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Anatomy

The periocular region is a common site for head and neck skin malignancy presentation. It is bounded by the brow superiorly, the infraorbital rim inferiorly, the nose medially and the lateral orbital rim. The main functions of the eyelids are to protect the eye by acting as a barrier to light and physical trauma, as well as prevent dessication by means of tear production. Although they are thin structures, both the upper and lower lids contain distinct layers which can be split into anterior and posterior lamellas. The anterior lamella consists of skin and the orbicularis oculi muscle. The posterior lamella consists of the tarsus and the conjunctive. The upper lid is much thinner than the lower lid.

The tarsus provides rigidity to the upper and lower lids. It is made up of dense, fibrous tissue and contains meibomian glands. The tarsus is about 25 mm in horizontal length, one mm thick and varies in height. The upper tarsal plate is about 10 mm in height. The lower tarsal plate is 4 mm in height.

The orbicularis oculi muscle is a sphincter that facilitates eye closure. Since there is very little subcutaneous tissue in the periocular region, it lies just below the skin. The periosteum and orbital septum lie one layer deep to the orbicularis muscle. The orbital septum is a fascial barrier that prevents the spread of superficial infection into the orbit.

Basal Cell Carcinoma (BCCA)

Basal cell carcinoma is the most common skin malignancy. It is locally destructive and slow growing with an extremely low metastatic rate (0.0028 to 0.55%). Most cases (80%) present in the head and neck because of its chronic sun exposure. Almost all (80-95%) of lid and medial canthal malignancies are BCCA. In the periocular region, the lower lid is the most common site (43%), followed by the medial canthus (26%), upper lid (12%) and the lateral canthus (8%).

The incidence of BCCA is increasing up to 10% per year. In North America the overall incidence is 300/100,000. In Australia, the incidence is 1772/100,000 for men and 1610/100,000 for women. The main risk factors for BCCA are sun exposure and fair skin. Immunocompromised patients are at higher risk also. Solid organ transplant recipients are at increased risk, especially cardiac transplant patients. There are patients with a genetic predisposition for BCCA, including those with Basal Cell Nevus syndrome, xeroderma pigmentosum, albinism and Bazex syndrome.

Once a patient is diagnosed with BCCA, a diligent search for other suspicious lesions must be performed. Up to 60% of patients present with multiple lesions and between 20-40% of lesions are missed clinically. Some patients present with large and locally destructive lesions that are referred to as rodent ulcers. Periocular lesions typically grow and extend laterally because of the tarsal plate. If left untreated, the lesions can extend into the orbit via the periosteum. They can eventually enter the cranial cavity and paranasal sinus involvement for large, neglected lesions is common.

Microscopically, BCCA is a proliferation of basaloid cells from the epidermis that invade the dermis. There are four major types of BCCA: nodular, superficial, infiltrative and mixed. Nodular BCCA makes up 50% of lesions and presents grossly as a pearly papule with a rolled border and telangiectasias. A linear variant of nodular BCCA tends to occur in the periocular region and may be more aggressive clinically. Superficial BCCA accounts for 15% of lesions and is more common on the trunk than the head and neck. Grossly, it presents as a scaly, erythematous plaque or patch that may mimic psoriasis, discoid eczema or carcinoma in situ. Infiltrative BCCA makes up 10-20% of cases. It presents as a more indurated lesion with indistinct margins. Microscopically, the tumor cells are parts of irregular groups. The morpheic variant is marked by a dense, sclerotic stroma and it has a higher rate of perineural invasion. Perineural invasion (PNI) is an uncommon feature for BCCA, occurring in one to three percent of cases histologically. When present, PNI is a risk factor for recurrence.

High risk lesions occur in the setting of prior non-surgical therapy, recurrence and prior incomplete excision. Other risk factors include: size greater than 2 cm, H-zone location, medial canthal extension, poorly defined margins, infiltrative/morpheic/micronodular subtypes, perineural invasion and Immunosuppression..

Molecular markers associated with BCCA include p53 and Bcl-2. p53 is associated with sclerosing subtypes and more aggressive behavior. In contrast, Bcl-2 is associated with low risk lesions and slower tumor growth. One unique molecular difference between BCCA and SCCA is that nearly all BCCA lesions express Gli1. This protein is regulated by sonic hedgehog (Shh) transcription factors. The deregulation of the Shh-Gli pathway has been found in both familial and sporadic cases of BCCA.

