no	not known	not known
18	MALT (expansive)	no	surgical excision	not known

Histiocytosis

3 of our patients had a histiocytosis. All of them were male. Two of them had a Langerhans-cell-histiocytosis LCH). The first patient was 24 years of age and had unilateral painless lid swelling. The neoplastic process was situated

in the anterior orbit and caused bone destruction with infiltration of the frontobasal dura, and displacement of the rectus superior muscle and obliquous superior muscle without infiltrating them. The second patient was 27 years of age and had exophthalmos caused by an expansive intraconal tumor situated in the great wing of the sphenoid bone. The tumor destroyed the bone and infiltrated the dura. Both tumors showed an intense gadolinium uptake in MRI-scans and had a central necrotic zone. Other bone or systemic involvement was excluded. The diagnosis was confirmed by orbital biopsy. The first patient was treated with total tumor extirpation in a neurosurgery clinic and was free of disease clinically and in MRI- scans one year after the operation. The clinical course of the second patient is not known to us.

One patient had an Erdheim-Chester-disease (ECD). This patient was 60 years of age and presented with bilateral exophthalmos and progressive visual acuity deterioration of the left eye. The MRI showed a bilateral intraconal tumor surrounding the optic nerve. In funduscopy bilateral choroidal and retinal folds were seen. Orbital biopsy established the diagnosis. Further examinations revealed retroperitoneal fibrosis; other systemic involvement was excluded. A clinical deterioration was observed despite systemic Interferon-α therapy and bilateral orbital decompression was performed. A decrease of exophthalmos and an improvement of the visual acuity of the left eye were achieved and the further treatment regarding other therapeutical options was undertaken by oncologists.

Finally, one of our patients presented with unilateral exophthalmos caused by an intraconal infiltration of an acute myeloid leucaemia. The exophthalmos was the first sign of the disease. The patient died 5 months after diagnosis.

2). Mesenchymal tumors (5 cases): 1 patient with malignant fibrous histiocytoma, 2 patients with liposarcoma, 1 patient with malignant solitary fibrous tumor, 1 patient with rhabdomyosarcoma.

The first patient was male, 68 years of age and presented with a progredient exophthalmos. Orbital biopsy performed ex domo established the diagnosis of

an orbital pseudotumor. Systemic therapy with corticosteroids and methotrexate had not been successful. In orbital MRI a relatively well circumscribed intraconal tumor with high gadolinium uptake was shown. An orbitotomy with partial tumor excision and biopsy established the diagnosis of a malignant fibrous histiocytoma. Metastases were excluded. An exenteration and subsequent orbital radiotherapy with a dose of 60 Gy followed. Two years after there were no signs of tumor rest in orbital MRI.

The second patient was female, 53 years of age and presented with lid swelling and a palpable mass of the medial lid of her last eye. The other eye had been enucleated in the childhood after a perforating injury. In funduscopy choroidal and retinal folds were seen. The orbital MRI showed an intraconal well circumscribed tumor with high gadolinium uptake causing displacement of the rectus inferior muscle, the rectus medial muscle, the optic nerve and the globe, without infiltrating them. The tumor was high vascularised in the angiography of the carotid internal artery. Orbitotomy with biopsy was performed and the initial histological diagnosis was haemangiopericytoma, however a giant cell angiofibroma could not be excluded. A radical tumor excision was recomended by the pathologists. A second orbitotomy with tumor excision was performed and the final histological diagnosis was that of a solitary fibrous tumor with focal sarcomatous (malignant) transformation. Metastases were excluded. The patient was free of disease both clinically and in MRI scans two years after the operation. Three years after the operation new tumor growth with high gadolinium uptake and infiltration of the rectus superior muscle and levator palpebral muscle was shown in MRI. Orbitotomy with tumor excision was again performed and the histological examination showed this time a sarcomatous transformation of the whole tumor with infiltration of the excision margins. Radiotherapy with a dose of 60 Gy followed and the patient was free of tumor in MRI scans one year after.

The third patient was male 40 years of age and presented with exophthalmos and lid swelling caused by a relatively well circumscribed tumor of the anterior orbit, as shown in MRI. The tumor showed a high gadolinium uptake, as well. Orbitotomy with local excision and biopsy was performed, and a well differentiated liposarcoma was diagnosed. Metastases were excluded. No

other therapy followed. The patient was free of disease both clinically and in MRI scans one year after surgery.

The fourth patient was female, 26 years of age and presented with ocular motility restriction and diplopia. The MRI showed a tumor situated in the anterior orbit infiltrating the rectus superior muscle and the lacrimal gland. Orbitotomy with partial tumor excision and biopsy was performed and the initial diagnosis was that of a dermoid. Five months after the operation increase of lid swelling was observed and the MRI showed new tumor growth and infiltration of the bony orbit and intraconal extension. A new orbitotomy was performed and the final diagnosis was that of a liposarcoma (myxoid type). Metastases were excluded. Exenteration followed and the patient was free of disease clinically and in MRI scans seven months after the operation. The further clinical course is not known to us.

The fifth patient was male, 17 years of age and presented with rapidly increasing exophthalmos and lid swelling. The orbital CT scan showed a tumor of the maxillar sinus with bone destructions and extension in the nasal cavity, the ethmoid cells, epipharynx, sphenoid sinus and orbit. The lymph nodes of the neck region were also involved. Biopsy established the diagnosis of an alveolar rhabdomyosarcoma. Metastases were excluded. Chemotherapy according to CWS-protocol and radiotherapy with a dose of 30 Gy were administered. The initial response was very good, since no residual tumor was evident clinically and in MRI 7 months. However, 8 months after end of therapy new tumor growth was observed in the medial lid. Biopsy confirmed a relapse of the rhabdomyosarcoma and chemotherapy according to CWS-protocol was again performed. Metastases were once more excluded. 4 months later residual tumor was present in orbital MRI scans, which increased in size 1 month later. Tumor excision with partial excision of the medial rectus muscle and brachytherapy with a dose of 20 Gy followed. 1 month after treatment the visual acuity was 0,8 and the patient had diplopia in all directions of gaze, which could not be compensated with prisms. The further clinical course is not known to us.

Table 6. Findings, treatment and clinical course in 5 patients with malignant mesenchymal tumors.

Patients: Sex, age	***Histology***	***Symptoms***	***Orbital imaging***	***Initial therapy***	***Clinical course – Last follow-up***
Male, 68	Malignant fibrous histiocytoma	Slowly progredient exophthalmos	**MRI**: well-circuscribed intraconal tumor, high gadolinium uptake	Exenteration, radiotherapy 60 Gy	Free of disease 2 years after treatment
Female, 53	Malignant solitary fibrous tumor	Lid swelling, palpable mass	**MRI**: well-circuscribed intraconal tumor, high gadolinium uptake	Local excision	Relapse 3 years after primary surgery – subtotal excision, radiotherapy 60 Gy, free of disease 1 year after second treatment
Male, 40	Well differentiated liposarcoma	Slowly progredient exophthalmos, lid swelling	**MRI**: well-circuscribed tumor, anterior orbit, high gadolinium uptake	Total local excision	Free of disease 1 year after treatment
Female, 26	Liposarcoma (myxoid type)	Diplopia	**MRI**: infiltrative tumor, anterior orbit	Exenteration	Free of disease 7 months after treatment
Male, 16	Alveolar rhabdomyosarcoma	Rapidly progressive exophthalmos, lid swelling	**MRI/CT**: infiltrative mass, paranasal sinuses, orbit, nasal cavity, bone distruction	Chemotherapy, Radiotherapy 30 Gy	Initial resolution, but later relapse – New chemotherapy course/partial excision/ brachytherapy 20 Gy – Outcome of last treatment not known

3). Lacrimal gland tumors (3 cases): All of them were adenoid cystic carcinomas. The patients were 47, 65 and 70 years of age, two female and one male.

The first patient presented with lid swelling and ptosis without pain. There was a restriction of up gaze. The orbital MRI showed a tumor in the lacrimal fossa with intraconal extension to the apex and gadolinium uptake. Bone erosion could not be radiographically excluded. Metastases were excluded. Biopsy established the diagnosis of an adenoid cystic carcinoma and exenteration with subsequent radiotherapy with a dose of 63 Gy followed. The patient was free of disease clinically and in MRI scans 4,5 years after radiotherapy.

The second patient presented with lid swelling and ptosis without pain. There was restriction in up gaze. The orbital CT showed a tumor in the lacrimal

fossa with calcification, bone erosion and infiltration of the rectus superior muscle and the Levator palpebrae muscle. Orbital biopsy showed an adenoid cystic carcinoma and the same treatment as in the first patient was performed. The clinical course is not known to us.

The third patient presented with rapid progressive exophthalmos and visual acuity deterioration of the left eye. In funduscopy optic disc swelling and choroidal and retinal folds were seen. The orbital MRI showed an infiltrative intraconal and extraconal tumor with optic nerve compression and intracranial and miningeal extension. In CT scans the sphenoid bone and the lateral orbital wall were eroded. Biopsy showed an adenoid cystic carcinoma. Exenteration with dura excision and treatment of the infiltrated bone with the CO2 laser as well as radiotherapy with a dose of 62 Gy were performed. Ten months after initial treatment the patient presented with visual acuity deterioration of the right eye. The MRI showed intracranial growth, infiltration of the scull base, frontal sinus, ethmoid cells and chiasm. Pterional craniotomy with optic nerve decompression was performed without any other adjuvant therapy. This patient succumbed 14 months after the initial diagnosis.

4). Orbital metastases (3 cases): The first patient had a prostate carcinoma which had been diagnosed 3 months before and had already been under chemotherapy treatment. He had no ocular symptoms, but in the bone scintigraphy and in orbital CT scans an osteosclerotic metastasis was suspected in the great wing of the sphenoid. Orbital biopsy confirmed the diagnosis of a metastasis. One year later the patient continued to have no ocular symptoms, the further clinical course is not known to us. The second patient had undergone radical prostatectomy 11 years and extirpation of an endocrine tumor of the heart 7 years before reference to us. This patient had no ocular symptoms. In an MRI scan performed due to chronic headaches, an extraconal circumscribed tumor was found in the anterior orbit with contact to the obliquous superior muscle without infiltrating the muscle. The tumor was excised and the histological examination confirmed an orbital metastasis of the neuroendocrine tumor. 4 months later the patient was free of symptoms. The third patient had had a surgical excision of a breast carcinoma 5 years

before reference to us. The patient presented with lid swelling and diplopia due to ocular motility restriction. There was no exophthalmos. The orbital MRI showed an intraconal infiltrative tumor with contrast medium uptake. Biopsy confirmed a metastasis of the breast carcinoma and the patient died of metastatic disease 2 years after.

Our series also included one patient with a basosquamous carcinoma of the canaliculi. The patient was 59 years of age and presented with a palpable tumor of the medial lid without pain. The CT showed a subcutaneous tumor of the medial lid with contrast medium enhancement, without infiltration of the nasal cavity and paranasal sinuses. Biopsy established the diagnosis and resection of the tumor, canaliculi, lacrimal sack and ethmoidal region was performed, followed by radiotherapy with a dose of 60 Gy. Metastases were excluded. One year after treatment a new tumor growth was observed. New orbitotomy and tumor excision along with the adjacent periost took place. The histological examination confirmed a tumor recurrence and the excision margins were free of tumor. Metastases were once more excluded. The further clinical course is not known to us.

3.2.2.2. Benign tumors

1). Vascular tumors (16 cases): 14 patients with cavernous haemangioma, 1 patient with lymphangioma and 1 patient with an angiomyoma.
The cavernous haemangiomas were in their vast majority intraconal (13 cases) lesions. 1 was situated extraconally in the anterior orbit. The patients were 29 to 78 years of age (mean age 54,5 years). 7 patients were male and 7 patients were female. 11 patients (78%) had moderate to severe exophthalmos. 5 patients (36%) had optic disc swelling and choroidal and retinal folds, with 3 of them having a visual acuity deterioration and 1 of them having localized visual field defects due to optic compression by apical tumor. 3 patients (21%) had ocular motility constriction with subsequent diplopia. In 2 patients the tumor was a coincidence finding in MRI scans performed for other reasons. In all patients orbitotomy with tumor excision was performed. In 12 patients (86%) the tumor was completely excised and the postoperative

course was without any complications. In one patient with severe exophthalmos (14 mm difference in Hertel exophthalmometry) the tumor could not be completely excised due to close contact to the optic nerve. Exophthalmos was persistent (9 mm difference in Hertel exophthalmometry), but since the visual acuity remained normal, no other treatment followed. One patient presented with exophthalmos (11 mm difference in Hertel exophthalmometry), motility restriction in all directions of gaze, optic disc swelling and retinal and choroidal folds caused by a cavernous haemangioma with thromboses and phleboliths in close contact to the optic nerve, as shown in CT scan. The tumor was only partially excised and the patient suffered vision loss directly after the operation due to central retinal artery occlusion. The visual acuity failed to recover.

1 patient presented with exophthalmos (7 mm difference in Hertel exophthalmometry) caused by an expansive intraconal tumor with contrast medium uptake, as shown in MRI scan. The tumor was in close contact to the optic nerve and only partially definable from it. We performed a partial tumor excision and histological examination showed an angiomyoma. The patient had a postoperative keratopathy with persistent corneal erosion due to incomplete lid closure caused by oculomotor nerve paresis. Despite twice performed amnion membrane transplantation, a perforating corneal ulcus developed. Keratoplasty followed, but transplant rejection occurred, and final visual acuity was as a result only light perception.

1 22 years old patient presented with exophthalmos caused by a known lymphangioma which was twice operated ex domo. At first presentation the patient had severe exophthalmos (15 mm difference in Hertel exophthalmometry), visual acuity deterioration (50/100) with a relative afferent pupil defect and choroidal and retinal folds in funduscopy. Ocular motility was restricted in all directions of gaze. In MRI scans an intraconal relatively well circumscribed tumor, was seen, which was homogenous and hyperintense in T1 and T2 weighed images and showed a moderate gadolinium uptake. The apex was free of tumor. The optic nerve was displaced. Lateral orbitotomy with partial tumor excision was performed. Histological examination showed a cavernous lymphangioma (mixed venous-lymphatic malformation). The visual acuity was postoperatively stable, but the exophthalmos persisted. The

patient presented 18 months later with unaltered exophthalmos (15 mm difference in Hertel exophthalmometry). Visual acuity and ocular motility were unaltered, as well. We advised the patient against a new operation due to high risk of postoperative complications including postoperative hemorrhage, cyst formation, recurrence with increase of the vascular component of the haemangioma and visual loss. The patient demanded emphatically a re-operation and unfortunately suffered total visual loss due to apical hemorrhage with optic nerve compression on the first postoperative day. Enucleation was subsequently performed.

2). Neoplasia of the lacrimal gland (6 cases): Histologically, all of them were pleomorphic adenomas. The patients were between 40 and 70 years of age, 3 male and 3 female.

3 patients presented with exophthalmos and inward and downward displacement of the globe without any motility restriction or diplopia. 1 patient presented with lid swelling, normal ocular motility and no exophthalmos. The orbital MRI showed in all of them a well circumscribed tumor with medium gadolinium uptake causing globe displacement. In CT scans no bone erosion was found. In 2 of these patients the tumor had a slightly nodular configuration. Lateral orbitotomy with tumor extirpation (3 complete, 1 incomplete) was performed and established the diagnosis of a pleomorphic adenoma. In the case with incomplete excision recurrence of the tumor with diplopia was observed 3 years after the initial operation. Surgery was again performed and the patient was free of disease 2 years after second surgery.

2 patients presented with a relapse of a pleomorphic adenoma operated ex domo. The first of them had motility restriction with diplopia in up gaze. This patient had undergone an incomplete tumor excision 5 years before reference to us. An extraconal multinodular tumor was shown in MRI scans. New orbitotomy followed and histology excluded malignant transformation. 1 month postoperatively a small rest was found to be present in MRI scan without any progression 3 years later. The second patient had been operated 23 years before reference to us, had no ocular symptoms and the tumor relapse was coincidentally discovered in an MRI performed for other reason. Orbitotomy with total tumor excision followed. Histological examination excluded

malignant transformation. Postoperatively, esophoria with diplopia occurred and strabismus surgery was performed 6 months after the operation. The further clinical course is not known to us.

3). Neurogenic neoplasia (3 cases): 2 patients with a neurinoma (schwannoma) and 1 patient with a neurofibroma.

The first patient was 72 years of age, male and presented with a slowly progredient exophthalmos over the past 20 years (difference of 8 mm in the Hertel exophthalmometry). There was a hypotropia with restriction of ocular motility in up gaze. MRI scan showed a well circumscribed tumor with contact to the orbital roof causing bone expansion but no bone erosion. The tumor had a cystic part extending intraconaly. The tumor was excised and histological examination showed a neurinoma without signs of malignity. Postoperatively, no other signs or symptoms were present except for a very mild exophthalmos (3 mm difference in Hertel exophthalmometry).

The second patient was 73 years of age, female and presented with slowly progredient exophthalmos (difference of 14 mm in the Hertel exophthalmometry), downward globe displacement and motility restriction in all directions of gaze. The tumor was well circumscribed and in contact to the orbital roof causing bone expansion but no bone erosion, consisting of a cystic and a solid part, as seen in MRI scan. Orbitotomy with partial tumor excision was performed. The diagnosis was that of a neurinoma without any signs of malignity. The postoperative exophthalmos was 8 mm in Hertel exophthalmometry and further clinical course was uneventful.

The third patient was 30 years of age, male and presented with bilateral exophthalmos with normal motility. In orbital CT and MRI we saw a bilateral well circumscribed tumor of the upper orbit causing bone expansion. The tumor showed only a peripheral contrast medium enhancement. Excisional biopsy was unilaterally performed and the diagnosis was that of a neurofibroma. This patient was referred to a dermatology clinic where neurofibromatosis was confirmed. Three years after the operation the patient had a slight bilateral constriction of adduction without diplopia and no other treatment was performed.

3.2.3. Vascular lesions

Our series included 19 patients with vascular pathology other than vascular tumors. 9 patients had an arteriovenous fistula, 6 patients had a venous malformation, 2 patients had a thrombosis of the ophthalmic superior vein and 2 patients had a haematic cyst.

