CHAPTER
24 Tumors of Special Senses

TUMORS OF THE EYE

Tumors of the eye will be discussed under four main sections, namely: eyelid cancer, ocular melanoma, retinoblastoma and orbital tumors.

EYELID CANCER

The eyelid is covered anteriorly by skin and posteriorly by conjunctiva. Skin appendages of the eyelids include: the sebaceous glands (glands of Zeis and meibomian glands), apocrine glands (glands of Moll) and eccrine sweat glands. The four major cancers of the eye lid are: basal cell carcinoma, squamous cell carcinoma, sebaceous carcinoma and malignant melanoma.

Basal cell carcinoma accounts for about 90% of all eyelid malignancies (P 24-1). The inner canthus of the lower lid is the most common site. Whereas, *squamous cell carcinoma* accounts for only 8% of cases, commonly arising at outer canthus of the lower eyelid. *Sebaceous carcinoma* is less common, contributing about 1% of cases. The tumor may originate from the meibomian glands or the eyelash follicles (glands of Zeis) or from a caruncle. Two thirds of the cases arise from the upper eyelid. *Primary melanoma of the* lid is rare and accounts for less than 1% of all eyelid cancers. In general, malignant melanomas of the lid carries a grave prognosis, because they tend to metastasize early by lymphatics and bloodstream. This is in contrast to malignant melanomas of the bulbar conjunctiva and of the uvea which have a more favorable prognosis.

OCULAR MELANOTIC TUMORS

Conjunctiva

Conjunctival squamous mucosa normally contains mucous glands both intraepithelial, as well as, in the stroma (P 24-2 and P 24-3). *Conjunctival nevi* may pose diagnostic problems because of their hypercellularity, common dense pigmentation and associated lymphocytic infiltration or squamous metaplasia (P 24-4 and P 24-5). It may extend in the subepithelial layer to affect the submucous glands (cystic compound nevus). Cystic glandular inclusions within the tumor favors a benign nevus (P 24-6). Moreover, in benign nevus, melanocytes in the deeper layer of tumor are smaller than those in superficial layers (maturation).

Conjunctival melanosis refers to increase of melanin pigmentation limited to basal epithelial layer, and not associated with atypia. However, when atypical melanocytes are evident in basal layer, the case is considered melanoma in situ. This lesion must be distinguished from squamous carcinoma in situ (P 24-8).

Conjunctival *malignant melanoma* is characterized by destructive invasion erasing glandular structures (P 24-7). The cells in the deep part of the tumor are of the same large size as those near the surface.

Iris

Melanotic tumors of the iris have a most favorable prognosis in view of early detection. Moreover, most of the tumors are low grade spindle cell type.

Ciliary Body and Choroid

Two thirds of these tumors are malignant. Melanomas of ciliary body and choroid (*uveal melanoma*) are more aggressive tumors and usually, are not detected early. However, the ciliary body may rarely be affected by two non-melanotic tumors namely: (1) *Diktyoma* of ciliary body (also known as medulloepithelioma or teratoneuroma). It is a neuroectodermal tumor characterized by tubular structures and may contain teratoid or glial elements. It may be benign or malignant (2) *Leiomyoma* of ciliary body is the second rare tumor. These two tumors must not be misdiagnosed as amelanotic melanoma.

Uveal malignant melanoma is the most common primary intraocular tumor of adults. The median age at diagnosis is 53 years. Lesions believed to predispose to uveal melanomas include: uveal nevi, neurofibromatosis type I, the dysplastic nevus syndrome and the extensive diffuse melanocytosis. Tumors are bilateral in 2% of cases.

Macroscopy

The choroid and ciliary body are more frequent locations than the iris. Three gross types are recognized, namely: (1) localized nodular or collar-stud type, (2) diffuse type and (3) ring melanoma which is observed in cases of tumors of ciliary body with circumferential spread. The tumors appear gray to black in color (P 24-9).

The complications of intraocular melanomas include: hemorrhage, cataract, glaucoma, retinal detachment and inflammation.

Histopathology

Four histologic types are observed: (1) spindle A-cell type have spindle nuclei without nucleoli (Fig 24-1), (2) spindle B-cell type have larger nuclei with prominent nucleoli, (3) epithelioid cell type shows polygonal cells with abundant cytoplasm and distinct cell borders, and (4) mixed cell type contains combinations of the previously mentioned cell types (P 24-10) and (Table 24-1).