The Australian Mohs Database review of periocular BCCA shows that nodular lesions are the most common primary BCCA (45%) while infiltrating lesions were the most common recurrent lesions (39%). The overall recurrence rate for periocular BCCA is between 1-35% depending on the surgical treatment modality. Two thirds of recurrences happen within three years of treatment and eighteen percent of recurrences happen between five and ten years post treatment. The best treatment is Mohs micrographic surgery which has been shown to have a 1-

2% recurrence rate for primary tumors and 5.6-7.8% recurrence rate for recurrent tumors. For non-Mohs excision, recurrences range widely. En face frozen section techniques, which mimic Mohs excision has similarly low recurrence rates of 2.1% for primary tumors and 4.4% for recurrent tumors.

Squamous Cell Carcinoma (SCCA)

SCCA accounts for 5-10% of periocular malignancies. It typically presents as a keratinzed plaque that eventually erodes tissues and ulcerates. It is characterized by more rapid growth rates and a much higher metastatic rate (4-45%) when compared to BCCA. The overall metastatic rate is less than 10%. Its incidence mirrors BCCA when comparing Australia to North America but the overall incidence is much lower. For Australian men the incidence is 600/100000, women 298/100000. In the USA male incidence ranges between 40-158/100000 and women 13-56/100000.

In the periocular region most lesions are well differentiated (50%). Moderately differentiated lesions make up 37% and poorly differentiated lesions occur in 6% of cases. As with BCCA, perineural invasion is a poor prognostic indicator but it is much more common (2.5-14%). PNI is associated with large tumors (> 2cm), head and neck primary, prior recurrence, poor differentiation and overall aggressive tumor behavior.

High risk lesions occur in the setting of incomplete excision, recurrence and prior non-surgical therapy. They also occur on the lip, ear, lids. Other risk factors include: size greater than 2 cm, poor differentiation, deep lesions (greater than 4 mm), perineural invasion, scar carcinomas and immunocompromised patients.

Patients that fall into the high risk category should undergo a more extensive evaluation of the neck and parotid gland. These areas should be imaged appropriately and treatment adjusted accordingly. Patients at high risk should be counseled regarding parotidectomy and neck dissection. Patients with advanced parotid disease (nodes greater than 6 cm, facial nerve or skull base involvement) have a statistically significant lower survival rate.

The Australian Mohs database for periocular SCCA shows that 5 year local recurrence rates for non-Mohs therapies range between 3-23%. For patients treated by Mohs techniques, the study demonstrated a recurrence rate of 4%. Based on prior Mohs studies, excision margins of 4 mm for low risk SCCA and 6 mm for high risk SCCA should produce negative margins in 95% of patients. High risk lesions should be excised with subcutaneous fat because up to 30% invade to this level.

Hybrid lesions have been named Basosquamous carcinoma. The presence of both squamous cell characteristics and basal cells is a confounding sight. There are three reasons for this to happen. Differentiation from BCCA to SCCA or vice versa is theoretically feasible and immunostaining has demonstrated true basal and squamous transition zones in lesions. Another possibility is the presence of individual BCCA and SCCA lesions occurring at the same time and lie adjacent to one another. The third possibility is a variant of nodular BCCA named keratinizing BCCA. It is important to make the distinction between these possible etiologies because treatment regimens will differ. Keratinizing BCCA can be treated as a low risk lesion if it is recognized. Likewise, adjacent lesions, or collision tumors, may be treated as separate low risk lesions. True differentiation between tumor types is considered to be a highly aggressive lesion with reported recurrence rates of 52% and metastatic rates of 9.7%.

Mohs micrographic surgery

Frederick Mohs introduced his excision technique in 1941. His initial report on 1986 periorbital cases boasts a 5 year cure rate of 99% for BCCA and 98% for SCCA. These results have been reproduced by numerous studies. The technique hinges on the fact that the entire surface of the excised lesion is examined microscopically. If any margins are positive, further excision is performed. The lesions are sliced in the plane of the lesion instead of vertically. Each cycle of excision and microscopic evaluation is termed a stage. The other key factor for Mohs surgery is that the surgeon and pathologist are the same person. The precision of Mohs surgery allows for maximal tissue preservation and function of surrounding structures. In the periocular region, BCCA Mohs defects are 4.2 to 4.6 times larger than the original tumor. Morpheic lesions are up to 6.1 times larger than the original tumor and require the most stages. SCCA Mohs defects are up 2.6 times larger than the original tumor.