1). Arteriovenous fistulas (9 cases): 3 patients were male and 6 female. The patients' ages were between 53 and 82 years. 2 patients with an indirect dural fistula between the external carotid artery (ECA) and the cavernous sinus (CS) , 2 patients with an indirect dural fistula between the internal carotid artery (ICA) and the CS, 1 patient with a complex direct and indirect fistula between ICA and ECA and the CS, 1 patient with a direct traumatic fistula between the ICA and the CS, 1 patient with a fistula between the ECA and the superior ophthalmic vein (SOV), 1 patient with a fistula between the ophthalmic artery (OA) and the SOV and 1 patient with a complex fistula between the ECA and OA and the CS. 8 patients (89 %) had dilated conjuctival and episcleral vessels, 2 patients (22%) ptosis, 3 patients (33%) visual acuity deterioration with 2 of them having a relative afferent pupil defect, 4 patients (44%) abnormal findings in funduscopy such as papillary edema, venous engorgement and retinal hemorrhages, 3 patients (33%) abnormal intraocular pressure. All patients had exophthalmos (moderate to severe) and ocular motility restriction in at least one direction of gaze. 1 patient with minimal symptoms (exophthalmos of 2 mm difference in Hertel exophthalmometry and abduction deficit with diplopia in extreme gaze) due to an indirect ECA and CS fistula received no treatment. In 5 patients the fistula was embolised by a neuroradiologist: 1 patient had a fistula between the ACE and SOV, 1 patient had an indirect dural fistula between the ECA and the CS, 1 patient had a direct fistula between the ICA and CS and 2 patients had an indirect dural fistula between the ICA and SC (1 of them with drainage by the contralateral SOV). In 3 of them there was a complete regression of the symptoms postoperatively. In 2 of them recanalisation of the fistula occurred: 1 of them received a second embolisation with complete regression of symptoms; the other had a minimal arterial flow after recanalisation and the

symptoms resolved due to thrombosis of the junction between the superior ophthalmic vein and the angular vein, and therefore no further embolisation was performed. 3 of the patients were treated in a neurosurgery clinic; 1 of them had a complex indirect and direct fistula between the ICA and ECA and CS and only the ECA component could be embolised, but the patient had full recovery from symptoms and no retrograde flow in the orbit was shown in the postoperative angiography. The clinical course in the rest of the patients is not known to us.

2). Thrombosis of the superior ophthalmic vein (SOV) (2 cases): The first patient was male, 39 years of age and presented with acute visual acuity deterioration, massive chemosis and conjuctival injection and exophthalmos of 8 mm difference in Hertel exophthalmometry. The patient had no pain. The visual acuity was no light perception. Sonographically, an intensely dilated SOV was seen. In CT scans a completely thrombosed SOV and partially thrombosed (cavernous sinus) CS and superior and inferior petrous sinuses were evident. The patient had a known mutation of the V Leyden factor. Immediate orbital decompression was performed but visual acuity failed to recover. The second patient was female, 71 years of age and presented with visual acuity deterioration, chemosis and conjuctival injection, exophthalmos (3 mm difference in Hertel exophthalmometry) and painful restriction of abduction. In funduscopy choroidal detachment and macular edema were seen. Angiographically a thrombosis of the inferior petrous sinus, the CS and the adjacent part of the SOV was shown. Anticoagulant therapy followed and symptoms regressed.

3). Venous malformation (6 cases): 4 patients had a non-distensible venous malformation. 2 of them had a palpable indolent mass in the nasal lid. CT scans revealed in both patients a well circumscribed mass with minimal contrast medium uptake. MRI was additionally performed in one patient. The process was isointens in T1 weighed and hyperintens in T2 weighed scans, with inhomogenous gadolinium uptake. Anterior orbitotomy with excision of the lesion followed and postoperatively no complications occurred. 1 patient had axial exophthalmos and restrictions in ocular motility with diplopia. The

process was situated intraconaly, displacing the medial rectus muscle and the optic nerve and had isointens signal in T1-weighed and heterogenous signal (isointens with hyperintens areas) in T2-weighed. The hyperintens part of the lesion showed minimal and the rest of the lesion showed medium gadolinium uptake. Lateral orbitotomy with total excision was performed and histological examination showed a partially thrombosed venous malformation. Postoperatively the patient had no exophthalmos, but diplopia was still present 7 months after the operation. The further clinical course is not known to us. 1 patient presented with visual filed defects and ocular motility restriction with diplopia. Visual acuity was normal in both eyes. A CT scan was performed and showed a well circumscribed apical mass with minimal contrast medium uptake. Lateral orbitotomy with total excision was performed and histological examination showed a thrombosed venous malformation with benign reactive intravascular endothelial hyperplasia. Since ocular motility restriction persisted after surgery, strabismus surgery followed and the patient was free of symptoms thereafter.

2 patients presented with intermittent exophthalmos after Valsalva maneuver. Visual acuity and ocular motility were normal. MRI scans showed an intraconal process in the first case and an extraconal lesion with intraconal component in the second case. Both lesions were isointens in T1 weighed and moderately hyperintens in T2 weighed images and showed marked gadolinium uptake. No surgical treatment was performed.

Table 7. Findings and treatment in 6 patients with orbital venous malformations

Patients	***Symptoms***	***Orbital imaging***	***Therapy***	***Diagnosis***	***Clinical course – Last follow-up***
1	Palpable mass	**CT:** well-circumscribed lesion, minimum contrast medium uptake, anterior orbit	Anterior orbitotomy, excision	Non-distensible venous malformation (histology)	Free of symptoms, no complications

2	Palpable mass	**CT:** well-circumscribed lesion, minimum contrast uptake, anterior orbit **MRI:** T1:isointens, T2:hypeintens, inhomogenous contrast medium uptake	Anterior orbitotomy, excision	Non-distensible venous malformation (histology)	Free of symptoms, no complications
3	Visual field defects, diplopia	**CT:** well-circumscribed apical lesion, minimal contrast medium uptake	Lateral orbitotomy, excision	Thrombosed non-distensible venous malformation (histology)	Persistent diplopia – Strabismus surgery Free of symptoms
4	Axial exophthalmos, diplopia	**MRI:** well-circumscribed lesion, intraconal, T1:isointens, T2:isointens with hyperintens areas, inhomogenous contrast medium uptake	Lateral orbitotomy, excision	Thrombosed non-distensible venous malformation (histology)	Persistent diplopia, no complications
5	Intermittent exophthalmos, increase with Valsava maneuver	**MRI:** well-circumscribed intraconal lesion, T1:isointens, T2:moderately hyperintens, marked contrast medium uptake	Observation	Distensible venous malformation	No complications
6	Intermittent exophthalmos, increase with Valsava maneuver	**MRI:** well-circumscribed intraconal lesion, T1:isointens, T2:moderately hyperintens, marked contrast medium uptake	Observation	Distensible venous malformation	No complications

4). Haematic cyst (2 cases): The first patient was male, 56 years of age and had no symptoms. The lesion was coincidentally discovered in an MRI scan performed due to chronic headaches. Clinical examination revealed exophthalmos (3 mm difference in Hertel exopthalmometry) and downward globe displacement. MRI scans showed a well circumscribed intraconal encapsulated process situated above the optic nerve. Only the capsule was

enhanced by gadolinium. Surgery with extirpation of the lesion was performed. Biopsy showed an organizing hematoma, fibrous tissue, histiocytic inflammatory cells and hemosiderin and hematoidin deposits without epithelial or endothelial lining, and established the diagnosis of an orbital hematic cyst. The second patient was male, 49 years of age and presented with acute exophthalmos, lid swelling and hypotropia after nausea with intense vomiting. MRI scans showed a subperiostal well circumscribed encapsulated process which was hypointense in T1 weighed and had hypointense and hyperintense areas in T2 weighed images corresponding to an acute bleeding in a haematic cyst. Only the capsule showed gadolinium uptake. No further therapy followed. The patient had only minimal exophthalmos (2 mm difference in Hertel exophthalmometry) 1 month after first examination. The patient refused an operation and he was advised to avoid Valsalva maneuver.

3.2.4. Structural and degenerative lesions

This last group of patients included 4 patients with an orbital dermoid, 1 patient with an orbital amyloid and 1 patient with a mucopyocele. 3 patients with orbital dermoid presented with upper lid swelling (2 laterally and 1 medially) and 1 patient presented with axial exophthalmos. In all of them the lesions had been known since childhood and were situated in the anterior orbit. In MRI scans (performed in 2 patients) we saw well circumscribed orbital process with relatively high signal in T1 weighed and T2 weighed images. Only the capsule enhanced with gadolinium. In CT (perfrormed in 2 patients) the tumor was hypodense without bone infiltration or erosion or contrast capture. Tumor excision was performed in all of them and there were no postoperative complications.

1 patient presented with an infiltrative anterior orbital process causing bilateral indolent lid swelling. The lesion showed moderate contrast capture in orbital CT scans. The conjuctiva showed a yellowish infiltration. Biopsy was performed and confirmed the diagnosis of an amyloid. Systemic amyloidose was excluded.

1 patient presented with an indolent palpable soft orbital mass and hypotropia of the right eye. CT scans showed an expansion of the frontal sinus, a

destruction of the floor of the frontal sinus and the frontoethmoidal region and a displacement of the lateral rectus muscle and globe. The diagnosis of a mucopyocele was made and further treatment was undertaken by ENT specialists.

4. Discussion

4.1. Inflammatory disease

4.1.1. Non-specific inflammation (NSI)

In our series the lacrimal gland region was found to be the most common site of location of non-specific inflammation (NSI), accounting for 45% of all cases. In a series of 90 cases with idiopathic orbital inflammation (Yuen et al 2003) the lacrimal gland region was also found to be the most common site of involvement. In order to establish the diagnosis, we performed an orbital biopsy in all patients independent of the site of involvement. Many authors, though, suggest sparing an orbital biopsy in the presence of typical symptoms and signs (clinically and in orbital imaging), and perform it only when steroid treatment has no or minimal effect. It is our tactic to perform a biopsy before initiating a therapy, because lymphoproliferative lesions including lymphomas can also have an initial positive response to steroid therapy and the diagnosis of such lesion could be delayed. When acute symptoms, such as pain, erythema and proptosis, dominate the clinical picture, the presence of an acute inflammation is highly likely. In that case, an initial treatment with steroids without first performing a biopsy could be considered. However presentation of NSI can be variable and subacute, and chronic cases of NSI lacking a history of pain are not uncommon (Cytrin et al 1997). Several CT and MRI features such as site, shape, CT-attenuation, contrast enhancement and signal intensity in T2-weighed images, have been used to differentiate between NSI and lymphoma in the orbit (Weber et al 1996, 1999, Gufler et al 1997, Won-Jin-Moon et al 2003). However, in many cases the radiological characteristics overlap, and only orbital biopsy can establish the right diagnosis. According to Rootman (Rootman 1998) the diagnosis of NSI should be made extremely cautiously and may more often require biopsy because of the risk of misdiagnosis, especially when two locations are affected: the apex and the lacrimal gland. According to the same author

lacrimal lesions are associated with a systemic disorder in 50% of the cases, while processes localised in the apex are very frequently misdiagnosed. In our series, however, only 2 of 22 (9%) patients with lacrimal inflammation were found to have systemic disease. Among 44 patients with NSI in our series 10 of them had severe degree of fibrosis in biopsy specimens in terms of a sclerosing non-specific orbital inflammation (SNSI). 7 patients (70%) had lacrimal involvement, 2 patients (20%) had intraconal involvement and 1 patient (10%) had apical involvement. As by other authors reported (Hsuan et al 2006), we found a predilection for the lateral orbit, as well. It is postulated that the lacrimal gland is prone to involvement because it is the only orbital site which normally contains lymphoid tissue (Garner 1992). It has been suggested that lymphocytes play a critical role in the development of fibrosis (Mc Carthy et al 1993).

The clinical course in 8 patients of our series (1 with sclerosing inflammation) is not known to us.

1 patient with intraconal SNSI and diplopia, who was not severely disturbed in daily life, refused therapy after exclusion of malignancy. One year later no progression was observed.

The follow-up period of the rest of the patients varied between 2 months and 24 months. 15 patients of the group of NSI, excluding myositis, were initially treated with systemic steroids; 11 out of them (73,3%) had complete regression of symptoms, 1 (6,6%) had partial regression with persistent exophthalmos and minimal ocular motility restriction with diplopia, and 3 (20%) had no improvement of symptoms. 2 of the latter patients underwent orbital radiation therapy; complete regression occurred in one patient and partial regression occurred in the other one (persistent diplopia). The third patient who had no improvement after steroid therapy, underwent bilateral orbital debulking surgery due to bilateral exophthalmos with ocular motility restriction in all directions of gaze. Bilateral reduction of exophthalmos was achieved, but postoperatively diplopia persisted and strabismus surgery followed.

1 patient was treated with ibuprofen with complete regression of the disease. Systemic steroid therapy is the established first-line treatment for NSI of the orbit. NSI is exquisitely sensitive to systemic steroids, however some authors

(Yuen S.J.Y, Rubin P.A.D 2003) found that a considerable number of patients had unsatisfactory outcomes. According to the same authors steroid dependence with recurrence or increase of symptoms during or after steroid taper has also occurred in patients with good initial response to therapy. A very low cure rate of only 37% and high recurrence rate of 52% after systemic steroid administration along with considerable adverse effects, were reported in other retrospective studies, as well (Mombaerts et al 1996). In order to minimize systemic side effects, the intraorbital injection of steroids (20 to 40mg/ml triamcinolon acetonide intralesionally or perilesionally) has alternatively been proposed. In a series of 10 patients with anterior inflammatory process (7 with NSI and 3 with SNSI) receiving intraorbital steroid injections, 9 patients had very good response with regression of disease (Leibovitch et al 2007). 5 of these 9 patients responded after only one injection, while in 4 patients repeated injections had been necessary. The authors concluded that steroid injections could be an alternative in steroid responsive but steroid intolerant patients with anterior NSI; moreover, periocular injections may need to be repeated until the desired therapeutical effect is achieved. The same authors claimed that patients with resistance to periocular steroid treatment were unlikely to respond to systemic steroid therapy. However, as the dose equivalent between steroid injections and systemic steroids is not known, the authors suggested that a trial of high-dose steroid treatment should be done in all cases, before immunosuppressive agents or radiotherapy are considered. Intraoperative injection of triamcinolon has also been considered as effective in cases of SNSI (Harris 2005). Because there are only few reports on this type of treatment and additionally multiple complications of orbital steroid injections (even if not usually) have occured (skin depigmentation, intractable elevated intraocular pressure, ptosis, globe perforation, corneoscleral or conjuctival melting, retinal artery occlusion from embolisation, pressure-induced optic compression, proptosis and fat atrophy), we have not used intraorbital steroids for the treatment of our patients with NSI. In our cases of NSI where steroids had not been effective or well-tolerated, we considered the alternative of orbital radiotherapy (2 patients) or debulking surgery (1 patient). Orbital radiotherapy has been reported to be successful in the treatment of upto 70-75% of cases with NSI

(Orcutt et al 1983, Sergott et al 1981). This percentage includes patients with complete resolution or patients with partial resolution with significant improvement without the need of steroids. The response to steroid treatment may be a predictor factor for the response to radiotherapy. In a study (Orcutt et al 1983) including 22 patients receiving orbital radiotherapy due to NSI, 12 out of 13 patients (93%) with initial good response to steroids showed subsequent good response to radiotherapy. However only 2 (33%) out of 6 patients with no response to steroids showed response to radiotherapy. Since the patients who responded to radiotherapy, had not suffered any recurrence of their disease in a mean follow-up time of 22,3 months, response to radiotherapy might present a permanent cure. In the same study, the average time for response to occur, was 3,2 months for full responders and 7,9 months for partial responders. The authors concluded that radiotherapy should be considered as a treatment option in patients with NSI who show an initial steroid response but relapse after steroid tapering, or for those cases where steroids have adverse effects or are contraindicated. However, findings of other authors (Sergott et al 1981) failed to prove a correlation between steroid and radiotherapy response. The histological composition of the inflammatory lesion may also predict the response to radiotherapy. It has been postulated that the dominance of lymphocytes can predict a favorable outcome of the therapy (Kim, Roth 1978, Kennerdell et al 1979, Sergott et al 1981, Orcut et al 1983). The presence of eosinophils could generally imply a poor response to radiotherapy, however not all authors agreed on this. The presence of fibrosis has not been shown to be a predictor factor of effectiveness. Moreover, small discrete masses may respond better than large diffuse masses (Orcut et al 1983).

As reported above, 3 of our patients with NSI underwent radiotherapy: 2 of them had had no response to previous steroid administartion, and one of them had had good initial response to steroids, but the administration of steroids had to be stopped due to severe side effects. The latter patient as well as one of the patients with no response to steroids, showed a complete regression, whereas the other patient only partial. Our results agree with those of Sergott, and we think that orbital radiotherapy should be tried independent of initial response to steroids.

10 of our 44 patients with NSI had SNSI. In 1 of them steroid treatment was recommended after the diagnosis had been established, but the further clinical course is not known to us. 1 patient received no therapy and no progression was observed 1 year later. 1 patient had apical involvement with visual acuity of hand movement perception. Despite immediate decompression, visual acuity failed to improve and no further treatment occurred.

4 patients with SNSI were initially treated with steroids: 1 of them (25%) had partial response, while 2 others (50%) had no response. Only 1 of them (25%), who had SNSI of the lacrimal gland, had very good initial response; yet, relapse occurred 5 months after initial diagnosis with apical involvement and visual acuity of hand movement perception. Despite immediate decompression visual acuity failed to improve. In the first patient without response to steroids, orbital radiotherapy was recommended; the further clinical course is not known to us. The second patient without any response to steroids had intraconal involvement and received methotrexate, which also proved ineffective. Surgical debulking was subsequently performed with reduction of his exophthalmos and only minimal restriction in ocular motility remained.

3 patients with well circumscribed lacrimal SNSI were operated with en-block resection of the lacrimal gland region. 2 of them were completely free of symptoms and no further treatment occurred. In 1 of them the clinical course is not known to us.