Spread

Local spread is common, either by traversing the sclera, or along the course of the optic nerve. Because the eye lacks, lymphatics, uveal melanomas do not spread by this route. About 50% of patients with ocular melanomas die from widespread hematogenous metastases, and the liver is eventually involved in more than 90% of cases, being a site of predilection. The staging of ocular melanoma is presented in (Table 24-2)

Prognostic Factors

The prognosis of the tumor depends on two main established risk factors (Table 24-3):

1. Cell type: Tumors composed entirely of spindle A cells are most favorable. The 10-year survival is presented in (Table 24-4) as related to hitologic type.

2. Tumor size: The 10-year survival of small (less than 11 mm), medium (11-15 mm) and large (more than 15 mm) melanomas are 76%, 51% and 41% respectively (Table 24-5).

Extrascleral spread occurs in 20% of cases and is the main cause of local recurrence after enucleation. The 5-year survival is about 67% for tumors confined within the eye, and only 34% in patients with orbital infiltration.

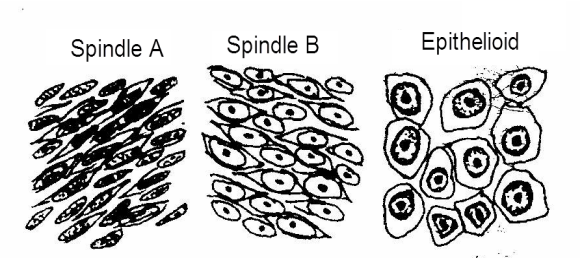

Fig 24-1 *Histologic classification of choroidal and ciliary body melanomas. A. Spindle A: elongated nuclei with fine dispersed chromatin and indistinct nucleoli, B. Spindle B: Spindle cells with small nucleoli and C. Epithelioid type, polygonal cells with prominent nucleoli*

Table 24-1 Callender histologic classification of Choroidal and Ciliary Body Melanomas

Type	Frequency %
Spindle A	5
Spindle B	39
Epithelioid	3
Mixed	45

(Yanoff and Sassani, 2009)

Table 24-2 Staging of Ocular Melanoma

Stage	
I	Confined to iris
II	Confined to ciliary body or choroid
III	Scleral invasion
IV	Extrascleral or distant metastases

(Edge, 2010)

Table 24-3 Risk Factors of Uveal Melanoma

Established
Histologic type
Tumor size
Potential
Chromosomal abnormalities (No 3,6,8)
Mitotic count
Microvessel density
Insulin growth factor receptor (IGF1-R)

(Edge et al, 2010)

Table 24-4 Prognosis of Uveal Melanoma Related to Histologic Type

Type	10-year survival (%)
Spindle A	92
Spindle B	75
Epithelioid	28
Mixed	41

(Yanoff and Sassani, 2009)

Table 24-5 Prognosis of Uveal Melanoma Related to Tumor Size

Tumor size (mm)	10-year Survival (%)
< 11	76
11-15	51
> 15	41

(Silverberg 2006)

RETINOBLASTOMA

Incidence

Retinoblastoma is the most common intraocular tumor in children. The incidence is l/30000. It is most common below the age of 2 years and there is no sex predilection. Clinically, 90 % of the cases are sporadic and 10 % are familial. It is commonly (70%) unilateral. The frequency of bilaterality is 25 % in sporadic type and 90 % in familial type. About 6% of bilateral cases may be associated with pineal tumor (trilateral).

Molecular Oncogenesis

Retinoblastoma is caused by loss or inactivation of Rb gene (13q 14) and is inherited as an autosomal dominant trait. Rb protein normally functions as a negative regulator of the cell cycle. The tumor follows the double-hit model of Knudson which explains the early age of onset and the high incidence of bilaterality in familial cases. Thus, in the familial type, there is an initial germline mutation (first hit) followed by a postnatal second somatic mutation. But, in sporadic cases, both mutations are somatic and postnatal. Retinoblastoma gene inactivation may be caused by viral products (e.g. HPV). Moreover, amplification of other proto-oncogenes (e.g. N-myc) may also play a role in carcinogenesis.