Non-Mohs excision

Mohs surgery is not widely available; so many surgeons have to excise cutaneous lesions without the precision that it provides. Traditional surgical excision with delayed margin evaluation has recurrence rates ranging from 23 to 35%. Other non-Mohs modified margin control techniques have recurrence rates that match standard Mohs surgery. Standard excision with immediate repair and postoperative histology for BCCA is not uncommon. Site directed frozen sections in this technique are not always accurate and re-excision in a repaired site may not be straight forward if a rotational flap was utilized. Excision with delayed repair, leaving the wound open while traditional paraffin sections are processed overnight yields good results but is not as expedient as Mohs. Excision with en face frozen section margin control mirrors Mohs results but requires the combined effort and coordination of both the surgeon and pathologist in the operating room.

For periocular BCCA, Hamada et al showed that initial tumor excision with 4 mm margins completely removed the tumor in 84% of lesions. Re-excision of positive margins only revealed malignant cells in 53% of cases. The 5 year recurrence rate was 4.35%. This study utilized standard paraffin sections for histologic analysis and performed delayed closure for poorly demarcated tumors or large defects requiring complex repair. Khandwala et al had a recurrence rate of 1.23% for primary BCCA lesions and 12.5% for recurrent BCCA lesions using an overnight paraffin section analysis of the margins. Wong et al use en-face frozen section analysis that is similar to Mohs because of the quick feedback and communication between the pathologist and surgeon.

For SCCA, frozen section control of margins is much more effective. Standard surgical excision for periocular SCCA has a recurrence rate of 2.8% at 6 years. Goysal et al reviewed 76 patients over ten years with periocular SCCA. The lesions were excised with 4-5 mm margins and were closed primarily if possible or delayed if the defects were large. Post op radiation therapy was given to 20% of patients. Patients with lesions less than one centimeter (n=21) had no recurrences. One of 22 patients with lesions greater than one centimeter recurred and almost 50% of patients with orbital invasion recurred (n=33).

Radiation Therapy (XRT)

Primary radiation therapy is reserved for periocular skin malignancies is a useful treatment option. Patients that are poor surgical candidates, have unresectable tumors or do not desire surgery should be advised that XRT is an option. Relative contraindications to XRT are patients younger than sixty, readily excisable tumors and lesions lying over the lacrimal gland. Side effects of XRT in the periorbital region include: erythema, skin atrophy, subcutaneous fibrosis, ulcers, epiphora, dry eyes, cataracts, neovascular glaucoma, retinopathy and optic neuropathy. Zagrodnik et al reviewed 148 patients with BCCA. These lesions were treated with primary XRT and were located on all body sites. The overall recurrence rate for all sites was 15.8%. Nodular lesions had a 8.2% rate, superficial 16% and sclerosing 27.2% recurrence rate. Rodriguez-Sains et al reviewed 631 patients with periocular BCCA, of which 55 were treated with primary XRT. The average time to recurrence following therapy was 5.3 years. There were 7 recurrences, which were all located in the medial canthus. Almost half of patients that recurred required orbital exenteration. Lesions greater than one centimeter were much more likely to recur also (9.5% vs 2%).

Orbital invasion

Because of the orbital septum, orbital invasion by periocular skin malignancies is rare. SCCA is more likely to invade due to its more aggressive nature, with reported frequencies ranging from 0.2 to 8.2%. BCCA can invade the orbit, but at a lower rate (0.8 to 3.6%). The time from first detection of the lesion and orbital invasion ranges from 2-25 years. SCCA lesions averages only one year from detection to invasion, while BCCA lesions average 9.8 years. The most common signs and symptoms of orbital invasion are: painless mass, tumor fixation to bone, limited ocular motility, extreme gaze diplopia (early sign, globe displacement, ptosis and proptosis (uncommon). Tumors spread along the periosteum into the orbit but rarely invade the globe itself. They can spread intracranially via the superior orbital fissure and intranasally. Perineural invasion is found in 19% of patients with orbital invasion. Patients with suspected orbital invasion should undergo both CT and MRI in order to evaluate bony erosion, involvement of orbital contents and intracranial spread. Orbital exenteration is the standard therapy with or without radiation therapy depending on the tumor characteristics and margin status. Leibovitch et al’s review of BCCA patients found that 56% of patients underwent exenteration without any radiotherapy. 19% of patients underwent exenteration with post op radiotherapy, 6% underwent excision, 9% underwent excision with post op radiotherapy and 6% underwent primary radiotherapy.