The treatment of SNSI has been controversial. Most studies included few patients, and there have been no randomized or controlled trials. No treatment can be expected to reverse established fibrosis. Steroids continue to be the first line therapy although results have been in many cases disappointing. In the largest retrospective review published on this subject, including 31 patients from 5 orbital centers, 27 patients were initially treated with steroids. Only 9 (33%) had good response and 11 (40%) had partial response (Hsuan et al 2006). Steroids were found to be more effective in patients with shorter duration of disease. Other authors also suggest early and aggressive treatment with steroids should be considered in cases with short duration of disease (Brannan et al 2006). It has been suggested that

SNSI should be separated from NSI leaving the former as an independent entity among orbital inflammations. Idiopathic sclerosing inflammation of the orbit is considered as a unique clinicopathologic entity, similar to retroperitoneal fibrosis, which is characterized by primary, chronic, and immunologically mediated fibrosis. As a matter of fact only poor response to corticosteroid treatment or radiotherapy is generally to be expected, and early and aggressive immunosuppressive therapy seems to be justified (Rootmann et al 1994). The partial effectiveness of immunosuppressants, such as cyclophosphamide and azathioprime, has been reported in the literature in isolated cases. Cyclophosphamide was found to be effective in a case of SNSI in combination with steroids (Uy et al 2001). Cyclophosphamide prescribed to 3 patients with partial or no response to steroids, achieved partial resolution in only 1 patient (Hsuan et al 2006). The use of stereotactic radiotherapy in combination with the immunosuppressant rituximab achieved complete remission in a case of SNSI without response to high dose systemic steroids (On et al 2006). Another therapeutical alternative for SNSI is surgical debulking (Mombaerts et al 1996, Moreiras 2004). Moreiras favors surgery for sclerosing dacryoadenitis, even if this does not always guarantee reduction or disappearance of pain. Out of 7 patients with sclerosing dacryoadenitis he operated, 4 patients had complete resolution, while 3 patients had persistent fibrosis because the lesion had not been completely excised. According to the same author surgery could also be considered for intraconal sclerosing inflammations simulating neoplasia, as radical as possible. Kennerdell (Kennerdell 1991) also reported good results after surgical excision of lesions with severe and established fibrosis. He recommended complete surgical removal for local lesions and debulking surgery with or without steroid treatment, followed by radiation therapy for diffuse lesions. Hsuan (Hsuan et al 2006) reported good results after surgical debulking, as well. In his series of 31 patients, 4 patients underwent surgical debulking with 2 of them having complete and 1 of them partial resolution.

We operated 4 patients with SNSI. 3 of them (1 with intraconal lesion and 2 with dacryoadenitis) had complete or almost complete resolution; in 1 of them the clinical course is not known. Considering the high failure rate of steroids and radiotherapy and the potential adverse effects of immunosuppessants,

which might not always lead to regression of disease, we favor surgical treatment especially in cases with relatively well circumscribed lesion and involvement of the lacrimal gland. Cases with intraconal involvement could also benefit from partial surgical excision if other therapeutical alternatives fail and reduction of exophthalmos is aimed.

Besides, we performed debulking surgery in further 3 patients with NSI: 2 of them had lacrimal gland involvement and 1 bilateral diffuse involvement. 1 of the first two patients was free of symptoms, whereas the other one had diplopia after the operation, so that strabismus surgery was performed. The patient with the diffuse inflammation had formerly been treated with steroids due to exophthalmos without any success; we performed bilateral lateral orbitotomy achieving distinct reduction of exophthalmos. Postoperative diplopia demanded, however, subsequent strabismus surgery.

In our opinion, systemic steroids should be the first line therapy for NSI and SNSI. If treatment fails, orbital radiotherapy should be tried, especially in cases of NSI. In sclerosing inflammation, especially when the lesion is relatively well circumscribed and involves the lacrimal gland, surgical removal should be seriously considered, given that: i.) steroids and radiotherapy have high failure rate, ii.) steroids can be associated with adverse effects, and iii.) the efficacy of immunossuppressants is controversial.

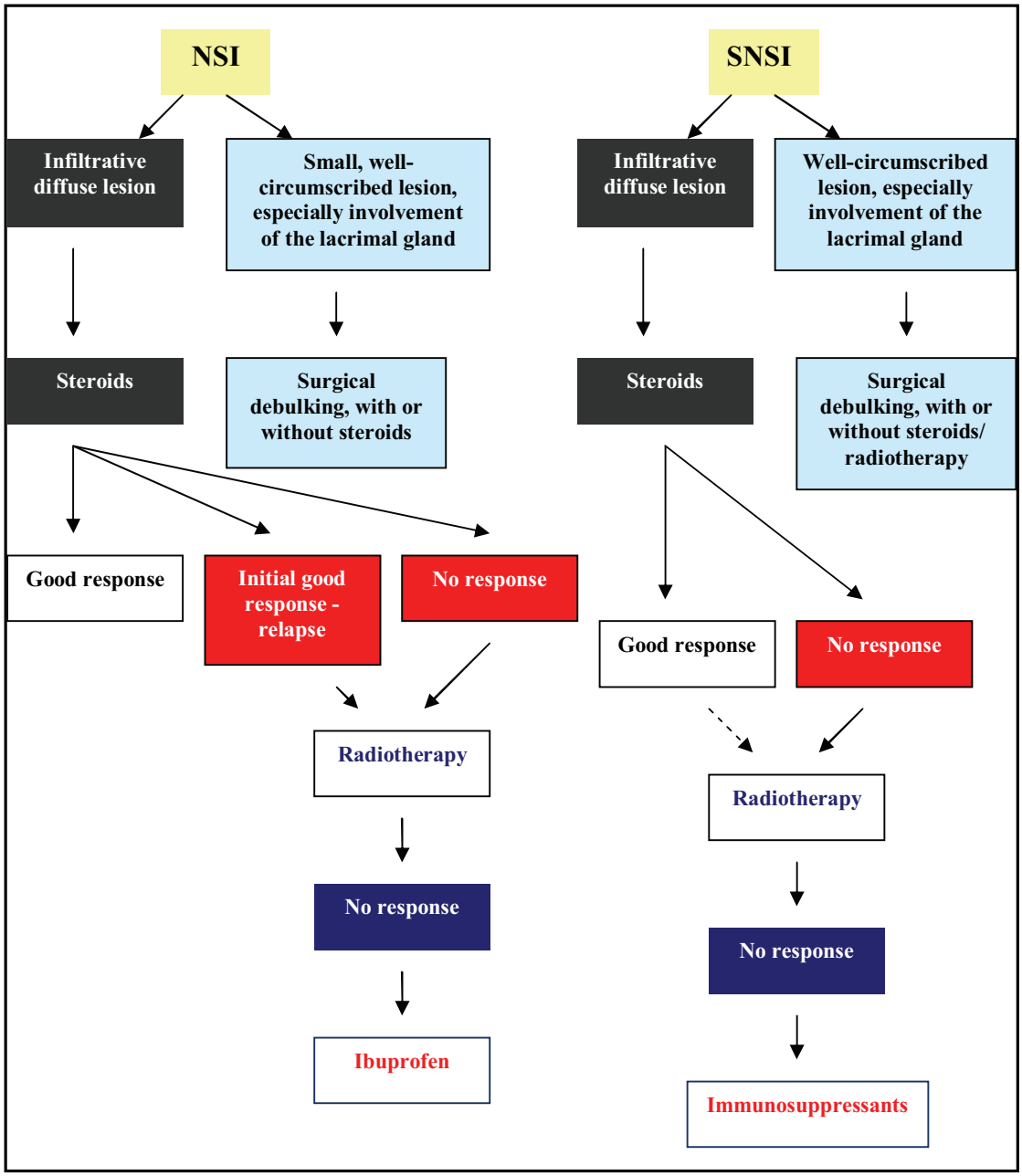

Figure 18. Treatment of non-specific orbital inflammation.

4.1.2. Specific inflammation

Our series included 2 patients with Wegener granulomatosis. Both of them were female. 1 of them had a known systemic disease, and additionally bilateral blindness due to optic nerve atrophy caused by a pituitary adenoma. This patient presented with a subacute painful exophthalmos with inflammatory signs. Treatment with cyclophosphamide led only to partial

reduction of exophthalmos. The second patient had subacute exophthalmos and ocular motility restriction with diplopia. The disease was limited to the orbit and paranasal sinuses without any other systemic involvement. Cyclophosphamide led to complete resolution. Wegener granulomatosis is a necrotizing granulomatous inflammation which occurs in two forms, localized and generalized. In the localized form there is no renal involvement and prognosis is better (Stavrou et al 1993, Cassan et al 1970). Ocular and orbital involvement is seen in up to 50% of cases of Wegener granulomatosis (Rootman 2001). In the localized form orbital involvement tends to be more indolent, whereas in the generalized disorder orbital disease may follow a course from rapid progression to long-term intermittent activity. Wegener granulomatosis may only present as an orbital mass without upper respiratory or systemic features at the beginning of disease. However, ear, nose and throat features tend to become universal during the follow-up period (Perry et al 1997). Main ocular symptoms are decreased vision, redness, and ocular pain; main findings are proptosis, scleritis, and lid inflammation. The diagnosis might be difficult to establish especially in localized forms of disease. This happens due to the fact that up to 50% of orbital biopsies for suspected Wegener granulomatosis are nonconclusive (Woo et al 2001). Accurate interpretation of biopsies is essential. In a study of 13 orbital biopsies of patients with well documented Wegener granulomatosis (Kalina et al 1992) only in 7 (53%) the classic triad of vasculitis, tissue necrosis and granulomatous inflammation was seen. In 4 biopsies (31%) vasculitis was seen, and in further 2 biopsies (16%) only perivascular infiltrates were seen. Moreover, ANCA antibody testing is often negative in cases of localized disease, with false negative results being as high as 68% (Woo et al 2001). Thus, the diagnosis of orbital Wegener disease should be based on a constellation of clinical, radiological, and pathologic features. The most important clinical features that should raise an index of suspicion are bilaterality, involvement of the respiratory tract or sinuses including the mastoids (which are often missed), scleritis at the time of onset, particularly when associated with the classical features of limbal corneal infiltrates, and systemic associations (Austin et al 1978). Comparison of orbital and extraocular biopsies (when available) is also recommended (Kalina et al

1992). The disease can affect a wide age range (Ziakas et al 2004). In our patient with localised disease ANCA antibodies were negative; this correlates with the references mentioned above. In the second patient with known generalised disease ANCA antibodies were not examined. Orbital biopsy was diagnostic for both patients. Classic treatment of Wegener granulomatosis is with a combination of cyclophosphamide and steroids. This therapy achieves remission in up to 90% of cases (Fauci et al 1983, Rootman 1988). Nowdays cyclophosphamide is used to induce remission of disease and its use rarely exceeds 6 months. After remission, other less toxic agents, such as azathioprime, methotrexate or leflunomide, are administered, with various relapse rates reported in the literature. However proptosis and subglottic stenosis might be sometimes refractory to treatment (Hoffman et al 1992). In case of refractory disease therapy with the monoclonal antibody rituximab has been proposed (Seo et al 2008). This agent was used in 8 patients who had failed therapy with immunossuppressants and achieved disease remission in all of them (Seo et al 2008). In general, collaboration with rheumatologists who have experience with the use of immunosuppressive drugs, guarantees the optimal management of such patients. The ophthalmologist should be aware of cases with limited disease which may initially present with solely ocular findings and establish timely the diagnosis based on clinical, radiological and histological findings, because early treatment can be dramatically effective with prevention of adverse local or systemic outcome.

4.2. Neoplasia

4.2.1. Malignant tumors

4.2.1.1. Neoplasia of the haemopoietic system

4.2.1.1.1. Orbital lymphomas

Orbital lymphomas are unusual neoplasms, constituting less than 1 % of all nodal and extranodal lymphomas (Keleti et al 1992, Calle et al 1975). Orbital

lymphoma is the most common primary orbital malignancy (Adam et al 1971, Rosenberg et al 1961). In our series orbital lymphomas were responsible for 30% of all neoplastic diseases, a percentage however much higher than the 10% reported in the literature (Reese 1976). They belong to the spectrum of orbital lymphoproliferative disorders. Orbital lymphoproliferative disorders include mainly lymphoid hyperplasia (LH) and orbital lymphoma. However there are lymphoproliferative lesions which defy categorization to one of the groups mentioned above. It has been suggested that lymphoproliferative disorders represent a continuous spectrum of disease which is not separable in a conceptual sense. This means that all pure lymphoproliferative lesions of the orbit can be considered as malignant or pre-malignant disease and LH could be the one end of the natural history of disease and the pure malignant variants the other (Garner 1992). In other words a neoplastic proliferation could supervene in an initially reactive disorder, in which case the two processes would be operating together for a time. Examples of this concept are extranodal lymphomas of the bronchus and the lacrimal gland and the same could be true for the orbit as well (Benerjee et al 1982, Schmid et al 1982). The differentiation between LH and orbital lymphoma is generally clinically and radiographically impossible. LH responds generally well to steroids, but orbital lymphomas can also show a partial initial regression after corticosteroid therapy, and thus response to anti-inflammatory treatment is not reliable for differentiation. The histological features of the lesion are the decisive criteria, but there are also lesions which cannot be categorized after biopsy. Germinal centers have usually been considered as one of the most reliable indicators of LH (Chavis et al 1978), but they are far from being an infallible guide (Garner 1992). Prominence of interstitial capillaries and presence of plasma cells and histiocytes support the diagnosis of LH. Evidence of monoclonality or even oligoglonality is a reliable index of neoplastic behavior. In our series MALT-Lymphomas composed 71 % of all primary localized orbital lymphomas (10 out of 14 cases). Histologically, the majority of orbital lymphomas are of the MALT-type. The percentage of MALT-type in primary localized lymphomas in the literature ranges from 30% to 100% (Smitt et al 1993, Chao et al 1995, Galieni et al 1997). This could be due to the fact that many low-grade MALT-lymphomas of the REAL-

classification were categorized as intermediate grade before introduction of this classification. 76% of our patients with primary orbital lymphoma had localized disease (Stage IE) and the rest had disseminated disease. 75 % of primary orbital lymphomas have been reported to be of Stage IE at the time of diagnosis (Jakobiec et al 1989), whereas other authors report a considerably lower percentage (49%) in a series of 59 patients (Polito et al 1996). Orbital lymphomas are confined in the orbit for long periods before metastasing. Different explanations exist. It is believed that they share a feature common among other types of extranodal lymphomas, namely homing back to their tissue of origin if they enter the general circulation (Issacson et al 1994). The absence of orbital lymphatic vessels could also play a role (Garner 1994). Bilaterality was observed in 11,7% of our patients with primary lymphoma. In a series of 63 patients (Polito et al 1996) bilateral involvement was found to be present in up to 19% of cases. Moreiras (2003) reports 15% bilaterality in 83 patients with lymphoproliferative orbital disease (LH included). The anterior orbit is the most frequent site of involvement (Rootman 1988).

The lesions are almost always infiltrative and surgical therapy is almost always impossible without any severe functional deficit. However, 2 of our patients with low malignity Stage IE MALT-lymphoma and well circumscribed lesion were initially treated with surgical excision alone. The first patient suffered a recurrence 2 years after surgery and 36 Gy radiotherapy followed achieving complete regression. The clinical course of the second patient is not known to us.

Radiotherapy is the first line therapy for primary localized orbital lymphomas of low malignancy. In our series 6 of 7 patients (86%) with primary Stage IE low malignancy lymphoma treated with radiotherapy exhibited complete remission 1-2 years after initial diagnosis. The dose was 36 Gy for bilateral disease or 40 Gy for unilateral disease. In one patient increase of the tumor mass was observed so that additional chemotherapy followed with complete regression of the tumor. Radiation therapy has been very effective in providing local control and cure in orbital lymphomas especially of low malignity; reported success rates have been > 90% (Reddy et al 1988, Letschert et al 1991, Galieni et al 1997, Lee et al 2002). Radiotherapy has also been proved effective in achieving complete remission in cases of local

relapse formerly treated with chemotherapy or surgical excision (Galieni et al 1997). In 1 of our patients, as mentioned above, relapse was observed 2 years after surgical excision of a well circumscribed low malignity Stage IE MALT lymphoma. Subsequent radiotherapy in this patient led to complete remission of disease. However, some studies reported systemic progression of the lymphoma even after successful primary local control with radiotherapy (Kim et al 1976, Letschert et al 1991). In their clinicopathologic study Knowles and Jakobiec (1980) found that the single most important feature determining the development of systemic disease and hence the prognosis, was the degree of cytologic differentiation. In a study of 18 patients, complete response to radiotherapy was observed in 100% of patients with low grade and 85% of patients with intermediate grade lymphoma (Lee et al 2002). The invasion of orbital walls is a negative prognostic factor for the efficacy of treatment, and the survival rate in such patients is generally poor (Bennet et al 1986, Lee et al 2002). The suggested dose of radiotherapy varies. Some authors propose a dose of 30 Gy for low malignity tumors (Letschert et al 1991, Lee et al 2002), whereas others propose a higher dose of 30-35 Gy (Smitt et al 1993) or even 36-40 Gy (Galieni et al 1997). We prefer a dose of 40 Gy for unilateral and 36 Gy for bilateral lesions, because complications at dose levels of less or equal to 40 Gy are to our knowledge extremely rare. In our case series, however, 1 patient developed occlusive radiation retinopathy with macular oedema and a final visual acuity of 1/15 after radiotherapy of 40 Gy. Serious complications of radiotherapy occur generally with dose levels higher than 40Gy and include radiation retinopathy, optic neuropathy and cataract formation. Contrary to low malignity lymphoma, in which radiation alone has a very high success rate, in intermediate or high malignancy lymphomas combination radiochemotherapy is needed, even in cases of localized Stage IE disease (Lee et al 2002, Moreiras 2004). There are some authors who suggest that radiotherapy alone in higher dose could be sufficient for orbital lymphoma of intermediate or higher malignancy (Letschert et al 1991), taking into account that orbital lymphoma is a disease with a peak incidence in the sixth and seventh decade of life and the results on 10 years survival equal the survival of a normal population of the same age distribution. Since, however, relapse-free survival might be improved by adjuvant

chemotherapy in patients with stage IE primary orbital lymphoma and unfavorable histology (Monfardini et al 1980, Nissen et al 1983, Somers et al 1987), the decision to perform adjuvant chemotherapy should be individualized and made after careful balancing against side effects of treatment.