Macroscopy

The tumor appears cream-colored, may be unifocal, multifocal or bilateral. The growth pattern may be endophytic (growing towards the vitreous) or exophytic (growing towards the choroid) with retinal detachment. Clinically, the tumor produces a white pupil (leukocoria or cat's eye reflex).

Histopathology

Retinoblastoma is composed of small round cells with hyperchromatic nuclei (retinoblasts) forming true rosettes around a central lumen (Flexner type rosettes), or forming flower-like structures or fleurettes due to photoreceptor differentiation (Fig 24-2) and (P 24-11 and P 24-12).

Undifferentiated retinoblastoma appears hypercelluar, lacks rosettes and show focal necrosis and calcification.

Differential Diagnosis

Retinoblastoma must be differentiated from other intraocular lesions causing leukocoria or cat's eye reflex (Table 24-6). The term is derived from the Greek (leukos) meaning white and (Kor) meaning pupil. Retinal hamartoma is an example of developmental malformation which may be misdiagnosed as retinoblastoma (P 24-13).

Table 24-6 Causes of Pseudo-retinoblastoma (Leukocoria)

Inflammatory
Endophthalmitis
Panophthalmitis
Parasitic
Toxocara canis larva
Developmental
Persistent primary vitreus
Retinal hamartoma
Preretinal glial nodules
Retroretinal fibroplasias
Congenital nonattachment of retina
Coloboma (absence) of choroid

(Yanoff and Sassani, 2009)

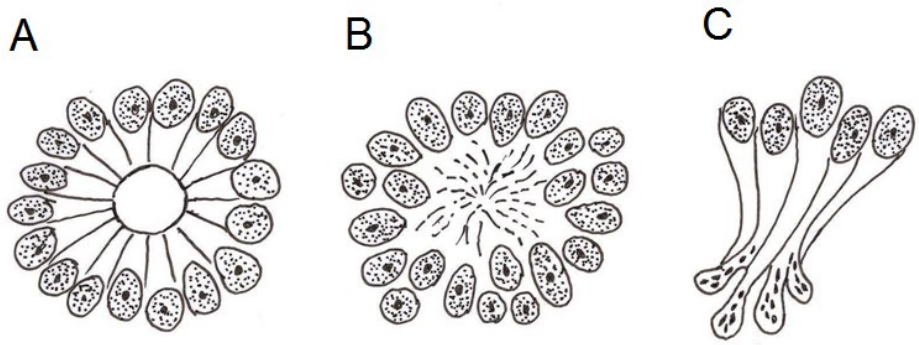

Fig 24-2 *Types of rosettes in retinoblastoma A. Flexner-Wintersteiner true rosette around a central lumen, (the most common). B. Homer Wright rosette around a central fibrillary material (acid mucopolysaccharides) C. Fleurette, grouped like a bouquet of flowers with prominent photoreceptor differentiation.*

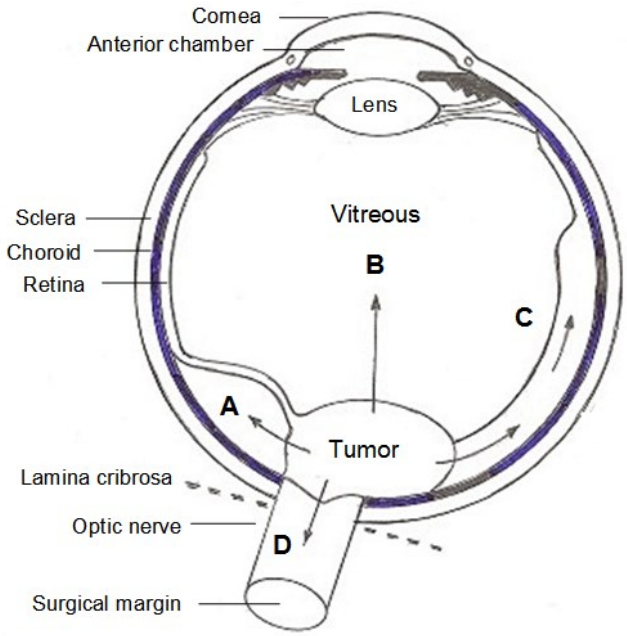

Fig 24-3 *Intraocular spread of retinoblastoma. A. Subretinal spread with detachment, B. Vitreous seedling, C. Transretinal spread and D. Optic nerve invasion. The prognosis is unfavorable in case of spread of optic nerve beyond lamina cribrosa, and worst if the tumor reaches the surgical margin. Invasion of optic nerve sheath leads to extension of tumor to brain through CSF seeding.*