Orbital exenteration

About half of patients referred to ophthalmologists for exenteration have periocular cutaneous malignancies. Orbital exenteration removes the globe and all orbital contents within the bony socket. The excision may extend to include the eyelids, bony orbital walls, nasal sinuses and skull base. Absolute indications for orbital exenteration include: orbital apex involvement, extraocular muscle involvement, bulbar conjunctiva involvement, sclera involvement, lid involvement beyond a reasonable hope for reconstruction and nonresectable full thickness invasion through the periorbita into the retrobulbar fat. The overall mortality rate for exenteration patients is 93% after one year but decreases to 57% at five years and 37% at ten years. In 54% of cases, mortality is linked to the orbital tumor but 38% of patients die of unrelated medical conditions and 8% are due to metastatic disease. Interestingly, there is no significant difference in the 5 year survival between BCCA lesions and all other tumors requiring exenteration.

Lid reconstruction

Reconstruction of the eyelids requires a detailed understanding of their anatomy and function. The basic principles of closure are the same for both upper and lower lid defects. Small lesions which are up to 33% of the lid may be closed primarily. Primary closure can still be performed for defects measuring 40% of the lid surface if the patient has lid laxity. Rotational flaps may be used for medium sized defects between 33-50% of the lid. For defects greater than 50% of the lid, bridging procedures are utilized to borrow tissue from the opposite lid.

Primary closure reapproximates the tarsus, orbicularis, conjunctiva and skin, using the grey line as a guide. To decrease tension, a canthotomy and cantholysis may be performed.

The primary rotational flap used for medium sized defects is the Tenzel flap. This flap is a semicircle based at the lateral canthus. A myocutaneous flap is raised and cantholysis and canthotomy are performed. The flap is then advanced and reapproximated in layers.

The Hughes procedure is a bridging procedure for the large lower lid defects. It uses the upper lid posterior lamella to create a new posterior lamella for the lower lid. A tarsoconjunctival flap is raised from the upper lid. This flap is sutured to the lower lid remnant to recreate the conjunctival layer. The lower lid anterior lamella is recreated using local myocutaneous flaps or skin grafts. The flap is left in place for a few weeks and then is taken down. Another option for large lower lid lesions is the single stage Mustarde cheek flap.

Upper lid lesions are repaired using the same basic scheme. The Tenzel flap is inferiorly oriented for upper lid repairs. For large upper lid regions, the Cutler Beard bridge flap may be utilized. This flap takes a full thickness pedicled graft below the ciliary line on the lower lid. The flap is split into the conjunctiva and the myocutaneous portion. Once split, the tarsus can be reconstructed using septal or conchal cartilage. The new anterior lamella is then sutured in to place. The flap is taken down after a few weeks and closed primarily.

Orbital exenteration reconstruction

The reconstructive ladder for the exenterated orbit starts with local options including spontaneous granulation, and skin grafting. Secondary intention healing takes several months and can produce skin contractures, brow ptosis and is at risk for infection. Skin grafting the site allows the cavity to heal much more quickly with less contracture. Regional options in clued temporalis muscle flaps, cervicofacial flaps, temperoparietal flaps, forehead flaps and frontal flaps. Distal options are typically microvascular free flaps. In patients with large cavities, rectus flaps are commonly used. With the advances in anterolateral thigh flap harvest, this flap may be used more frequently because of the more minimal donor site problems and the flap’s ability to fill in large defects. Free flap reconstruction has opened the door to surgical treatment of previously unresectable lesions. Craniofacial resections with dural exposure are now more easily repaired with free flaps. Also, the well vascularized tissue is able to withstand post op radiation more easily than patients that heal by secondary intention or are akin grafted. Another reasonable alternative to reconstruction is prosthesis placement. Prosthetics are used in conjunction with local and regional reconstructions because the prosthesis is able to fit into the repaired cavity.