In patients with disseminated disease chemotherapy is the first line therapy. In this study 4 patients had systemic Stage IV disease. 3 had low malignity and 1 high malignity lymphoma. 1 died 4 months after diagnosis. 1 was treated with chemotherapy alone, 1 received radiotherapy and chemotherapy and 1 received initially only radiotherapy. In all patients local remission was achieved, but the systemic status thereafter is not known to us. Although radiation therapy has been very effective especially in cases of localized lesions of low malignity, there are problematic cases, in which local or systemic relapse occurs despite initial control of the disease. MALT-lymphomas have a more favorable prognosis than other lymphoid proliferations (Jakobiec et al 1986, White et al 2006), but long term follow-up has shown that extraorbital recurrence and death can occur occasionally in cases of MALT-lymphomas and more frequently in other forms of orbital lymphoma (Jenkins et al 2000, Auw-Haedrich et al 2001). Furthermore, some patients have already disseminated disease at first presentation or secondary orbital involvement of a systemic lymphoma. In such cases where chemotherapy and radiotherapy protocols fail to control the neoplastic disease, the use of the monoclonal antibody rituximab has been proposed (Esmaeli et al 2002, Sullivan et al 2004). Clinical trials established the efficacy of rituximab in the treatment of both low-grade and more aggressive lymphomas. Other authors have studied the efficacy of the combination of this agent with standard chemotherapy (Coiffier et al 2002) or the efficacy of the linking antibodies with radioisotopes (Knox et al 1996) in cases of relapsed or aggressive lymphoma. In one of our patients with low malignity lymphoma and no response to radiotherapy this agent was used in combination with chemotherapy and complete remission was achieved. Sullivan et al (2004) reported good response in 6 of 7 patients with orbital lymphoma and systemic disease with complete or partial resolution. The authors concluded that

rituximab could be a treatment modality with low side effects available for repeated use in local and systemic relapses.

In conclusion, we think that radiotherapy alone is the first line therapy for patients with orbital lymphomas, since the vast majority of them have localized Stage IE disease and lesions of low malignity, as shown in our series and in series of other authors. We recommend a dose of 40 Gy for unilateral and 36 Gy for bilateral involvement because serious ocular complications are very rare with dose equal or less of 40 Gy. In patients with localized disease and high malignity lymphoma adjuvant chemotherapy should be seriously considered, especially in patients with good systemic status, since histology has been proven to be a very significant risk factor for local or systemic relapse. In cases with systemic disease chemotherapy is the treatment of choice, whereas in patients with refractory disease or relapse after initial control the use of the monoclonal antibody rituximab in combination with chemotherapy could be an alternative. Relapse duration is generally less than 24 months (Foster et al 1971, Lee et al 2002), but can be more than 5 years. Lymphoma-associated deaths can occur many years after diagnosis and the proportion of patients who died of lymphoma at 5 years was found to be 12% for MALT-lymphoma, 19% for lymphoplasmocytic immunocytoma, 22% for follicular lymphoma and 48% for diffuse large cell lymphoma in a series of 192 patients (Jenkins et al 2000). Therefore, even after good initial response all patients should be ophthalmologically and systemically evaluated for a long period, especially if histology is not favorable.

4.2.1.1.2. Histiocytosis

2 of our patients were diagnosed with Langerhans-Cell-Histiocytosis (LCH). Both of them were male and had unifocal bone lesion of the orbit, without any evidence of other involvement. LCH is an uncommon disease with a clinical spectrum that includes benign unifocal disease (eosinophilic granuloma), chronic multifocal disease (Hans-Schuller-Christian disease) and acute or subacute fatal disseminated disease (Letterer-Siwe disease). It accounts for 1% of biopsied orbital tumors (Henderson 1980). When it occurs in the orbit it

is almost always unilateral and localized. However, bilateral orbital disease has also been reported (Demirci et al 2002). The disease is generally diagnosed in children and young adults, and has a predilection for males (Shields et al 1999). Histopathology shows a proliferation of large histiocytic cells, which under the electron microscope exhibit characteristic cytoplasmic granules (Birbeck granules). Moreover, a various number of eosinophils, plasma cells, lymphocytes and multinucleated giant cells can be seen. Histiocytic cells show positive reaction for S-100 protein and CD1 antigen. The pathogenesis of the disease is not clear. A disorder of immune regulation has been postulated (Egeler et al 2004), but given the monoclonality of the Langerhans-cell histiocytes a neoplastic process cannot be ruled out (Leonidas et al 2003). The orbital lesions of LCH are usually situated in the superior lateral orbit, are typically osteolytic and have irregular margins, which can be sclerotic. MRI imaging may be useful in order to determine the extent of intracranial involvement (Stromberg et al 1995, Azouz et al 2005). Differential diagnosis in the orbit includes dermoid cyst, lacrimal gland tumor, primary bone tumors, such as osteosarcoma, aneurysmal bone cyst, fibrous dysplasia and Ewing sarcoma, and metastasis of neuroblasoma. Diagnosis is made by biopsy (Moreiras 2004, Binning et al 2008). The natural history of LCH is poorly understood. Systemic forms with involvement of vital organs are usually seen in younger children and carry a bad prognosis with mortality rate of 55 % to 60% (Rootman 1988). On the contrary, local disease limited to bone carries a very good prognosis. In a review of 348 cases treated in pediatric hematology/oncology centres the survival rate was 96% to 100% for LCH limited to bone (The French Langerhans' Cell Histiocytosis Study Group 1996), although considerable case-to-case variation does exist. Treatment of unifocal lesions of the skull typically consists of surgical curettage, which may necessitate an interdisciplinary approach depending on the extent of lesion (Binning et al 2008). Additional low dose radiotherapy can follow (Harris 2003). That was also the case in one of our patients with intracranial extension, who was treated in a neurosurgery clinic. Local recurrence rate is 6% and new lesions present in 22% of patients according to some authors (Stromberg et al 1995). Spontaneous regression following biopsy has also been reported (Glover et al 1987, Demirci et al 2002, Harris et al 2003, Key et

al 2004, Harzallah et al 2005). Another treatment option in cases of localized LCH is the intralesional injection of steroids. In a series of 3 patients with localized bone involvement of the mandibulla treated with intralesional steroids alone, no evidence of residual disease was present one year after treatment (Putters et al 2005). Intralesional steroids in combination with surgery have been used in orbital involvement with good results, as well (Kindy-Degnan et al 1991, Harris et al 2003). Patients with multiple lesions, organ system involvement, those who are younger than 2 years, and patients with recurrent or progressive disease need chemotherapy (Jubran et al 2005). In our series, one patient was treated with tumor excision alone in a neurosurgery clinic; 2 years later he was free of disease. The clinical course of the second patient after establishment of the diagnosis is not known to us.
Erdheim-Chester-Disease (ECD) is a non-Langerhans-cell-histiocytosis. The differential diagnosis from LCH is based on the age of manifestation, with the ECD affecting older individuals and the LCH being mainly a disease of the childhood, the pattern of bone lesions (typically osteosclerotic, symmetric involvement of the long bones in ECD and typically osteolytic involvement of the axial skeleton in LCH) and immunohistological criteria. Orbital involvement is very rare and was found in only 25 of approximately 250 published cases of ECD. The therapy of patients with ECD is generally individualized, as the disease is rare and no randomized controlled studies are available. INF-α could be a first-line long time therapy in ECD. Haroche et al (Haroche at al 2006) evaluated INF-α as a first-line therapy for ECD in eight patients. Xanthelasma, exophthalmos and retroperitoneal fibrosis completely regressed, whereas cardiovascular manifestations in the severe multisystemic forms of ECD responded to the therapy with varying results. The use of the purine-analogue Cladribine is reported to have led to complete regression of exophthalmos and to normal ocular motility, as well as improvement of the lung function in a case of ECD causing bilateral exophthalmos, ophthalmoplegia and lung disease (Myra et al 2004). Another patient, though, with bilateral ECD orbital involvement, who was treated with the same medicament, suffered toxic optic neuropathy with bilateral blindness. If treatment with Cladribine is instituted for orbital disease, careful monitoring of the optic nerve function is mandatory. Local radiotherapy to the orbits has

also been used, achieving only a short time improvement with high rate of recurrence (Miller al 2006). Regression of the exophthalmos was achieved by double autologous stem-cell transplantation in a case of orbital ECD, in which INF-α had been proven ineffective (Boissel et al 2001). In patients with orbital disease who develop signs of compression neuropathy despite conservative therapy, orbital decompression should be seriously considered, as shown in one of our patients, as well.

4.2.1.2. Mesenchymal tumors

Liposarcoma

2 patients of our series had a liposarcoma (1 myxoid and 1 well-differentiated). The histological subtypes mentioned above are based on the classification of Enziger and Weiss, which is the classification used by almost all authors in the literature (Enzinger, Weiss 1988). The histological subtype has a very important role for the prognosis. Well differentiated and myxoid liposarcomas have a relatively indolent course, whereas round cell and pleomorphic variants usually behave aggressively (Brennan et al 1997). Most of the cases described in the literature belong to the myxoid subtype. Liposarcomas represent 16% to 18 % of all malignant soft tissue tumors (Enzinger 1988) with the thigh and retroperitoneum being the most common sites. The orbit is a very rare site of primary involvement. Metastases of liposarcoma to the orbit have also been reported and are even rarer (Fezza et al 1997, Tehrani et al 2003). The most common symptoms are painless proptosis in a quiet eye and ocular motility restrictions with diplopia. Both of our patients had exophthalmos at first presentation. In one of our patients the main symptom was diplopia with motility restriction in up gaze. The tumor was situated between the rectus superior and the levator palpebral muscle with infiltration of the rectus superior, extraconal fat and lacrimal gland, as shown in MRI scan. Enlarged rectus superior muscle with contrast medium enhancement as restricted manifestation of primary orbital liposarcoma has been reported (Monteiro 2002). Computer tomography tends to reveal a well circumscribed lesion with faint internal radiodensities; a pseudocystic appearance may be present with borders of apparent pseudocapsulation

(Cockerham et al 1998). CT findings can vary from well defined homogenous lesions of soft tissue density, not evidently fatty (Naeser et al 1982), to heterogenous lesions containing fat (Lane et al 1988). In cases, in which computer tomography failed to reveal an identifiable tumor, abnormal signal from part of orbital fat in MRI, indicated presence of pathology in these patients (Lane at al 1988). MRI usually shows a relatively hypointense mass on both T1- and T2-weighed images (Cockerham et al 1998), but spin characteristics not typical for fat containing tumor have also been seen by some authors (Lane et al 1988). Signal hyperintensity in T2-weighed images can also be encountered (Costas et al 2001). The different intensities which appear in CT and MRI are due to the different proportion of fat existing in this kind of tumor. Both patients in this study were examined with MRI, none with CT. The lesions were hypointense in T2-weighed and hypo- or isointens in T1-weighed images and showed marked gadolinium uptake. One of the patients had a well circumscribed; the other had an infiltrative lesion. Because of the rarity of this tumor, the lack of specific findings in CT and MRI, and the commonly encountered well defined and encapsulated appearance without signs of malignancy in orbital imaging, the diagnosis is always established after surgery. In many cases biopsy can be initially misinterpreted (Lane et al 1988, Jakobiec et al 1989, Cockerham et al 1998), and therefore all suspected cases should be reviewed by experienced experts to avoid delay in definitive care. Misdiagnosis occurred in one of our patients, in whom the initial diagnosis was that of a dermoid. Although tumors appear well-encapsulated during surgery, in fact no true capsule exists. The “capsule” seen represents compressed orbital tissues, and this is evident on histological examination.

Local wide excision of liposarcoma occurring elsewhere in the body is advocated by most authors (Enterline et al 1960, Spittle et al 1970, Kinne et al 1973). Surgery with ample margins is generally considered as fundamental, since it admittedly improves survival and local control. In case of orbital involvement this usually means performing an orbital exenteration or even midfacial resection with or without subsequent radiotherapy. However, in a series of studies surgery plus radiotherapy were proven to have better results as compared to surgery alone (Saab et al 1996). Enterline (Enterline et al

1960) found that myxoid tumors are more sensitive to radiotherapy, whereas Spittle (Spittle et al 1970) reported surprisingly high response of poorly differentiated tumors. On the contrary, radiotherapy alone is not effective in achieving local control (Tran et al 1992). In a review of 29 orbital liposarcomas, 2 were pleomorphic and 1 was round cell. Most of the other cases were of myxoid type (Costas et al 2001). There were only 4 deaths among these patients. In 3 out of the 15 best documented cases (20%) there was a tumor relapse. The 2 of these patients underwent simple excisions and radiotherapy and the other one underwent radiotherapy alone. The remaining 12 cases included 2 simple resections, 1 simple resection with radiotherapy, 1 craniofacial resection, 2 craniofacial resections with radiotherapy, and 6 exenterations. Survival was 94% in patients with a follow-up ranging from 2 months to 4,5 years (Costas et al 2001). In cases with subtotal excision, radiotherapy has been reported to significantly decrease the risk of recurrence and is always recommended. Most of the tumors relapse within the first year, although relapse has been reported even 5 years after diagnosis despite radical excision, subsequent radiation and favorable location and histology (Cockerham et al 1998).

In our series, 1 patient with myxoid liposarcoma involving bone was treated with exenteration alone and 1 patient with well differentiated tumor was treated with total excision. In both patients no relapse was observed clinically and in MRI scans during a follow-up period of 7-12 months. None of our patients had metastasis on diagnosis or in the follow-up period. Therefore wide local excision seems to be the rational approach for this kind of tumor. As histology is the most important prognostic factor for survival (Kindblom et al 1975), the decision to perform additional radiotherapy should be based on histology, provided that total excision has formerly been conducted. In any case of subtotal excision or in cases, in which uncertainty regarding the radicality of excision exists, subsequent radiotherapy should be the rule. In patients with well-differentiated and well-circumscribed lesions, however, local excision with or without radiotherapy is justified, provided that close follow-up will be performed.

Malignant fibrous histiocytoma

This study included 1 male patient with a malignant fibrous histiocytoma (FH). The patient presented with exophthalmos of very slow evolution (4 years). An ex domo performed biopsy had established the diagnosis of non-specific inflammation; repeated therapy with corticosteroids and immunosuppressive medicaments, however, achieved no clinical improvement. The tumor was relatively well circumscribed and situated mainly intraconaly. It enhanced contrast medium intensively. Excisional biopsy was performed and histological examination showed a malignant fibrous histiocytoma. Exenteration with subsequent radiotherapy followed with the patient being free of disease 2 years after treatment.

FH constitute 1% of all orbital tumors, and are considered the commonest primary mesenchymal tumors of the orbit in adults (Ulloa et al 1999). It is believed to be of histiocytic (Kempson et al 1972) or primitive mesenchymal cell origin (Fu et al 1975, Weiss et al 1978). In the greatest review of orbital FH in the literature including 150 cases (Font et al 1982) tumors were classified according to histological criteria in 3 groups: benign (94 cases), locally aggressive (39 cases) and malignant (17 cases). Benign FH are well circumscribed and some of them encapsulated, whereas local aggressive and malignant lesions display infiltrating margins. The duration of symptoms and size of the tumor were found to correlate with the possibility of malignity. Small lesions with a duration of several years were most likely benign (Font et al 1982). In the same study, almost 30% of the lesions showed foci of increased vascular proliferation and many irregularly dilated capillaries. Some of them had been initially misdiagnosed as hemangiopericytoma, haemangioendothelioma or angiosarcoma. Jakobiec (1978) hypothesized that FH and hemangiopericytoma probably arise from the same primitive mesenchymal cell, which may differentiate either to fibroblast/ histiocyte or to pericyte. In the series of Font et al (1982) various treatment modalities were performed, such as in toto excision, incomplete excision, piecemeal removal, exenteration, enucleation and craniotomy. The authors, however, provided no exact data of treatment modalities applied to each histological category mentioned. The incidence of local recurrence was 31% in the benign group, 57% in the locally aggressive group and 64% in the malignant group. 9

patients died of tumor, either due to local invasion or due to metastatic disease. All patients with metastases belonged to the malignant category. Recurrence of tumor was sometimes combined with more aggressive clinical and histological characteristics. Radical tumor excision is the treatment of choice for malignant FH and for locally aggressive tumors, especially if they recur. A recurrence rate of 51% of patients with malignant FH despite total removal of the tumor has been reported by some authors (Kearny et al 1980); radical surgery was found by the same authors to improve the survival rate to 68% after 5 years. In the study of Font et al (1982), the 10 year survival rate was 100% in benign, 92% in locally aggressive and only 23% in malignant FH. In case of orbital involvement, radical excision usually means exenteration, unless the tumor is small. Benign tumors can be treated with total excision. We performed exenteration with additional radiotherapy. No relapse was noted clinically and in MRI two years after treatment.

Radiation therapy for the treatment of FH is controversial. Font et al (1982) report low tumor sensitivity to radiation therapy, since 13 of 18 patients treated with radiotherapy (72%) for whom follow-up information was obtained developed recurrence. Other authors however state that radiotherapy as well as chemotherapy may be useful for patients with surgical risk or more than 2 lesions, and could also be used in addition to surgery (Hirano et al 1996). The decision to perform chemotherapy should be individualized by oncologists dealing with sarcomas after consideration of possible side effects and general health of the patient.