Table 24-7 Pathologic TM Categories of Retinoblastoma

Tumor (T)	
T1	Confined to retina
T2	Optic nerve invasion short of lamina cribrosa, focal invasion of choroid (mass< 3mm)
T3	Optic nerve invasion past lamina cribrosa, Massive choroidal invasion (Mass > 3 mm)
T4	Optic nerve invasion to surgical margin and/or extrascleral spread to orbit
Metastatic (M)	
M1	Metastases present (specify if CNS or other distant sites)

(Edge et al, 2010)

Spread

1. *Local spread*: Intraocular spread occurs in 4 directions, namely: subretinal, vitreous seeding, transretinal and optic nerve invasion (Fig 24-3). Extraocular spread occurs by invasion of sclera through neurovascular channels and hence infiltrates orbital tissue. However, to reach the sclera, the tumor must first infiltrate Bruch's membrane and choroid.

2. *Lymphatic spread* does not occur as long as the tumor is confined within the globe since the eye contains no lymphatics. Only when the tumor reaches the orbit, lymph node metastases will occur at preauricular and jugular cervical chain.

3. *Hematogenous spread*: occurs only when the tumor reaches the vascular choroid. Bones, especially skull, are the main sites of metastases.

Recently, a TM Staging system was introduced for retinoblastoma (Table 24-7) based mainly on extent of invasion of optic nerve and choroid, as well as, the presence or absence of CNS or distant metastases.

Prognosis

The 5-year survival of unilateral retinoblastoma with modern therapy is about 90%. Unfavorable prognostic factors are invasion of optic nerve or massive invasion of choroid. (Table 24-8 and Table 24-9).

Long-term survivors of familial retinoblastoma have an increased risk, of about 20%, to develop extraocular tumors within 10 years, mainly osteosarcoma, Ewing sarcoma, pineoblastoma, lung and breast cancers. This is attributed to the germline mutation of Rb gene which affects all cells of the body.

Table 24-8 High-Risk Factors of Retinoblastoma

Invasion of choroid (distant metastasis)
Invasion of optic nerve (CNS spread)
Bilateral or trilateral (die of other cancers)
Undifferentiated tumor (lack of rosettes)
Recurrence after previous globe sparing
RB mutation or family history

(Edge et al, 2010)

Table 24-9 Grading of Optic Nerve Invasion by Retinoblastoma and Prognosis

Grade	Extent of Invasion	Survival %
I	Short of lamina cribrosa	90
II	To lamina cribrosa	70
III	Past lamina cribrosa	58
IV	To surgical margin	33

(Yanoff and Sassani, 2009)

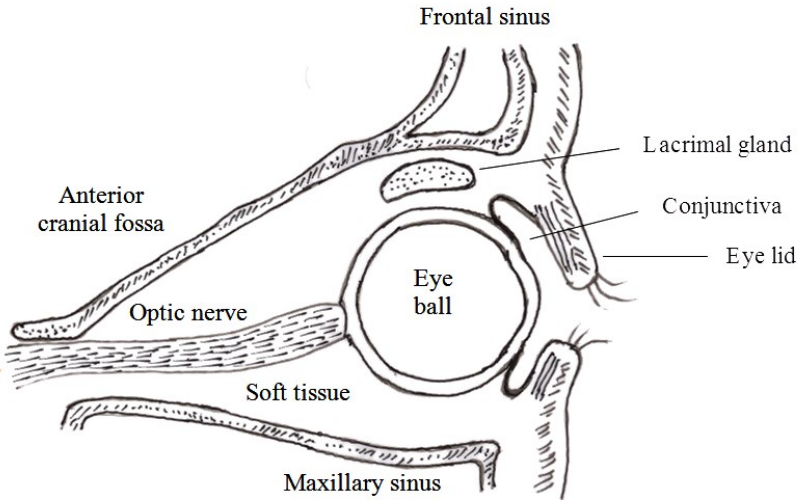

Fig 24-4 *The Anatomy of orbit in a sagittal section. Important relations are the conjunctiva, paranasal sinuses (anteriorly) and anterior cranial fossa (Superiorly). The main contents are: the eye, optic nerve, lacrimal gland, lacrimal sac and soft tissue.*