Bibliography

1. Arlette, JP et al. Basal Cell Carcinoma of the Periocular Region. Journal of Cutaneous Medicine and Surgery. Vol 2. Number 4, 1998.
2. Prabhakaran, V et al. Basal Cell Carcinoma of the Eyelids. Comprehensive Ophthalmology Update. Vol 8, Number 1. 2007.
3. Zagrodnik, B et al. Superficial Radiotherapy for Patients with Basal Cell Carcinoma Recurrence Rates, Histologic Subtypes, and Expression of p53 and Bcl-2 . Cancer 2003;98:2708–14.
4. Carter, KD et al. Clinical Factors Influencing Periocular Surgical Defects After Mohs Micrographic Surgery. Ophthalmic Plast Reconstr Surg. 1999 Mar;15(2):83-91.
5. Malhotra, R et al. The Australian Mohs Database, Part I Periocular Basal Cell Carcinoma Experience over 7 Years. Ophthalmology 2004;111:624–630
6. Malhotra, R et al. The Australian Mohs Database, Part II Periocular Basal Cell Carcinoma Outcome at 5-Year Follow-up. Ophthalmology 2004;111:631–636.
7. Kumar, B et al. A review of 24 cases of Mohs surgery and ophthalmic plastic reconstruction. Australian and New Zealand Journal of Ophthalmology (1997) 25, 289-293.
8. Altaba, AR et al. Gli and Hedgehog in Cancer: Tomours, Embryos and Stem Cells. Nature Reviews. 2002. Vol 2; 361-372
9. Malhorra, R et al. The Australian Mohs Database Periocular Squamous Cell Carcinoma Ophthalmology Volume 111, Number 4, April 2004
10. Goysal, HG et al. Invasive Squamous Cell Carcinoma of the Eyelids and Periorbital Region. Br J Ophthalmology. 2007;91:325-329.
11. O'Brien, CJ et al. The Parotid Gland as a Metastatic Basin for Cutaneous Cancer. ARCH OTOLARYNGOL HEAD NECK SURG/VOL 131, JULY 2005
12. Maloney, ML. What is Basosquamous Carcinoma? Dermatol Surg 26:5:May2000.
13. Carter, KD et al. Clinical Factors Influencing Periocular Surgical Defects After Mohs Micrographic Surgery. Ophthalmic Plast Reconstr Surg. 1999 Mar;15(2):83-91.
14. Kumar, B et al. A review of 24 cases of Mohs surgery and ophthalmic plastic reconstruction. Australian and New Zealand Journal of Ophthalmology (1997) 25, 289-293.
15. Kumar, B et al. A review of 24 cases of Mohs surgery and ophthalmic plastic reconstruction. Australian and New Zealand Journal of Ophthalmology (1997) 25, 289-293.
16. Hamada, S et al. Eyelid basal cell carcinoma: non-Mohs excision, repair, and outcome. Br J Ophthalmol 2005;89:992–994.
17. Khandwala, MA et al. Outcome of Periocular Basal Cell Carcinoma Managed by Overnight Paraffin Section. *Orbit*, 24:243–247, 2005
18. Wong, VA et al. Management of Periocular Basal Cell Carcinoma With Modified En Face Frozen Section Controlled Excision. Ophthalmic Plastic & Reconstructive Surgery. Volume 18(6), November 2002, pp 430-435
19. Prabhakaran, V et al. Basal Cell Carcinoma of the Eyelids. Comprehensive Ophthalmology Update. Vol 8, Number 1. 2007.

20. Rodriguez-Sains, RS et al. Radiotherapy of Periocular Basal Cell Carcinomas: Recurrence Rates and Treatment with Special Attention to the Medial Canthus. Br Journ of Ophthalmology, 1988, 72, 134-138.
21. Amoaku, W.M.K. et al. Orbital infiltration by eyelid skin carcinoma. International Ophthalmology 14: 285-294, 1990.
22. Leibovitch, I et al. Orbital Invasion by Periocular Basal Cell Carcinoma. Ophthalmology 2005;112:717–723
23. Howard, G et al. Clinical Characteristics Associated with Orbital Invasion of Cutaneous Basal Cell and Squamous Cell Tumors of the Eyelid. American Journal of Ophthalmology. 113:123-133, Feb, 1992.
24. Tyers, AG. Orbital exenteration for invasive skin tumours. Eye (2006) 20, 1165-1170.
25. Nassab, RS et al. Orbital exenteration for advanced periorbital skin cancers: 20 years experience. Journal of Plastic, Reconstructive & Aesthetic Surgery (2007) 60, 1103-1109
26. Rahman, I et al. Mortality following exenteration for malignant tumours of the orbit. Br. J. Ophthalmol. 2005;89;1445-1448
27. Kroll, D. Management and reconstruction of periocular malignancies. Facial Plastic Surgery. 2007. Vol 23(3): 181-189.
28. Levin, PS et al. Orbital exenteration the reconstructive ladder. Ophthalmic Plastic and Reconstructive Surgery 7(2):84-92, 1991.
29. Wax, MK et al. The Role of Free Tissue Transfer in the Reconstruction of Massive Neglected Skin Cancers of the Head and Neck. Arch Facial Plast Surg. 2003;5:479-482.
30. Chen, WP. Oculoplastic Surgery The Essentials. 2001.Thieme Medical Publishers.