Malignant solitary fibrous tumor

Solitary fibrous tumor (SFT) is a rare spindle-cell neoplasm, which most commonly arises from the serosal surface of the pleura. However it has been encountered in many other sites including the orbit. Its intense immunoreacivity for CD34 and the fibroblastic nature of tumor cells on electron microscopy have definitely demonstrated their mesenchymal origin. The histological diagnosis may be missed and the tumor may be misdiagnosed as hemangiopericytoma, or schwanomma (Polito et al 2002). The differential diagnosis between SFT and a special form of angiomatous tumor called giant cell angiofibroma is still under discussion. Some authors

suggest that giant cell angiofibroma be a morphologic variant of SFT (Gouillou et al 2000, Gouillou et al 2002). The differential diagnosis also includes fibrous histiocytoma, menigioma and spindle cell melanoma. A misdiagnosis occurred initially in our case, as well; the tumor was initially diagnosed as a hemangiopericytoma or a giant cell angiofibroma. Immunohistology plays a very important role in the differential diagnosis; SFT are intensely positive for CD34 and negative for S100, which helps differentiate them from tumors mentioned above (Westra et al 1994, Heathcote et al 1997). Orbital MRI can also provide characteristic features suggesting the diagnosis of a SFT. The tumor is isointens in T1-weighed and more frequently hypointense in T2-weighed images to grey matter, as was observed in our case, as well. This helps distinguish SFT from the T2-hyperintensity found in other spindle-cell neoplasms, such as fibrous histiocytoma and hemangiopericytoma (Gigantelli et al 2001). SFT are well circumscribed tumors (Gigantelli et al 2001, Polito et al 2002, O' Donovan et al 2002, Romer et al 2005). This differentiates them from other collagen containing lesions, which share a similar T1 and T2 pattern in MRI, such as sclerosing non-specific inflammations or scirrhous carcinoma metastases, which are lesions of infiltrative nature. Clinically the tumor can occur at any age, even in children (Alexandrakis et al 1998, Lucci et al 2001). Proptosis and eyelid swelling are the prevailing symptoms in the cases described in the literature. SFT are in their majority tumors with benign behavior, but cases of aggressive lesions have been also documented (Dorfman et al 1994, Ing et al1998, Carrera et al 2001, Polito et al 2002). As to the prediction of clinical behavior, although worrisome histological features of malignancy have been described (hypercellularity, cytologic atypia, tumor necrosis, and increase mitotic rate), there is no strict correlation between morphology and behavior. Histologically, atypical tumors with no evidence of recurrence or metastasis and recurrent tumors with benign histological profiles have been described (O'Donovan et al 2002). In our case, histology showed increased mitotic activity, and recurrence was observed 3 years after surgery. Radical surgery is the treatment of choice and is thought to be more advantageous for a good prognosis than histological signs of malignity, and this applies to pleural and orbital sites of involvement (Briselli M et al 1981, Gigantelli et al 2001). Recurrence of the tumor in our patient was

accompanied by more aggressive clinical and histological characteristics than the initial lesion, as sarcomatous transformation of the entire lesion and infiltrative growth were noticed. The same has been reported by other authors, as well (Carrera et al 2001 Bernardini et al 2003). Recurrence can occur many years after initial treatment; therefore, long term follow up is recommended. In our patient recurrence could not be treated with radical surgery as this would lead to total blindness (the other eye was enucleated in childhood). We performed subtotal excision in combination with radiotherapy, and the patient was free of disease one year after. A number of pleural malignant SFT have been successfully treated with postsurgical radiotherapy (Hayashi et al 2001). However, the efficacy of radiotherapy and chemotherapy remains overall unclear. Nevertheless, radiotherapy could be applied in exceptional cases like ours, in which radical surgery would lead to blindness.

Rhabdomyosarcoma

Rhabdomyosarcoma (RMS) is a rare tumor with an annual incidence of 4.3 cases per million children (Gurney et al 1999). The orbit is the primary site in approximately 10% of these tumors. From the ophthalmologist's standpoint, however, RMS is the most common malignant orbital tumor of childhood (Maurer et al 1993, Crist et al 1995). The histopathologic types of RMS include embryonal, alveolar, and pleomorphic. The embryonal form is the most common; the alveolar variety is less common and carries the worst prognosis. In a large series, 264 patients with orbital RMS were studied (Kodet et al 1997). Embryonal RMS was diagnosed in 221 patients (84%). The 5-year survival rate for these patients is approximately 95%. In contrast, the 5-year survival rate for the 24 children with alveolar RMS was approximately 75%.The pleomorphic type rarely occurs in the orbit (Newton et al 1995, Shields et al 2001). The most characteristic clinical presentation is the rapid onset and progression of exophthalmos and displacement of the globe. RMS should be suspected whenever the clinical presentation of a rapidly progressive unilateral exophthalmos is observed in a child. The clinical differential diagnosis includes most causes of proptosis in childhood. Benign and malignant neoplasms need to be considered, along with inflammatory disease, vascular tumors, leukemia, Burkitt lymphoma, allergic sino-orbital

aspergillosis, non-specific orbital inflammation, orbital cellulitis, histiocytosis, and metastatic neuroblastoma (Mafee et al 1998, Cota et al 2000, Karcioglu et al 2004, Chung et al 2007). Although imaging, clinical signs and symptoms are helpful in delineating the differential diagnosis, the decisive diagnosis is based on histopathologic confirmation (Karcioglu et al 2004). In orbital CT bone destruction is common, as was also observed in our case (Scotti et al 1982). Bone erosion and intracranial extension can occur, as well. Management of patients is based on tumor staging according to the classification system of the Intergroup Rhabdomyosarcoma Study (IRS) (Shields et al 2001, Karcioglu et al 2004). RMS is best managed with combination treatment of chemotherapy, external-beam radiation therapy, and surgery. At some centers, the therapeutical role of surgery is limited to excisional biopsy, while in other centers, extensive surgery is performed to remove or debulk the tumor (Wexler LH et al 1997, Lanzkowsky 2000, Karcioglu et al 2004). In case of recurrent refractory tumors, some authors advocate radical surgery, which usually means exenteration, with or without chemotherapy and radiotherapy (Mannor et al 1997). The prognosis for patients with orbital rhabdomyosarcoma has greatly improved in recent years. Overall survival rate of patients with orbital rhabdomyosarcoma is now 93%. Embryonal type, tumor size less than 5 cm, patient age of >1 year carry the best prognosis (Shields et al 2001, Chung et al 2007). Since radiotherapy and surgery may lead to undesirable side effects, such as bony hypolplasia, facial asymmetry, cataract, dry eye, keratopathy, retinopathy and visual acuity deterioration (Raney et al 2000), it seems that the challenge of the future is to identify patients who can be safely treated only with chemotherapy and reserve radiotherapy and surgery for patients at risk of recurrence (Ducrey et al 2002).

In our case, we preferred wide local excision in combination with brachytherapy for tumor recurrence, despite unfavourable histology, in an attempt to preserve ocular function and reduce the radiation dose. The clinical effect is unfortunately not known to us.

4.2.1.3. Tumors of the lacrimal gland

Adenoid cystic carcinoma of the lacrimal gland is a rare malignant tumor generally associated with a grim prognosis. The difficulty in achieving a cure is due to the aggressive infiltrative behavior of the tumor though bone, distinct propensity for perineural infiltration with retrograde intracranial extension and hematogenous or lymphatic invasion. Although conventional therapy (surgery and radiation) may achieve local control in many patients, it is possible that occult metastases have already developed at the time of presentation (Forrest 1971, Bertley et al 2002). Subsequently frequently death results from intracranial tumor extension or metastatic disease (Lee et al 1985). This also explains local recurrences in sites remote from the primary excision bed, such as ethmoid sinus mucosa, skull base and dura in many published series (Wright et al 1992, Font et al 1998, Esmaeli et al 2004). By anatomic definition, finding of tumor cells in the ethmoid sinus mucosa suggests that intracranial expansion and perineural extension to the trigeminal ganglion has already occurred. One such patient, who was included in our series, died 14 months after initial diagnosis. The tumor affects relatively young subjects between 35 and 50 years of age, but the 2 of the totally 3 patients in our study were older than 60 years of age. It is believed that adenoid cystic carcinoma of the lacrimal gland in childhood and adolescence has a better survival (Tellado et al 1997). Radiographically, the tumor can be relatively well circumscribed resembling a pleomorphic adenoma (Tse et al 2005). Suspicion of malignancy should be raised if bone erosion, infiltration of the orbital muscles and fat or calcifications is observed. Pain in the lateral orbital region, which is reported to be present at 35-70% of the cases according to various authors, and relatively short time history of symptoms (less than a year), may also imply malignancy. In MRI scans the tumor becomes hyperintense with gadolinium injection. The 2 of our patients had a relatively well-circumscribed lesion, but in both of them extraocular muscle infiltration in orbital imaging was shown, with one of them having additional tumor calcification. In all cases the tumor enhanced contrast medium intensely. In 2 patients bone erosion was observed. None of our patients had pain.

Controversy exists regarding the appropriate therapy. Some authors advocate conservative surgical resection of tumor followed by external beam radiation therapy or proton-beam therapy. The alternative use of brachytherapy has also been proposed (Shields et al 2003). Others advocate an aggressive surgical approach with or without radiotherapy. Wright et al (1992) reported a series of 50 patients who had malignant lacrimal gland tumors, 38 of whom had adenoid cystic carcinoma; 12 patients (32%) died, all but one within 4 years of treatment. Moreover, only 6 (35%) out of the other 17 patients described as disease-free had a follow-up of more than 4 years. Cranioorbital resection did not decrease the rate of tumor recurrence or improve the rate of disease free survival. The patients who underwent an aggressive surgical approach however constituted a greater proportion of those who lived for more than 10 years after treatment than those treated more conservatively. In a series of 7 patients (Esmaeli et al 2006), all of them with locally advanced adenoid cystic carcinoma of the lacrimal gland, the survival outcome was poor, with 5 of 7 patients dying of metastasis in a mean of 21 months after diagnosis, although radical orbital and skull base surgery followed by radiation therapy had initially achieved good local control. In one patient metastasis was known before surgery, however in the rest of the patients metastasis developed after surgery. All of the patients had perineural invasion and 6 of them had basaloid (solid) pattern, both of which are considered as bad prognostic factors (Tellado et al 1997, Font et al 1998). It seems that patients with advanced local disease are more likely to develop metastasis or to have occult metastasis at the time of diagnosis; therefore, radical surgery usually performed in these patients will not improve survival. Moreover, other studies found that disease free survival may not be improved by aggressive surgery (Esmaeli et al 2004, Lee et al 1985). Nevertheless, keeping with basic principles of oncology most authorities would agree that it is desirable to achieve local control of the disease and eradicate the clinically and radiographically apparent tumor even by means of radical surgery. Another potential option for local therapy of adenoid cystic carcinoma of the lacrimal gland is the preoperative intra-arterial chemotherapy followed by tumor excision (Meldrum et al 1998, Tse et al 2006). Since the tumor may have already escaped the orbital confines by perineural dissemination by the time

of presentation, the introduced intra-arterial administration of chemotherapy could constitute a rational therapeutical option. This approach intends to decrease systemic side effects and simultaneously increase the dose in the tumor region. This sort of treatment is not intended to replace but to augment surgical and radiation therapy and to achieve a higher survival rate reducing the possibility of distant disease relapse. Intra-arterial chemotherapy may also permit surgical resection of a formerly considered unresectable tumor with intracranial invasion, by shrinking the tumor and bringing its margins to within the orbit. In the study of Tse et al (2006), in 2 patients with extensive intracranial infiltration, shrinking of the tumor was achieved with this method and subsequent radical surgery with radiotherapy followed. Both patients remained free of disease 16,5 and 5 years after treatment. In the same study the cumulative 5-year carcinoma cause specific death rate in the treated group was 16,7% compared to 57,1% in the conventional treatment group. The cumulative 5-year recurrence rate was 23,8% in the treated group compared to 71,4% in the conventional treatment group.

In our series, 1 patient had advanced disease with intracranial dural involvement at first presentation. We performed orbital exenteration with treatment of suspicious bone foci with CO2-laser and postoperative radiotherapy. The tumor relapsed with involvement of frontal sinus, ethmoid sinus, skull base and optic chiasm 10 months later and the patient died 14 months after initial diagnosis. 1 of our patients had a tumor extending close to the apex, without obvious bone infiltration (radiographically and intraoperative) or intracranial invasion. Exenteration without bone removal with postoperative radiotherapy was performed. This patient was free of relapse and metastasis in MRI 4,5 years after treatment. The third patient in our series had also no intracranial involvement. Bone erosion could not be definitively excluded. We performed orbital exenteration with subsequent radiotherapy. Histological examination showed tumor cells in all excision margins and perineural infiltration. The clinical course in this patient is not known to us. All of our patients had solid (basaloid) type of adenoid cystic carcinoma which is considered as bad prognostic factor. In a review of 94 adult patients from 4 major centers a distant metastasis rate of 50% (47 of 94) at 5 years is reported (Lee et al 1985, Wright et al 1992, Font et al 1998, Esmaeli et al

2004). The prevention of metastasis is a major challenge and could improve the prognosis in patients with adenoid cystic carcinoma of the lacrimal gland. Future efforts that will concentrate on targeted biological therapies may alter the generally bad prognosis of this malignancy.

4.2.1.4. Metastasis

This study included 3 patients with orbital metastases: 1 from breast carcinoma, 1 from prostate adenocarcinoma and 1 from neuroendocrine heart tumor. Only the first patient had symptoms in form of ptosis and lid swelling. The diagnosis of the orbital disease was made 5 years, 3 months and 7 years respectively after diagnosis of the primary tumor. The patient with the breast carcinoma and the patient with neuroendocrine tumor had already been operated due to their primary tumor. In the third patient the tumor was found in scintigraphy performed for staging of a newly diagnosed prostate adenocarcinoma. In the patient with the neuroendocrine tumor, the orbital tumor was a coincidental finding in MRI performed for other reason.

The patient with prostate adenocarcinoma had an osteoplastic metastasis in the sphenoid bone; chemotherapy followed and the patient was free of orbital disease 1 year after. The further course is not known to us.

The patient with breast carcinoma died of metastatic disease 2 years after diagnosis of the metastasis.

The patient with neuroendocrine tumor had no residual disease after tumor extirpation, but follow-up was for a short period of time (4 months).

According to various authors metastatic tumors account for 2-9% of orbital neoplasia. Breast carcinoma has been reported to be the most frequent cause of orbital metastasis (Henderson 1980, Shields et al 1988, Goldberg et al 1990). Orbit is a crowded area and therefore expansion of a mass will cause symptoms earlier than in other sites. Therefore orbital symptoms can precede symptoms caused by the primary tumor in as many as 14-42% of the cases (Font et al 1976, Henderson 1980, Shields et al 1988, Goldberg et al 1990). The mean interval between the diagnosis of the primary tumor and metastasis also varies between 2,5 and 5 years (Goldberg et al 1990, Tijl et al 1992, Moreiras 2004). The longer mean interval is that of breast carcinoma

compared to all other tumors (mean interval 6 years, Moreiras 2004). This is in agreement with our case of metastatic breast carcinoma. According to Rootman (1988) bilaterality occurs in 14% of cases. Histopathologic examination is adequate in diagnosing most tumors but in some instances of undifferentiated tumors electron microscopy (Jakobiec et al 1978, Riddle et al 1982) and immunohistochemistry (Winkler et al 1981, Tell et al 1985) are necessary. The treatment of patients with orbital metastasis is almost always palliative and depends on primary tumor. Orbital surgery is indicated only in cases where the tumor is small, well circumscribed and easily accessible, or when it threatens vision or causes extreme proptosis and pain (Tijl et al 1992). Mean survival varies in different studies from 10,2 to 25 months (Shields et al 1988, Goldberg et al 1990, Tijl et al 1992). It is obvious that survival depends on primary tumor. Breast carcinoma has a mean survival of 22 months in the larger series and this was also observed in our case (24 months).

4.2.2. Benign tumors

4.2.2.1. Vascular tumors

Cavernous hemangiomas are the most common benign tumors of the orbit in adults (Henderson 1994, Rodgers et al 2000). Yet cavernous hemangioma is an uncommon finding; the incidence is between 0,6-2 per year (Wright 1974, Jakobiec 1978). Orbital cavernous hemangiomas are seen more frequently in females with a peak incidence in the fifth decade of life (Gloor et al 1992, Gunalp et al 1995). However, in our series we noticed no sex predilection and this has been reported by other authors, as well (Thorn-Kany 1999). All our patients had unilateral single lesions, but bilateral or multiple lesions in the same orbit have also been described (McNab et al 1989, Wolin et al 1990, Sullivan et al 1992, Paonessa et al 2008). The most common symptom is exophthalmos of slow evolution with subsequent globe displacement. Ocular motility is usually normal, even in cases of large tumors. Unlike many other vascular orbital lesions, acute symptoms due to tumor hemorrhage are exceedingly rare. In a large series of 162 cavernous hemangiomas (Selva et

al 2001) an acute or subacute hemorrhagic episode was never documented. Therefore, acute hemorrhage in an orbital tumor makes the diagnosis of a cavernous hemangioma extremely unlikely. The vast majority of these tumors are intraconal (93% in our series, 80-82% in the literature). In CT and MRI, cavernous hemangiomas present as well circumscribed oval tumors (Acciari et al 1993, De Potter et al 1995, Wilms et al 1995). In T1-weighed images in MRI the tumor typically shows a homogenous isointense signal with respect to the extraocular muscles and a hypointense signal relative to orbital fat. In T2-weighed images the tumor has homogenous signal intensity with respect to fat and muscles. Calcified phleboliths are occasionally seen in CT (De Potter et al 1995). The CT appearance and MRI signal in T1-weighed and T2-weighed images are however of no value for differential diagnosis, because many other orbital lesions may show similar signal characteristics and present as well-circumscribed oval masses, such as: neurofibroma, hemangiopericytoma, schwannoma, fibrous histiocytoma. MRI can specify the diagnosis of orbital cavernous hemangioma after administration of gadolinium, especially if delayed sequences are repeated after contrast medium administration. An initial heterogenous patchy enhancement of the lesion which increases on delayed scans and becomes homogenous, is highly suggestive for cavernous hemangioma as reported by some authors (De Potter et al 1995, Wilms et al 1995, Thorn-Kany et al 1999). However others suggest that similar characteristics can be observed in other orbital lesions, as well, such as schwannomas, and not the enhancement gradient but the enhancement spread pattern on dynamic MRI be more useful for the differential diagnosis (Tanaka et al 2004). The differential diagnosis of orbital vascular lesions, which include cavernous hemangiomas, varices, lymphangiomas, hemangiopericytomas and arteriovenous malformations, can be difficult, since some orbital vascular lesions exist on a continuum and only subtle differences may be noticed on conventional CT and MRI. A classification of these lesions according to their hemodynamic characteristics has been proposed (Harris 1999). On this basis, determining blood flow characteristics alongside high-resolution soft tissue images can be very important for the right diagnosis and treatment in certain cases. For these purpose 3 alternatives exist: combining separate soft tissue imaging with

invasive angiography, dynamic CT-angiography and dynamic contrast enhanced magnetic resonance angiography (MRA) (Kahana et al 2007). Although conventional angiography has been considered as the gold standard method for the study of orbital vascular pathology for many years, this technique is invasive and it is associated with minimal but definite risk of complications, such as cerebral infraction or ophthalmic artery thrombosis or embolization. Computed tomography angiography and dynamic MRA with different system modalities (TRICKS, Syngo TWIST, 4D-TRAK) can provide extremely useful information when difficulties in the differential diagnosis are encountered (Kahana et al 2007). It is however true that in the majority of patients with cavernous hemangioma diagnosis can be made on the basis of clinical findings and conventional MRI (Scheuerle et al 2004, Yan et al 2004). We suggest that more detailed investigation should be spared for untypical cases or lesions whose anatomical site of involvement makes surgical excision problematic and is associated with high risk of complications. In case of such lesions simple observation may be more beneficial than surgery; exclusion of lesions with the potential for malignant transformation, such as hemangiopericytoma or solitary fibrous tumor, is then of great importance. Surgical treatment is indicated in symptomatic patients. For patients with small lesions without any symptoms simple observation may be sufficient. Total excision is not mandatory, especially when it is difficult due to tumor location, because recurrences are extremely rare and growth is very slow (Orcutt et al 1991, Gloor et al 1992, Gunalp et al 1995). Removal can be performed through several surgical approaches such as lateral, medial, anterior or transconjuctival, dependent on the tumor location. In case of tumors located in the anterior orbit, extraconally or intraconally, a transconjuctical approach can be chosen (Yan et al 2004, Cheng et al 2008). In case of lesions located deeper in the orbit close to the apex or lesions combined with large draining veins, standard lateral orbitotomy should be considered. Some authors advocate a transcranial approach for large lesions superior and medial to the optic nerve, which involve the orbital apex (Scheuerle et al 2004).