ORBITAL TUMORS

Anatomy

Six bones contribute in the formation of orbital cavity (frontal, sphenoid, zygomtaic, maxilla, ethmoid and lacrimal bone). Anteriorly, it is related to the upper and lower conjunctival fornices and eye lids. Posteriorly, the orbit communicates through the orbital fissure with the pterygopalatine and infratemporal fossa. The medial wall and floor are thin, related to ethmoid and maxillary sinuses respectively; hence carcinomas of these sinuses can easily invade the orbit.

The orbit contains the globe, ocular muscles, and lacrimal apparatus (Fig 24-4). The optic nerve has a sheath of three layers (pia, arachnoid and dura). The lacrimal gland is located at the upper outer part of orbit and drains into the conjunctival sac, whereas, the lacrimal sac is located at the lower medial part of the orbit and drains into the inferior meatus of nasal cavity.

Pathology

Orbital masses may result from several lesions of diverse biologic behavior which may be classified into the following four main groups.

1. *Tumor-like lesions*: these include cysts, exophthalmos of thyrotoxicosis, reactive lymphoid tissue or pseudolymphoma, idiopathic lymphoid tissue (Castleman disease and Wegener granuloma) and lymphoepithelial lesion of lacrimal gland (Sjogren syndrome) which corresponds to mucosa-associated lymphoid tissue (MALT).

2. *Benign tumors*: mainly angiomas, lipoma and osteoma.

3. *Primary malignant tumors* related to the lacrimal gland, lacrimal sac, optic nerve, soft tissue or extranodal lymphoma.

4. *Secondary tumors* reach the orbit from intraocular malignancies (melanoma and retinoblastoma), from orbital bone (Langerhans histiocytosis and bone sarcomas), from ethmoid or maxillary carcinoma, and finally, hematogenous metastases.

The profile of orbital tumors is distinctively different in children as compared to adults (Table 24-10). The following are illustrative examples: (1) *Lacrimal tumors* are histologically similar in type to salivary tumors and occur mainly in adults (P 24-14). (2) In children, *pilocytic astrocytoma* (previously called optic glioma) commonly affects the optic nerve (P 24-15), whereas *meningiomas* predominate in adults. (3) In the pediatric age group, rhabdomyosarcoma is the most common orbital soft tissue tumor (P 24-16), but, in adults, malignant fibrous histiocytoma (MFH) and inflammatory myofibroblastic tumor are mostly seen. (4) In lymphoid malignancies, leukemic infiltrates and Burkitt lymphoma are commonly observed in children, whereas, MALT lymphoma and large cell NHL predominate in adults. These tumors must be distinguished from other reactive and inflammatory lymphoid lesion that commonly arises in the orbit (pseudo-lymphoma). The diagnostic features that help in the differential diagnosis are listed in (Table 24-11).

Table 24-10 The Profile of Pediatric and Adult Orbital Tumors Compared

Lesion	Pediatric	Adults
Cystic	Dermoid, Teratoma	Mucocele
Vascular	Capillary Hemangioma	Cavernous or angiomatosis
Neural	Neurofibroma	Neurilemmoma
Ocular	Retinoblastoma	Melanoma
Optic nerve	Pilocytic astrocytoma	Meningioma
Lacrimal tumors	Rare	Common
Sarcomas	Rhabdomyo-sarcoma	Non Rhabdomy-osarcom, MFH
Bone tu-mors	Langerhans histiocytosis	Osteosarcoma
Non Hodgkin lymphoma	Leukemia, Bur-kitt	MALT type
Metastases	Neuroblastoma, Wilms tumor	Breast, lung, prostate

(Fletcher, 2007) MFHS malignant fibrous histio-cytoma

Table 24-11 Histopathology of Orbital Lymphoma and Pseudolymphoma Compared

Feature	Lymphoma	Pseudo-lymphoma
Cell population	Monomorphic	Polymorphic
Germinal centers	Absent	Present
CD5	Positive	Negative
Clonality [a]	Monoclonal	Polyclonal
Phenotype (B/T)	Monopheno-typic (>80%)	Polypheno typic
Plasma cell inclusions	Dutcher bodies [b]	Russel bodies [c]
Epidermo-tropism	Present	Absent
Vascularity	Absent	Present
Fibrosis	Absent	Present