We performed 11 lateral, 2 medial and 1 anterior orbitotomy. Lateral orbitotomy offered a very good tumor exposure in the majority of intraconal

lesions. The surgical approach chosen depends not only on tumor location but also on experience and personal preference of the surgeon. Independent of surgical approach, the majority of patients obtain benefit from surgery particularly in their exophthalmos and motility impairment (McNab et al 1989, Hassler et al 1994, Acciari et al 1995, Scheuerle et al 2004, Yan et al 2004, Cheng et al 2008). In 12 of our 14 patients, complete tumor excision without any postoperative complications was achieved. In 1 patient with large cavernous hemangioma surrounding the optic nerve, partial tumor excision led to reduction of exophthalmos (14 mm difference preoperatively, 9 mm difference postoperatively in Hertel exophthalmometry). Since visual acuity was normal, no other treatment followed. Only in 1 out of 14 patients visual acuity loss occurred after partial excision of a tumor in close proximity to the optic nerve due to retinal central artery occlusion; visual acuity failed to recover in this patient.

Orbital lymphangiomas are defined as abortive, non-functional vascular systems that arborize through variable portions of the orbit (Harris et al 1990). Contrary to Wright, who considered them as primary orbital varices (1974), many orbitologists and finally the Orbital Society in its annual meeting in 1998, classified them as distinct vascular malformations (Harris 1999). This classification was based on the hemodynamic characteristics of orbital vascular malformations, and lymphangiomas were separated from orbital varices due to their isolation from the systemic circulation. Mixed forms, including venous and lymphatic (no flow) components were classified as venous flow malformations, in order to emphasize the clinical importance of the venous relationship. Although hemodynamically isolated from the systemic circulation, nutritient vessels within their flimsy walls may be the source of hemorrhage in their lumens, which transforms microscopic channels and cysts to large macrocysts. These lesions are present at birth but they can be hidden for years, becoming manifest after trauma and intralesional hemorrhage. It must be emphasized that vascular malformations are considered as a continuum that runs the gamut from purely arterial to purely venous, lymphatic or capillary vascular lesions, and as such this continuum includes a potential combination of lesions that have elements of one, two, three or four of the various types of vessels (Mulliken et al 1988, Harris et al

1990, Rootman 1998). In fact many lesions display a spectrum of mixed lymphatic and venous characteristics based on the clinical, radiological, hemodynamic and histological evidence (Rootman et al 1986, Katz et al 1998). Predominantly lymphatic lesions with foci of irregularly shaped cystic spaces showing direct filling from tiny branches of the ophthalmic artery in selective arteriograms have been recently described. These lesions have been termed as arteriolymphatic communications (Bisdorff et al 2007). Lymphangiomas are rare tumors accounting for less than 2% of orbital tumors in large series (Shields et al 1984, Henderson et al 1994). Clinical presentations are slowly progressive proptosis, globe displacement, ptosis, and restriction of eye movements, spontaneous intraorbital hemorrhage with acute exophthalmos or optic neuropathy and even loss of vision. In children with marked ptosis deprivation amblyopia may develop. Lymphangiomas usually present in the first two decades of life (Tunc et al 1999, Selva et al 2001). However, lesions becoming clinical evident over the age of 50 years have been described; some of them had been initially diagnosed as cavernous hemangiomas (Selva et al 2001). In order to establish the right diagnosis, orbital imaging with CT or preferably with MRI is of utmost importance. MRI better delineates the heterogenous and often multiloculated nature of the lesion, and is certainly the definite method for imaging any hemorrhagic cysts (Bond et al 1992, Moreiras 2004). Imaging findings have been reported to correlate with the surgical outcome (Gunduz et al 2006). From a clinical point of view, lesions are classified as superficial, deep or mixed.

In general, treatment of lymphangiomas may be challenging and many of them may require multiple operations for visual preservation and cosmesis (Tunc et al 1999 Gunduz et al 2005). Total excision of the lesion is in most cases impossible due to its infiltrating nature. Excision of relatively well circumscribed lesions situated in the anterior orbit mainly extraconally or excision of the anterior part of a lesion with extra- and intraconal component is not generally considered to be combined with high risk or recurrence (Selva et al 2001, Moreiras 2004, Gunduz et al 2006). However, when moving posteriorly, there are dense fibrous adhesions, and aggressive surgical excision can lead to postoperative hemorrhage with optic nerve compression

or forming of new blood cysts. Moreover, excision of apical components carries a high risk of vision loss due to central retinal artery occlusion. This also held true in cases of very well delineated intraconal lymphangiomas, which had been initially misdiagnosed as cavernous hemangiomas in preoperative orbital imaging techniques (Selva et al 2001). This emphasizes the value of meticulous pre-operative MRI study for the right planning of the operative procedure. When surgery is performed and difficulty in posterior dissection is encountered, it is advisable to consider leaving a small residual component. This also prevents trauma to unexpanded parts of the anomaly, reducing new blood cyst formation (Harris et al 1990, Moreiras 2004). In some of these cases the carbon dioxide laser can be used during surgery, as it can facilitate surgical debulking and shrinkage of unresectable parts of the tumor (Kennerdell et al 1986, Harris et al 1990). Interestingly, subtotaly excised lymphangiomas have not recurred in a long period of follow-up (Selva et al 2001, Gunduz et al 2006). In the study of Tunc et al (1999), which included 24 operated patients, a recurrence rate of 58,3% was reported. A similar rate (52%) was reported in the study of Harris et al (1990) including 23 operated patients. Tunc et al (1999) found that presence of definite chocolate cyst appearance at initial MRI was significantly correlated with multiple recurrences. The same authors failed to disclose any relationship between histological findings and risk of recurrence. Many orbitologists advocate conservatism in surgical case selection and surgical dissection (Haris et al 1990, Moreiras 2004). In that sense, other treatment modalities which include administration of systemic steroids (Muallem et al 2000, Sires et al 2001) or intralesional injection of various sclerosing agents (Suzuki et al 2000, Larrane et al 2002, Schwarcz et al 2006) have been proposed with various results.

In our single case the lymphangioma recurred three times in a period of 6,5 years. For patients presenting in the second decade, like our patient, multiple recurrences have been reported by other authors, as well (Tunc et al 1999). However, no association between age at presentation and recurrence risk has been observed by others (Wright 1974, Illif et al 1979, Graeb et al 1990). Since multiple surgeries correlate with higher risk to vision and motility (Hemmer et al 1988, Wilson 1989), we advised the patient against a new operation due to the presence of a large intraconal tumor with close contact to

the optic nerve. The patient, however, demanded a re-operation due to cosmetic disfigurement caused by marked exophthalmos, and unfortunately suffered vision loss from apical hemorrhage with optic nerve compression.

4.2.2.2. Tumors of the lacrimal gland

Pleomorphic adenoma of the lacrimal gland accounts for approximately 12-25% of lacrimal gland tumors (Reese 1971, Shield et al 1989). The most important differential diagnosis includes malignant lacrimal gland tumors. A clinical algorithm taking into account duration of acute symptoms, persistent pain, sensory loss and radiological findings has been proposed by Wright et al (1979 and 1992) to assess the possibility of malignity of a lacrimal gland tumor. With the use of this algorithm these authors claimed to have correctly diagnosed preoperatively 55 of 63 (87%) patients with pleomorphic adenomas of the orbital portion of the lacrimal gland (Rose et al 1992). Preoperative diagnosis is crucial since incisional or fine needle biopsy is traditionally thought to increase the risk of recurrence (Font et al 1978, Wright et al 1979, Auran et al 1988) and it should be ideally avoided. However a recent review of the literature on biopsy of both lacrimal gland pleomorphic adenoma and pleomorphic adenoma of the salivary gland, questions whether preoperative biopsy correlates with high recurrence rate, if it is followed by total excision of the tumor including the biopsy tract. Rootman (2003) has also suggested that difficult cases should be biopsied. In a published series of 15 patients who had incisional biopsy (Rose et al 1992), 10 underwent total dacryoadenectomy with excision of the biopsy tract and none recurred in a mean follow-up of 6 years. As to the other 5 patients, 4 of them had incomplete excision, with 2 of them developing recurrence attributed to incomplete excision rather than biopsy. Only 1 patient developed malignant transformation, but he was initially operated 4 decades before his first presentation to the authors and no details were provided regarding surgical technique and radicality of excision. Incomplete resection is surely the main risk factor for recurrence, and the importance of initial complete excision of the tumor is emphasized by many authors (Font et al 1978, Rose et al 1992, Henderson 1994, Tang et al 1997). In the series of Font (1978), about 10% of

adenomas underwent malignant change by 20 years after first treatment and 20% by 30 years. In our study, 4 patients with newly diagnosed lacrimal gland adenoma underwent lateral orbitotomy, with 3 of them having total and 1 of them partial tumor excision; in a mean follow-up of 1,4 years only 1 of them recurred. Additionally, 2 other patients presented with tumor relapse; the first of them had had partial tumor excision 5 years before reference to us. We performed lateral orbitotomy and excision of a multinodular tumor. Malignancy was excluded histologically. A small rest was left after surgery and no increase was shown in MRI three years after. The second patient had been operated 23 years before reference to us. No details about the first operation are known. We performed total excision of tumor relapse. Histological examination again excluded malignancy. Since, however, pleomorphic adenomas have the tendency to late recurrence it is obvious that a true assessment of “cure rate” for our patients is precluded until many years have passed.

4.2.2.3. Neurogenic tumors

Schwannomas are uncommon orbital tumors that arise from the Schwann-cell sheaths of peripheral nerves. About 2% of space-occupying orbital lesions have been reported to be peripheral nerve tumors, with approximately 1% schwannomas (neurinomas) (Shields et al 2002). Schwannomas are almost always benign tumors, but extremely rare malignant varieties have been reported (Capps et al 1990, Miliaras et al 2008). Clinical symptoms evolve insidiously and include exophthalmos, diplopia, optic neuropathy and sinusitis (Rootman et al 1982). Histologically, these tumors are characterized by two distinct cellular patterns: Antoni A and Antoni B. Antoni type B pattern areas have undergone extensive cystic and mucinous degeneration, whereas Antoni type A pattern is more cellular. This reflects to the MRI findings of neurinomas, which may present as heterogenous tumors composing of a solid and a cystic component (Rawlings et al 2007, Kiratli 2007). Both patients with neurinoma included in our study, displayed these MRI characteristics. This MRI pattern and the non-specific clinical picture of a space occupying lesion of slow evolution makes differential diagnosis from other orbital lesions with

cavitary change, such as cavernous hemangioma and lymphangioma, problematic (Gunduz et al 2003). Both cases in our series had been initially misdiagnosed as cavernous lymphangioma (mixed venous-lymphatic malformation) by radiologists. Dynamic MRI can be helpful for the differential diagnosis from vascular neoplasms, especially from cavernous hemangiomas as already mentioned above. In a recent review of MRI findings of 62 patients with orbital schwannomas, an intense peripheral ring shaped contrast uptake seen in 25% of the cases has been considered as a specific characteristic of these tumors (Wang et al 2008). The surgical approach can be through anterior, lateral, or combined lateral-orbitotomy and frontal-craniotomy (Rootman et al 1982, Kiratli et al 2007) and it is dictated by the location of the lesion. Surgical removal may be total or subtotal, in piecemeal fashion, or by evacuation of the tumor from within its capsule. The type of removal is dictated by the location and attachments to adjacent structures. Due to their peripheral outpouching characteristic, schwannomas may be successfully stripped of the nerve of origin by microscopic techniques (Rootman et al 1982). We performed lateral orbitotomy in both cases with total and subtotal tumor excision respectively. In both patients the clinical course was uneventful and no other treatment followed.

4.3. Vascular lesions

4.3.1. Arteriovenous fistulas

Dural (indirect) arteriovenous fistulas (AF) are separated anatomically into three types: 1) shunts between meningeal branches of the internal carotid artery (ICA) and the cavernous sinus (CS), 2) shunts between meningeal branches of the external carotid artery (ECA) and the CS, and 3) shunts between meningeal branches of both ICA and ECA and the CS (Barrow et al 1985). Their pathogenesis remains controversial. The theory supported by most investigators assumes that most of these lesions develop in response to spontaneous venous thrombosis in the cavernous sinus and represent an attempt to provide a pathway for collateral venous outflow. In a study (Mironov

1994) residual angiographic findings implying past CS thrombosis were found in 62% of patients. Predisposing factors include pregnancy, systemic hypertension, atherosclerotic vascular disease, connective tissue disease (such as Ehlers–Danlos- syndrome), and minor trauma (Taki et al 1994, Mironov 1995). The symptoms and signs produced by these lesions are influenced by the size of the fistula, the rate of blood flow, and drainage route, especially if the drainage route is posterior, anterior, or both (Stiebel et al 2002). Some authors postulate that in most cases the initial drainage route of the fistula is posterior into the inferior petrosal sinus, basilar plexus or both, and when this pathway becomes thrombosed the fistula begins to drain anteriorly producing visual signs and symptoms (Grove 1984). These patients are usually initially asymptomatic or they may present with an acute, isolated cranial nerve paresis such as trigeminal neuropathy (Rizzo et al 1982), facial nerve paresis (Moster et al 1988) or an ocular motor nerve paresis (Eggenberger 2000) without any signs of orbital congestion. Further evaluation with cerebral angiography will reveal a posteriorly draining fistula. Shortly thereafter ocular symptoms will evolve. Ocular symptoms may be subtle or more severe mimicking a direct fistula. In some cases, redness of one, or rarely, both eyes, caused by dilation and arterialization of conjuctival and episcleral vessels may be the only sign, which can be misdiagnosed as episcleritis, conjunctivitis or thyroid orbitopathy. In more advanced cases with high flow-rate, however, proptosis, chemosis, diplopia resulting from ophthalmoplegia or orbital congestion or both mechanisms, and retroocular discomfort or pain, are present suggesting an inflammatory process or even the Tolosa–Hunt syndrome (Brazis et al 1994). Increased intraocular pressure can evolve due to multiple mechanisms, such as increased episcleral venous pressure (Keltner et al 1987), secondary angle–closure resulting from choroidal effusion and forward displacement of the iris–lens diaphragm (Talks et al 1997), or angle vascularisation resulting from retinal ischemia (Barke et al 1991, Moreiras 2004). Ophthalmoscopic abnormalities include venous stasis retinopathy, central retinal vein occlusion, proliferative retinopathy, retinal detachment, vitreous hemorrhage, choroidal folds, choroidal detachment, or optic disc swelling (Jorgensen and Guthoff 1988, Gonshor et al 1991, Barke et al 1991, Moldovan et al 1997). Visual loss, although less

frequent than in patients with direct fistulas, may be caused by ischemic optic neuropathy, retinal compications, or uncontrolled glaucoma. The ocular manifestations of unilateral dural fistulas are almost always ipsilateral to the fistula, but they may be solely contralateral or bilateral (Stiebel-Kalish et al 2002). Our series included 1 patient with dural fistula between the ICA and the CS with drainage by the contralateral superior ophthalmic vein. When unilateral fistulas cause bilateral manifestations, there is a high probability that the fistula is draining into cortical veins and this is combined with a high risk of intracranial hemorrhage (Stiebel-Kalish et al 2002). In these cases, absolute indication for therapy exists (Solymosi 2004). None of our patients had bilateral symptoms. Direct fistulas between the ICA and CS are usually of traumatic origin and cause the signs and symptoms mentioned above. Differential diagnosis includes conjunctivitis, dysthyroid orbitopathy, non specific orbital inflammation, orbital cellulitis, episcleritis, sphenoorbital meningioma, or Tolosa–Hunt syndrome (Grove 1984, Brazis et al 1994, Procope et al 1994, Oestreicher et al 1995). The correct diagnosis in some cases may not be able to be made until symptoms and signs worsen, new symptoms and signs develop and appropriate diagnostic studies are performed. When a dural carotis cavernous fistula is suspected, CT scanning, CT angiography, MR imaging, MR angiography, orbital ultrasonography, transorbital and transcranial color Doppler imaging, or a combination of these tests may be beneficial in confirming the diagnosis (Coskun et al 2000, Kilic et al 2001, Kawaguchi et al 2002, Rucker et al 2003). The gold standard diagnostic test, however, is a catheter angiogram, as in the case of the direct carotid cavernous fistula (Debrun 1995). Because many dural fistulas are fed either by meningeal branches of the ECA or by meningeal branches of both the ICA and ECA and others are fed by arteries from both sides or are fed by unilateral arteries but produce bilateral symptoms and signs, selective angiography of both the ICA and ECA on both sides should always be performed (Debrun 1995). When performed by an experienced neuroradiologist, catheter angiography has a morbidity rate of less than 1% and virtually no mortality rate, except in patients with connective tissue disorders such as Ehlers–Danlos syndrome, in whom the risks are much greater (because of excessive fragility of the extracranial and intracranial

vessels). Regardless of whether they drain anteriorly or posteriorly, 20–50% of dural fistulas close spontaneously or after angiography (Liu et al 2001). For this reason, patients with mild symptoms can be initially observed. In general, however, endovascular embolization is the optimum treatment for high flow dural fistulas or direct fistulas that produce progressive or unacceptable symptoms and signs including visual loss, diplopia, intolerable bruit, severe exophthalmos, and, most importantly, cortical venous drainage. Direct fistulas can be embolized with balloons or platinum coils which are usually introduced though a catheter placed in the arteria femoralis. In some cases the wall of the ICA is severely injured, and the interventionalist cannot be sure if a device (balloon or platinum coils) used to close the fistula was either in or compromising the lumen of the ICA. In these cases, complete occlusion of the ICA (trapping) was previously the only choice (Solymosi 2004). However, significant advances in stent and catheter design nowadays make it possible in many instances to deploy either balloon-expandable or self-expanding stents in the cavernous and supraclinoid segments of the ICA. In this way, it is possible to reconstruct a severely injured artery, and trapping can be avoided (Ahn et al 2003, Men et al 2003, Moron et al 2005). Indirect dural fistulas can be best embolized with platinum coils introduced though a transvenous route (femoral vein or internal jugular vein) (Solymosi 2004). If this fails, a variety of other approaches may be applied, most of which involve cannulation of the superior ophthalmic vein via an eyelid crease incision (Spinelli et al 1994, Goldberg et al 1996) or even a lateral orbitotomy (Badilla et al 2007). Alternatively the embolization material can be introduced via a microcatheter placed in the ECA and passed into the specific branch or branches that feed the fistula (Liu et al 2000). The ICA is not usually embolized unless the interventionalist can successfully catheterize the meningohypophyseal trunk or other meningeal feeders from the artery (Borden et al 2001). When a dural fistula is fed by branches from both the ECA and ICA, embolization of the feeders from the ECA may reduce the blood flow in the fistula sufficiently so that non-embolized feeders from the ICA will thrombose spontaneously (Liu et al 2001). This was observed in one of our patients with a complex fistula fed by both ECA and ICA. Embolization of feeders of the ECA only led to closure of feeders from the ICA and full recovery of symptoms. Embolization of

feeders from the ICA is in many cases inappropriate because of the significant potential neurological morbidity from distal embolization (Kupersmith et al 1988). The intravenous route is then the route of choice (Badilla et al 2007). With endovascular therapy the healing rate for patients with carotid cavernous fistulas is overall > 90% (Solymosi 2004). After successful closure, however, recanalisation of the fistula can occur in some cases. The decision to perform further treatment depends on the severity of symptoms.
5 patients with carotid cavernous fistulas and 1 patient with fistula between the ECA and SOV, included in this study, underwent endovascular embolization. In 2 patients recanalisation occurred; 1 of them underwent second treatment, whereas the second one received no further treatment, as symptoms resolved. In all 5 patients the postoperative course was uneventful and symptoms completely regressed.

4.3.2. Orbital Venous malformation (OVM)-Thrombosis of the superior ophthalmic vein (SOV)

As already mentioned, in 1999 a consensus statement on terminology of the orbital vascular disorders was published by the members of the Orbital society. The classification, which was proposed, was based on hemodynamic characteristics of orbital vascular malformations. Venous flow lesions or orbital venous malformations (orbital varices) were divided in distensible and non-distensible varieties (Harris 1999). Distensible lesions are those with rich and direct communication to the orbital vascular system, which is obvious clinically (enlargement with Valsalva maneuers or in dependent positions) or radiographically (enlargement with increased venous pressure-dynamic CT). Non-distensible OVM have minimal connection to the orbital vascular system and these lesions either produce a mass effect or can lead to acute symptoms due to hemorrhage or thrombosis. These symptoms include acute pain, exophthalmos, diplopia or even optic nerve compression. Episodes of thrombosis or hemorrhage may be recurrent. The non-distensible variety is often difficult to separate from lymphangiomas, which are considered as no-flow lesions (Rootman 1988). Non-distensible OVM have demonstrable connections to the orbital venous system by venography or direct intralesional

injections, whereas lymphangiomas do not (Rootman 1986, Harris 1990). Mixed lesions with lymphatic and venous component are classified as venous flow malformation, in order to emphasize the clinical importance of the venous relationship (Harris 1999). Episodes of thrombosis and/or hemorrhage may complicate distensible OVM, as well, but they are much less common (Lacey et al 1999). In a review of 22 cases of OVM, of whom 18 were distensible and 4 non-distensible, thrombosis or hemorrhage were observed in 17,6% in the distensible and 100% in the non-distensible group (Arat et al 2004). In our series, 2 out of 4 patients (50%) with non-distensible OVM had a histologically proven thrombosis. In the distensible group no thrombosis was evident in orbital imaging, but since these lesions were not biopsied we cannot exclude the presence of minimal thrombi in them. Non-distensible OVM tend to occur in older patients (Moreiras 2004, Arat et al 2004), and some authors postulate that many of them have been distensible and have remained clinically quiet for many years before diagnosis (Moreiras 2004). In our series of 6 patients with OVM no age predilection for both varieties was noticed. Histopathologically, in 2 of them with non-distensible OVM, intravascular benign endothelial hyperplasia was present. This unusual condition is reported by other authors as well, and it is considered as a reactive response developing secondary to a thrombus in vascular malformations or hemangiomas (Shields et al 1999, Arat et al 2004). Orbital CT and especially dynamic orbital spiral CT with contrast medium can be very useful for the diagnosis of OVM (Rubin et al 1995, Moreiras 2004). OVM are well circumscribed lesions and may show either an intense homogenous or an inhomogenous (partial thrombosis) contrast medium uptake. In cases of thrombosis phleboliths may be present in CT scans. An interesting finding of orbital wall defects has also been described in some patients with orbital varices (Islam et al 2004). In MRI the lesions are isointens in T1-weighed and iso-hyperintens in T2-weighed images. Signal intensity rises if intralesional blood flow decreases, as in cases of thrombosis. Heterogenous signal in MRI is seen in the presence of hemorrhage in various lytic stages (Moreiras 2004). Orbital varix thrombosis must be differentiated from other manifestations of orbital venous thrombosis: cavernous sinus thrombosis or thrombosis of the SOV (Takahashi et al 1984). The findings of a superior ophthalmic vein

thrombosis include: increased intraocular pressure, retinal venous congestion, and conjunctival chemosis, eyelid oedema, optic compression neuropathy retinal venous dilation and tortuosity or even macular oedema. 2 cases in our series involved a thrombosis of the superior ophthalmic vein; one of them was idiopathic and one due to factor Leyden mutation. The clinical signs above are secondary to thrombosis of a functional orbital vein and represent an acute compromise to the orbital venous drainage system. Such symptoms are not characteristic of OVM, since these anomalies do not replace a normally functioning venous drainage system. The main differential diagnostic possibilities for OVM are the cavernous hemangioma and the lymphangioma of the orbit (Bullock 1989). Orbital MRI can be valuable in some problematic cases (Moreiras 2004). Indications for therapy are intractable pain, hemorrhage leading to visual deterioration, severe exophthalmos and cosmetic disfigurement (Guigon-Souquet et al 2002). Lesions causing minimal symptoms should be initially observed. Thrombosed non-distensible OVM are best treated with surgical exposure and evacuation of clot followed by subtotal or total excision (Bullock et al 1990). Distensible lesions can be treated dependent on their location. In general, surgery can be extremely difficult in many cases, as OVM are very friable and intimately intermixed with normal orbital structures; the risk of visual loss as a result of hemorrhage or optic nerve damage especially in deep OVM, must always be taken into account. Superficial distensible lesions can be surgically excised if they are well-circumscribed or treated by carbon-dioxide laser ablation, either trancutaneously of after surgical exposure if they are diffuse. Both methods can be combined. For deep lesions surgical exposure, partial excision (total excision is rarely possible) and carbon-dioxide ablation can be performed (Moreiras 2004). Surgical excision can be facilitated by the use of clips (Beyer et al 1985, Lacey et al 1999) or by previous embolization with cyanoacrylate glue after surgical exposure (Lacey et al 1999). If a distensible deep lesion is not complicated by thrombosis and/or hemorrhage, endovascular embolization with platinum coils either via percutaneous transfemoral venous catheterization (Takechi et al 1994) or after surgical exposure (Weill et al 1998) can be chosen as less invasive treatment. Embolization is probably

more useful in case of saccular or segmental venous dilatations than in tangled plexus of venous channels (Weill et al 1998).

We treated 4 patients with non-distensible OVM, 2 of whom had extraconal lesions situated in the anterior orbit and 2 others had intraconal lesions. Tumor excision was performed via anterior orbitotomy (2 cases) and lateral orbitotomy (2 cases). In the 2 patients with intraconal lesions, both of whom had preoperative diplopia, diplopia persisted after the operation. 1 of them underwent strabismus surgery and was free of symptoms thereafter, whereas the clinical course of the second patient is not known. All patients had an uneventful postoperative course without any complications.

2 additional patients with minimal intermittent exophthalmos caused by distensible OVM, were simply observed.

4.3.3. Orbital hematic cyst

Numerous terms, including hematoma, hematocele, blood cyst, hematic cyst, cholesteatoma and cholesterol granuloma, have been used to describe orbital cystic collections of blood and its breakdown products. The term orbital hematoma should be reserved for an acute traumatic or spontaneous collection of blood which is absorbed in a matter of days to weeks (Henderson 1994). In most instances orbital hematomas break down and are absorbed without sequelae. However the degradation of blood to its breakdown products can occasionally lead to a granulomatous reaction, appearance of hemosiderin and hematoidin and cholesterol clefts in a fibrous background (Milne et al 1987, Henderson 1994). This procedure results in the formation of a hematic cyst. Hemorrhage into a preexisting lesion such as lymphangioma, dermoid or cavernous hemangioma (the latter is very rare) is usually referred to as chocolate or blood cyst. This lesion has an endothelial or epithelial lining. A hematic cyst has, in contrast, no epithelial or endothelial lining but rather a fibrous pseudocapsule. Orbital cholosteatomas and orbital dermoids are synonyms which describe lesions with epithelial elements, keratin, cholesterol clefts, lipid laden histiocytes, fibrous stroma and in some cases hemorrhage. As already mentioned, the main feature used to distinguish an orbital hematic cyst from these lesions is the absence of epithelial or

endothelial lining. Histopathologically, cholesterol granulomas and orbital hematic cysts are identical. Hematic cysts can be further classified into acute or chronic. Acute hematic cysts lack a thick capsule and present typically with posttraumatic ptoptosis, conjuctival chemosis and restricted ocular motility (Amrith et al 1990). Chronic hematic cysts may produce erosion of bone and consist of cholesterol clefts, hemosiderin, hematoidin and a fibrous pseudocapsule. Painless unilateral proptosis is the main clinical symptom. These benign lesions may increase in size (Amrith et al 1990). A proposed mechanism of growth is rebleeding into the cyst secondary to fibrinolytic activity (Shapiro et al 1986, Henderson 1994). Most of orbital hematic cysts are located in the superior orbit subperiostaly or in close contact to the periosteum, but intraconal lesions have also been described (Akira et al 2000). MRI shows a well circumscribed lesion and signal intensity is dependent on the age of the cyst, as shown in the table below. Only the pseudocapsule enhances with gadolinium (Moreiras 2004). Surgical excision is the typical treatment, although some authors contend that incomplete removal (Mund 1981, Akira et al 2000) or needle aspiration is adequate (Wolter et al 1976, Siegel et al 1982).

We operated 1 patient with the typical clinical and histological characteristics of an intraconal orbital hematic cyst. The postoperative course was uneventful. An additional patient with typical clinical and MRI findings of an acute subperiostal orbital hematic cyst after an episode of intense nausea and vomiting, refused an operation and was only observed.

Table 8. Signal intensity of hemorrhage in MRI (Moreiras 2004, modified)

	T1	**T2**
Very acute hemorrhage (hours-3 days)	hypointens	hyperintens (the first hours) , hypointens
Acute-subacute hemorrhage (4-7 days)	hyperintens	hypointens
Subacute hemorrhage (7-20 days)	hyperintens	hyperintens
Chronic hemorrhage (> 20 days)	hypointens	hypointens

4.4. Structural lesions

Dermoid cysts are developmental choristomas comprising 3 to 9% of all orbital masses (Grove 1981).10% of all head and neck dermoids are orbital and the superior temporal orbital quadrant is the most frequent location (Meenakshi et al 2009). From a clinical point of view, Grove (1981) divided them in superficial and deep. The natural history of dermoids is slow expansion and, depending on their site, displacement ofadjacent structures. Anterior or superficial dermoids are generally easily recognised and treated early. Deeper seated lesions frequently present later as 'giant' dermoids and may be misleading in terms of clinical size (Sherman et al 1984). Deep dermoids may have a palpable anterior margin but not easily palpable posterior margin and presence of oculomotor or visual disturbance should raise a suspicion for a deeper location. In cases where a deep located lesion is clinically suspected CT scan is the preferred method for the evaluation of the size, shape, extension and demonstrationo of the relation to bone (Moreiras 2004). Bone changes are usual especially in deep dermoids and may include (Nugent et al 1987): focal thinning on a pattern of irregular scalloping of adjacent bone , full thickness defects with loss of a portion of the orbital wall, linear defects through bone which represent widening of a suture line or sclerosis with thickening of adjacent bone. The lesion may display rim calcification (Nugent et al 1987, Moreiras 2004). In cases of location in the lacrimal fossa region with presence of bone erosion and/or of calcification difficulty in making the differential diagnosis from malignant lacrimal gland neoplasms exists; the presence of low signal density similar to fat is virtually pathognomonic of a dermoid in these cases (especially since orbital lipomas and hiposarcomas are extremely rare) (Hammerschlag et al 1983). However dermoids of muscle density also exist (Nugent et al 1987). Enhancement with intravenously administered contrast material may be then very useful for the differential diagnosis since dermoids show no or only rim enhancement whereas lacrimal gland tumors tend to enhance homogeneously (Nugent et al 1987). Rupture of the cyst capsule either traumatic or spontaneous leads to granulomatous reaction with granulomatous reaction, fibrosis and

attachement of the lesion to adjacent soft tissues; symptoms of acute inflammation may evolve or alternatively capsule rupture may display no clinical symptoms (Sherman et al 1984). If acute symptoms evolve, fat density and absence of contrast capture inside the cyst along with evidence of sclerosis and hyperostosis of the adjacent bony wall are valuable for the differential diagnosis from cellulitis and non-specific inflammation (Moreiras 2004). Complete surgical excision with intact capsule is the treatment of choice in order to prevent surgical dissemination of the contents which can induce an acute inflammation. This also helps avoid deposistion of cells which could lead to reccurence (Sherman et al 1984). However, some deep dermoids cannot be excised in this way due to their large size; dissection along the orbital side of the lesion and subsequent evacuation followed by microdissection of the remaining lining is then necessary (Rootman 1988). As long as the complete linings and contents of the dermoid cyst are removed in these cases intraoperative rupture does not appear to lead to late or early postoperative morbidity (Rootman 1988).

In this series 4 patients with dermoids located in the anterior orbit were operated with total tumor excision. No reccurences or postoperative complications occurred.

4.5. General considerations regarding the therapeutic approaches to orbital lesions

It can be generally said that the therapeutic procedure chosen in cases of orbital pathology should be based on the evaluation of 3 parameters: a. the pathophysiology of the lesion (expansive, infiltrative, vascular or myopathic). b. the anatomical site of involvement in the orbit c. the histology (malignant or benign lesion). Two lesions displaying the same pathophysiological and anatomical characteristics may require different treatments if the first of them is benign and the second of them malignant. In cases of malignant lesions every effort should be made to reduce the risk of mortality related to malignancy, even if this implies sacrifice of visual function. In this sense, which therapeutic procedure will be chosen is mainly determined by the histological nature of the lesion and secondarily by pathophysiology or

anatomical site of involvement. For example an infiltrative localized orbital malignant lymphoma of low malignity is to be treated with orbital radiotherapy with high success rate, as mentioned above. On contrary an infiltrative malignant lymphoma of high malignity will require chemotherapy with or without subsequent radiotherapy. A high malignant mesenchymal tumor will generally require wide excision, which usually implies exenteration if bone involvement is present, irrelevant if the tumor is expansive or infiltrative in orbital imaging techniques. A low malignant mesenchymal tumor can in contrast be treated with total excision if it is of expansive nature and close follow-up will be performed. As example the two patients with malignant expansive mesenchymal tumors of the orbit included in this study can be mentioned: the first of them had a well-differentiated expansive liposarcoma of low malignancy situated in the anterior orbit, and was successfully treated with total excision without any other therapy; the second patient had an expansive intraconal high malignant fibrous hystiocytoma which required exenteration. The decision to perform adjuvant chemotherapy or radiotherapy will again be made according to histology.

Perhaps in the category of vascular lesions more than any other, the whole spectrum of orbital imaging techniques may be necessary in order to determine the exact nature of the lesion. Since many clinical and radiological characteristics of such lesions overlap and, as already mentioned, mixed forms (for instance mixed venous-lymphatic malformations) are common, careful preoperative evaluation based on history, clinical examination and imaging findings is mandatory; it is for instance very important for a lesion situated deep in the orbit, to differentiate between a haemangioma and a lymphangioma (mixed venous lymphatic malformation) since attempt of total excision for the latter carries high risk of postoperative complications or even visual loss. One more example can be mentioned: a hemangiopericytoma may be associated with malignancy or high recurrence rate if total excision is not performed, and can be in many cases distinguished from a cavernous hemangioma preoperatively, if meticulous study of CT or MRI scans is performed by an experienced radiologist (Moreiras 2003). The same applies to distensible and non-distensible venous malformations, where indications for surgical treatment and treatment approaches are quite different. From the

examples mentioned above it is clear that the orbital surgeon should not be mislead by the expansive nature of most vascular “tumors”, something that per se would in most cases mean that total excision and healing will be possible. If he underestimates the value of accurate preoperative diagnostic, he may be confronted with unexpected difficulties in surgical field. In cases of vascular pathology, the anatomical site of involvement is of high importance for the therapeutic procedure which will be chosen. If decreased visual function is present (for instance cavernous haemangioma or non-distensible venous malformation of the apex causing visual field defects or intraconal cavernous haemangioma causing choroidal and retinal folds) surgery is the therapy of choice. For the same lesions situated elsewhere in the orbit and causing minimal symptoms, however, observation only can be justified. In cases of acute vision threatening complications which are relatively common in this category, it is clear that prompt surgery should be performed.