(a) Kappa/Lambda restriction (b) Intranuclear PAS positive immunoglobulin inclusions (c) In-tracytoplasmic immunoglobulin inclusions

TUMORS OF THE EAR

Anatomy

The ear is divided into external, middle and internal ear (Fig 24-5). The *external ear* includes the auricle and external auditory canal which ends at the tympanic membrane. The lining of external auditory canal is skin with accessory structures (hair, sebaceous and ceruminous glands which are modified sweat glands). The lymphatics of external ear drain to the preauricular parotid nodes, which ultimately drain into the jugular chain of cervical lymph nodes.

The *middle ear,* located in the petrous temporal bone, contains the ossicles and tympanic para-ganglia. The mucosa is lined by cuboidal or flat respiratory epithelium interspaced by secretory cells. It communicates anteromedially with the nasopharynx through the Eustachian tube, and posteriorly with the mastoid air cells.

The *inner ear* contains the cochlea and semi-circular canals and related endolymphatic sac (res-ponsible for hearing and balance) and is supplied by the cochlear and vestibular branches of the auditory (8th) cranial verve (Fig 24-5). This nerve enters the internal ear (in association with facial nerve) through the internal auditory canal.

The presence of anatomic canals related to the ear (external auditory canal, Eustachian tube and internal auditory canal) provide pathways for the spread of malignant tumors to the ear from nearby structuses (auricle, parotid, nasopharynx or intra-cranial cavity).

Pathology

Malignant tumors of the ear are rare, contributing only 1% of all cancers. However, they are important because of their location, since even benign tumors will cause serious clinical compli-cations. They are best classified on anatomic basis (Table 24-12). This helps to reach a correct diag-nosis since most of the tumors are site specific.

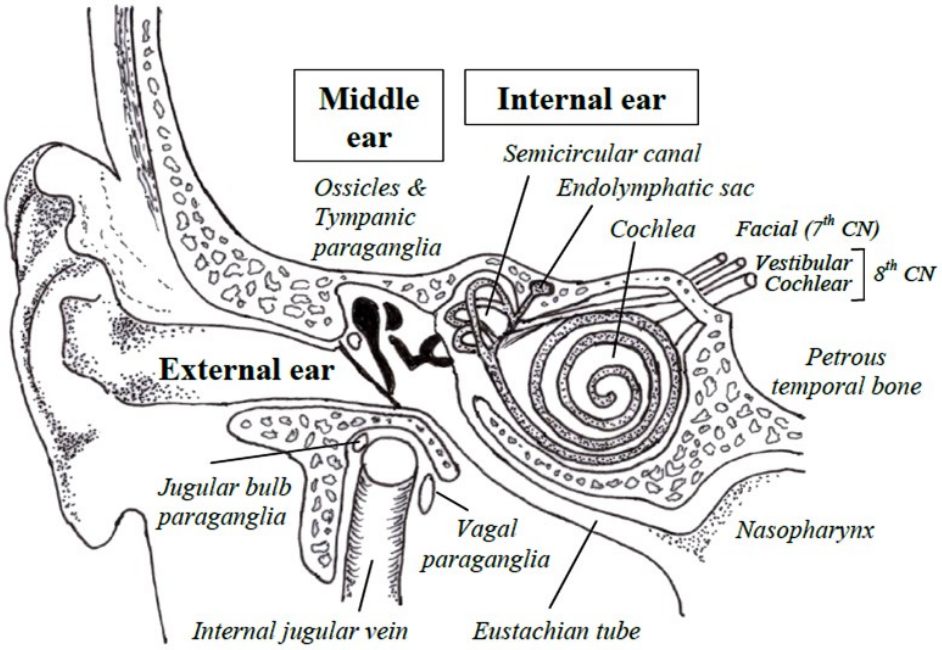

Fig 24-5 *Anatomy of the ear in a coronal section. It is divided into external, middle and internal ear. Their contents and relations are demonstrated in the Figure*