Myopathic lesions are almost always to be treated conservatively. In this category, however, careful diagnostic evaluation is mandatory, since increased muscle volume can have various causes: idiopathic non-specific inflammation, endocrine orbitopathy, lymphoproliferative lesions like lymphomas, rhabdomyosarcoma, metastatic disease, specific inflammation like Wegener’s granulomatosis or even arteriovenous dural fistulas. The signal characteristic in T2- weighed MRI images can be helpful for the differential diagnosis in some cases, but many times signal features overlap. High dose steroid treatment can be justified, at least at the beginning of disease, as non-specific myositis has a good and quick response to this therapy. The question for the clinician is when to perform biopsy in such cases, or in other words how long should be waited for steroid treatment to prove its efficacy. It is also true, that lymphoproliferative lesions such as lymphomas, may show an initial good response to steroids. All cases of idiopathic non-specific myositis of this study responded very well in a period to 1-3 days to steroid treatment. It can be assumed, that orbital biopsy is to be performed if no improvement in the clinical symptoms is observed after the first days of therapy.

For benign pathology treatment should be clearly based on pathophysiology and anatomical site of involvement. Location in the orbital apex causing

oculomotor, sensory or visual deficits in the presence or an expansive lesion is an indication for surgery. If the lesion is expansive total excision should be attempted, provided that meticulous care is taken not to injure vital structures. If an infiltrative lesion involves the apex and causes functional visual deficit the treatment approach is more complicated. Taking into account, that location in the orbital apex may have minimal inflammatory signs from the anterior orbit, diagnosis of non-specific inflammation cannot be easily made and presence of malignancy cannot be excluded, at least clinically. It is also well documented (Rootman 1994) that sclerosing idiopathic inflammation most commonly involves the anterior and superior lateral orbit also the apex; moreover 20% of sclerosing idiopathic inflammations (SNSI) are predominantly apical (Rootman 1994). Differential diagnosis between SNSI and other lesions causing desmoplasia and presenting with pain, proptosis and mild or no inflammation, such as Wegener' s granulomatosis, sinus disease, primary and secondary neoplasia or direct extension of sinus carcinomas can be problematic. In such cases early orbital biopsy with or without surgical debulking or orbital decompression should be considered for the following reasons: a. high risk of misdiagnosis, as mentioned above. b. in cases of SNSI steroid treatment or even radiotherapy have very often unsatisfactory results, as shown in this study and also reported in the literature. If diagnosis of SNSI is missed and response to steroids and/or radiotherapy is long awaited, irreversible visual deficits may evolve, which could have been avoided, if other treatment modalities, such as immunosuppressant therapy (Rootman 1994), surgical debulking or orbital decompression were promptly performed. Other authors state, as well, that in cases of SNSI quick identification and prompt surgical treatment is crucial to minimize residual functional deficits (Kennerdell 1991) c. cases of acute or subacute non-specific inflammations can also be steroid tolerant. In summary, location in the apex with functional deficit is indication for prompt surgery in both expansive and infiltrative lesions, aiming to preserve as much function as possible. For expansive lesions total excision should be attempted, whereas for infiltrative lesions surgical debulking or orbital decompression is to be performed. If the inflammatory nature of the lesion is confirmed by biopsy, adjuvant anti-inflammatory therapy or radiation therapy can also be performed

postoperatively on the basis of histology (specific or non-specific inflammation).

Lacrimal involvement is also an indication for prompt surgery for the same reasons as in apical involvement with the difference that in this case direct threat to vision is not present at the beginning of disease. Moreover, the lacrimal gland lesions are likely to be associated with a systemic disorder more than any other location in the orbit (Rootman 1998) and this is another reason why routine biopsy should be part of the treatment protocol. Diagnosis of non-specific inflammation is to be made extremely cautiously in this location.

For lesions of the anterior orbit presence of acute inflammatory signs can justify conservative anti-inflammatory treatment without need of early biopsy. Given however the fact that the majority of lymphoproliferative lesions are located in this site, failure of response or initial response with multiple recurrences should raise the suspicion of lymphoma and biopsy should be performed to exclude malignancy.

The intraconal space is a relatively rare site of involvement for non-specific inflammation. In this study only 5 of 32 intraconal lesions were inflammatory; in contrast 22 were neoplastic. Given the fact that neoplasia is very common in intraconal space, chronic presentations in this part of the orbit are almost always to be explored surgically.

Summary

1. The clinical and radiological characteristics along with the results of treatment of 132 cases of patients with orbital disease, who were treated from the year 1993 to the year 2008 in the University Clinic of Ophthalmology Rostock were studied.
2. Data was collected from patient's archives of the University Clinic of Ophthalmology Rostock. Postoperative follow-up examinations have taken place mainly in the University Clinic of Ophthalmology Rostock. Some patients were examined postoperatively by ophthalmologists in private practices. Information about the postoperative course for these patients was collected by questionnaires which were sent to and filled out by private ophthalmologists.
3. 48 patients (36 %) had inflammatory, 59 patients (45%) had neoplastic, 19 patients (14%) had vascular (tumors excluded) and 6 patients (5%) had structural lesions. Diagnosis was confirmed histologically in 103 cases.
4. In the age groups of 0-20 years inflammatory lesions were the most common. In the age group of > 60 years neoplasia dominated. In the age group of 20-60 years inflammatory lesions and neoplasia had the same frequency.
5. A pathophysiological classification based on clinical and radiological characteristics was made in the following categories: expansive 43 cases), infilrative (60 cases), vascular (tumors excluded) (19 cases) and myopathic (10 cases).
6. Anatomically, the intraconal space along with the lacrimal gland region were the most common sites of involvement for expansive and infiltrative lesions (103 cases): 32 intraconal (31%) and 32 lacrimal (32%) lesions were encountered. The anterior orbit was the third most common site with 27 cases (26%). 7 lesions (7%) were diffuse, 3 lesions (3%) affected the orbit by continuity (periorbital) and 2 lesions (2%) were apical.
7. The most common infiltrative lesions were non-specific inflammations and malignancy with domination of lymphomas. The differential

diagnosis between them is in many cases very difficult and the question whether to perform biopsy emerges. If acute symptoms, such as pain, erythema and proptosis dominate the clinical picture, the presence of an acute non-specific inflammation is highly likely and in that case, an initial treatment with steroids without first performing a biopsy could be considered.

8. Several CT and MRI features have been described to differentiate between non-specific inflammation and lymphoma in the orbit. However clinical and radiological findings overlap in many cases and biopsy is recommended for prompt diagnosis of a potential malignancy and subsequent treatment.
9. In cases of non specific inflammation of the orbit surgical debulking with additional steroids is the treatment of choice for relatively small and well circumscribed lesions, especially if the lacrimal gland involved. For diffuse lesions steroid therapy is the therapy of choice. If steroids fail or are contraindicated, radiotherapy is the next therapeutic option.
10. Surgical debulking or orbital decompression should not be delayed if the apex is involved and visual deficits are present, especially if sclerosing inflammation is diagnosed of if diagnosis remains clear.
11. Sclerosing inflammation of the orbit may be considered as a distinct clinicopathologic entity characterized by primary, chronic, and immunologically mediated fibrosis. Since poor response to steroids and radiotherapy is common, surgical removal is recommended for relatively well delineated lesions especially in the lacrimal gland region. For more diffuse lesions surgical debulking with additional steroids and/or radiotherapy should be tried. In cases of failure the administration of immunosuppressants can be discussed on case to case basis.
12. Orbital lymphomas were in their majority localized and of low-malignity. Radiotherapy was the treatment of choice with very good results. With dose of <40Gy serious complications were rarely seen. In cases of disseminated disease or lymphomas of high-malignity chemotherapy must be performed.

13. Malignant orbital mesenchymal tumors are rare and may be initially misdiagnosed. The differential diagnosis among them and vascular tumors such as hemangiopericytomas is often challenging in biopsy specimens. Surgical treatment in the form of total excision or exenteration was performed (rhabdomyosarcoma excluded). The efficacy of radiotherapy and chemotherapy (rhabdomyosarcoma excluded) is controversial and the decision to perform them additionally to surgery is to be made on case to case basis.
14. Tumefactions in the lacrimal gland region may be lymphoproliferative, inflammatory or malignant. Distinguishing between pleomorphic adenoma and lacrimal gland carcinoma is crucial and is guided by clinical and radiological features; however difficult cases may require biopsy. Lacrimal gland adenomas are managed by total excision of the tumor with its capsule. If meticulous surgery is performed recurrence drops virtually to zero. The adenoid cystic carcinoma of the lacrimal gland is a tumor with grim prognosis, due to early occult metastasis or intracranial extension at the time of diagnosis. Nevertheless, radical surgery with radiotherapy should be performed to achieve local control of the disease.
15. Vascular lesions of the orbit, including cavernous hemangiomas, lymphangiomas and venous malformations must be viewed in respect to their hemodynamic characteristics. Mixed clinical forms are often encountered and diagnosis presents a challenge to the orbital specialist. In this category of lesions the total spectrum of radiological examination methods including CT, MRI, MR-angiography, transorbital color Doppler imaging, invasive angiography may be needed for the establishment of the diagnosis. Differentiating between these lesions is crucial for treatment. Cavernous hemangiomas are surgically managed with very good results overall. For lymphangiomas, conservatism is generally recommended, especially for lesions situated deep in the orbit or in the apex, due to high risk or complications and recurrence. Anteriorly located lesions are much more easily managed with low complication rates.

16. Venous malformations are classified in distensible and non-distensible ones. Distensible malformations should be observed if they cause minimal symptoms. In cases of complications or cosmetic disfigurement, treatment is based on location and includes surgical excision, ablation or embolisation by neuroradiologists. Non-distensible venous malformations are treated by surgical excision.
17. Arteriovenous fistulas may cause multiple ocular symptoms from the anterior and posterior segment. Cases of therapy-resistant “conjunctivitis” or refractory, usually unilateral “glaucoma” or palsies of oculomotor nerves should raise suspicion of such a lesion. After confirmation of diagnosis therapy is undertaken by interventional radiologists.
18. Patients with orbital disease will need in many cases an interdisciplinary approach for their diagnosis and treatment. The ophthalmologist is in most cases the first reference specialist and the one who will organize the management of these patients.
19. When confronted with a patient suspected of having orbital disease the clinician may feel confused, since the symptomatic of orbital disease (endocrine orbitopathy excluded) is non-specific. A pathophysiological categorization of all orbital lesions in 4 groups, namely expansive, infiltrative, myopathic and vascular in combination with the anatomical site of involvement in the orbit provides a useful framework for analyzing each case.
20. The clinical analysis includes the complete spectrum of ophthalmological and neuroophthalmological examination methods and is supported by a considerable amount of information provided by modern diagnostic imaging methods. Since “good answers can be given only to good questions”, the clinical analysis remains a valuable tool.

Theses

1. Non-specific inflammation of the orbit (NSI) is one of the most common diagnoses in cases of orbital lesions. Steroid treatment is generally considered as the treatment of choice, but as already mentioned some authors question this. Some patients respond well, others show a partial response with recurrence and others show no response. The question which arises is how long should be waited before other treatment options are considered. Additionaly, if diagnosis has been made only on the basis of clinical and radiological findings without any biopsy confirmation the situation becomes more complicated: in this case suspicion of misdiagnosis also exists and biopsy is to be considered.

2. If muscle involvement dominates, it can be assumed that if no improvement is observed after the first days of treatment, biopsy should be performed because misdiagnosis is likely. In cases of other orbital involvement the right time for biopsy to be performed is a question for the clinician. If diagnosis has already been confirmed histologically but steroids are not effective or are contraindicated, radiotherapy could be another option. Controversy however exists if correlation between steroid and radiotherapy response exists and if failure of steroids is a negative prognostic factor for the results of radiotherapy.

3. Even if systemic steroid administration (intravenous or oral) is most commonly performed, local injection with good results and practically no systemic side effects is reported in the literature. These reports however include a relatively small number of patients. Periocular injection of steroids carries a very low risk for systemic complications, but local complications, which can be very serious, have been observed. Since the dose equivalent between local and systemic dose is not known and as mentioned only few reports on intralesional steroid administration exist, it is difficult to compare the efficacy of these methods.

4. For apical lesions or lacrimal gland lesions the diagnosis of NSI is to be made with caution. In these cases biopsy may be performed as soon as possible, in order to avoid misdiagnosis and (in cases of apical involvement) to preserve as much function as possible. It can be argued that surgery carries a risk of complications and these patients should be given the chance of steroid therapy before surgery is suggested. Since the exact time to wait for steroids to act is not known and may also be variable, it could be assumed that the risks of an operation should be taken into account and thus referral to an orbital centre is surely justified, at least in cases of visual dysfunction.

5. Controversy exists regarding the appropriate management of sclerosing orbital inflammation (SNSI). If SNSI is considered as a unique clinicopathological entity, where dysfunction of the immune regulation plays a significant role, early and aggressive immunosuppressant treatment may be considered; this sort of treatment however, caries the risk of systemic side effects. Anecdotal cases of treatment with immunosuppressant medicaments are reported in the literature: some patients responded well whereas others did not. On the other hand steroids and radiotherapy have high failure rates. Thus, it seems that surgery should be considered as the treatment of choice, at least in cases of relatively well circumscribed lesions or in case of lacrimal gland involvement. For more diffuse lesions treatment could be surgical debulking alone or in combination with steroids, immunossuppressants or radiotherapy on case-to-case basis.

6. For orbital lymphomas treatment approach is clear: radiotherapy for localized low-malignity tumors and chemotherapy for high-malignity tumors or disseminated disease alone or in combination with radiotherapy. Controversy exists regarding the appropriate dose: the dose should be sufficient for treatment but very high dose carries the risk of serious complications such as radiation retinopathy or cataract formation. It can be assumed that with dose of <40 Gy complication rate is very low.

7. For lacrimal lesions many reasons biopsy is often an essential part of the diagnostic protocol. In cases of neoplasia distinguishing between malignant

and benign lesion is of vital importance: careful evaluation of clinical and radiological findings, may be extremely helpful for this reason, however difficult cases requiring biopsy also exist. Traditionally biopsy in cases of benign pleomorphic adenoma is considered to carry high risk of reccurence; many authors though have questioned this and suggest that biopsy should be performed for difficult cases and if then diagnosis of benign pleomorphic adenoma is made, excision of the biopsy route practically minimizes reccurence to zero.

8. Controversy exists regarding treatment of lacrimal gland carcinoma. Surgery either radical in form of exenteration with or without removal of bone or primary resection of the tumor mass with radiotherapy is the conventional treatment. The overall prognosis is bad due to early perineural and hematogenic metastases which may initially be occult. Locally advanced disease is correlated with high rate of development of metastasis at the time of diagnosis; in these cases radical and aggressive surgery has not proven to improve disease free survival. Reports of higher survival rates after intraarterial chemotherapy followed by surgery and/or radiotherapy exist in the literature. Intraarterial chemotherapy however carries the risk of complications of endovascular catheterization and systemic toxicity of chemotherapeutic drugs. Questions arising in the management of these patients are: a. which patient will benefit from aggressive surgery and in which cases more conservative surgery with adjuvant radiotherapy or even intraarterial chemotherapy is should be preferred for a better quality of life? b. in which cases intraarterial chemotherapy is likely to improve local disease control and overall disease free survival? Generally, the prevention of metastasis and control of local disease is a major challenge for the clinician and treatment decisions are generally to be made on case to case basis.

9. Malignant mesenchymal tumors (rhabdomyosarcoma excluded) are generally to be treated surgically with total excision, even if this frequently implies exenteration. The efficacy of radiotherapy is for most of them unclear and decision to perform it is generally to be based on the radicality of surgical excision.

10. The differential diagnosis of vascular lesions of the orbit is in many cases very difficult since clinical manifestations and imaging characteristics overlap; moreover mixed forms are not unusual. In this category of lesions, perhaps more than any other, extensive preoperative diagnosis is very important and justifies the use of the whole spectrum of orbital imaging techniques (invasive and non-invasive). An example supporting this is the following: treating a lymphangioma as a cavernous haemangioma may cause serious complications; however distinguishing preoperatively between them may be extremely difficult. Taking into account that vascular lesions are in their majority benign, the question arising is in which cases surgical treatment is to be performed (especially if diagnosis is not clear) and on the contrary, which lesions should be initially observed. The absence of symptoms or presence of minimal symptoms is surely a main criterion. Since however some of these lesions, which initially cause minimal symptoms, carry the risk of acute and even vision threatening complications (acute hemorrhage of a non-distensible venous malformation spontaneously or posttraumatic is an example) it is obvious that other parameters must also be considered (socioeconomic, age, way of life, occupation).

PERSONALIEN

Name und Vorname:	Manousaridis, Kleanthis
Geburtsdatum:	02.12.1981
Geburtsort:	Ptolemaïda, Griechenland
Familienstand:	ledig
Vater:	Manousaridis, Georgios
Mutter:	Manousaridis, Eleni

SCHULISCHER WERDEGANG

1987-1993	4. Grundschule, Kozani, Griechenland
1993-1996	2. Gymnasium, Kozani, Griechenland
1996-1999	3. Lyzeum, Kozani, Griechenland
17.06.1999	Abitur

UNIVERSITÄRER WERDEGANG

10.1999	Beginn des Studiums der Medizin An der Universität Thessaloniki, Griechenland
10.1999-07.2005	Studium der Medizin
10.1999-07.2004	Vorklinischer und klinischer Abschnitt des Medizinstudiums
08.2004-07.2005	Praktisches Jahr
31.07.2005	Erlangung des Diploms (Ptychion Iatrikes)
12.12.2006	Beruflserlaubnis, Landesprüfungsamt für Heilberufe beim Landesamt für Gesundheit und Soziales Mecklenburg-Vorpommern
09.02.2009	Approbation, Landesprüfungsamt für Heilberufe beim Landesamt für Gesundheit und Soziales Mecklenburg-Vorpommern

BERUFLICHER WERDEGANG

12.2005-12.2006	Kreiskrankenhaus Grevena; primäre medizinische Versorgung-Landarztdienst
seit 01.01.2007	Assistenzarzt für Augenheilkunde, Klinik und Poliklinik für Augenheilkunde, Universitätsklinikum Rostock

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Statement of original authorship

Hereby I declare that this thesis is my own work and has not been submitted in any form for another degree or diploma at any university or other institution.

Information derived from the published or unpublished work of others has been aknowledged and a list of references is given.

Date Signature

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