Table 24-12 Classification of Tumors of the Ear

External ear
Squamous cell carcinoma
Ceruminous adenocarcinoma
Adenoid cystic carcinoma
Malignant melanoma
Osteoma
Middle ear
Cholesteatoma
Ectopic tumors (glial, meningeal, or salivary
Squamous cell carcinoma
Papillary adenocarcinoma
Jugulotympanic paraganglioma
Inner ear
Vestibular schwannoma
Meningioma
Endolymphatic sac tumors (ELST)
Secondary tumors
Local invasion from carcinoma of: parotid, nasopharynx or chordoma
Hematogenous metastases

In adults, the majority of tumors affect the external ear (due to solar radiation and inflammation). About 60% of tumors occur in the auricle alone. Squamous cell carcinoma predominates in external and middle ear tumors of adults. Conversely, rhabdomyosarcinoma is the most common tumor in children. The following are illustrative examples:

1. Ceruminous adenomas and adenocarcinomas arise in the outer part of external auditory canal from the apocrine sweat glands (P 24-19). The myoepithelial cell layer is preserved in benign tumors but lost in malignant ones.

2. Cholesteatoma is a misnomer as it contains keratin not cholesterol and it is not a neoplasm. The mucosal lining of middle ear, normally respiratory columnar, is changed into squamous with production of abundant keratin (P 24-20). The histogenesis is obscure, may be the result of metaplasia or ectopia.

3. Paraganglioma of the middle ear may arise from glomus jugulare or glomus tympanicum (Fig 24-5). Most of these tumors are benign, and locally invasive with high tendency to local recurrence (50%) but low risk of distant metastases (5%).

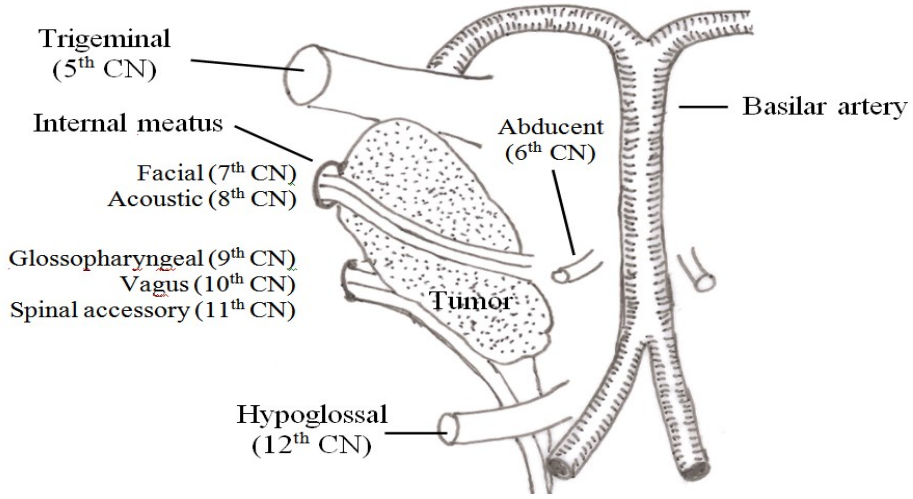

Fig 24-6 *Anatomy of cerebellopontine angle. The close relation of acoustic neurinoma to several cranial nerves (especially 7 and 8) is demonstrated. Deafness, imbalance and facial palsy are early clinical manifestations*

4. Acoustic neurinoma (vestibular schwannoma) account for about 7% of all intracranial tumors, 78% arise from the vestibular branch of eighth cranial nerve at the cerebellopontine angle (Fig 24-6). About 95% of cases are sporadic, affects adults and are unilateral. However, 5% are familial, affecting children, present bilaterally and associated with NF-2 tumor suppressor gene mutation. The protein product of this gene (Merlin) was confirmed to have a negative effect on cell proliferation, particularly cell contact inhibition. The histology of the tumor is characterized by the palisade pattern of neurilemmal cells and symplastic changes (P 24-22 and P 24-23). The latter, must not be confused with malignancy.

5. Meningiomas of internal ear may arise intracranially and reach the ear through the internal ocuditory canal or arise from ectopic meningothelial cells in the ear (P 24-24).

6. Endolymphatic sac tumors (Fig 24-5 and P 24-25). This rare tumor is considered benign but locally destructive. The histology shows follicular and papillary structures.

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