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Orbital Exenteration: A 15-Year Study of 38 Cases

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Purpose: To determine the clinical indications and outcomes after orbital exenteration when histologic margins were reported as "clear," examining factors affecting local and systemic recurrences and mortality.

Methods: Retrospective case review of exenterations performed in Sydney Eye Hospital in Sydney, Australia, between 1990 and 2004. Reviewed data indications for exenteration, histopathologic diagnosis, and recurrences on follow-up.

Results: Secondary intraorbital spread of malignant adnexal tumors was the most common indication for exenteration (34 of 38). Among these, the site of the primary neoplasm was the eyelid in 19 cases and the ocular surface in 12 cases. Exenteration was total in 26 cases, subtotal in 8 cases, and extended in 4 cases. In 11 cases, a dermis-fat graft was used for socket reconstruction; 24 cases were allowed to granulate spontaneously. The average healing time was 5 months (range, 4–6 months) for spontaneous granulation, and 6 weeks (range, 4–8 weeks) for dermis-fat grafts. Perineural spread was demonstrated histopathologically in 7 specimens. During follow-up (median, 48 months), there were 9 recurrences (23.7%): 3 local and 6 systemic. Seven patients (18.4%) died of the disease during the follow-up period.

Conclusions: Dermis-fat grafts for reconstruction of the exenterated socket seem to optimize the aesthetic results. The first year is the most important period for follow-up of local recurrences, but systemic examination is needed for the longer follow-up. This may have implications in terms of reconstruction and adjunctive treatment following exenteration surgery.

Orbital exenteration involves removal of the soft-tissue contents of the orbit, including the globe.[1] It is indicated in cases of extensive spread of a malignant tumor or a nonresponsive infection.[1,2] Exenteration may be subtotal, total, or extended. The traditional procedure includes the removal of the globe, eyelids, conjunctiva, and entire orbital contents including the periorbita.[3] "Superexenteration" or "extended exenteration" may include the bony orbital walls, adjacent paranasal sinus tissues, and/or intracranial tissue. Subtotal exenteration involves removal of the globe, conjunctiva, and extraocular muscles, without a subperiosteal dissection.[4] Orbital exenteration is infrequently performed. In certain orbital malignancies, such as those derived from eyelid basal cell carcinoma (BCC) or squamous cell carcinoma (SCC), more conservative management may provide local tumor control similar to that afforded by exenteration.[3,4]

In earlier studies, secondary orbital spread from eyelid, intraocular, and conjunctival malignant tumors was the most frequent indication for exenteration (accounting for 70% to 81% of cases),[5,6] followed by primary orbital malignant tumors. Other rarer indications for exenteration have included sclerosing inflammatory pseudotumors and invasive fungal disease of the orbit.[7]

This study of exenterations performed at a tertiary eye hospital over a 15-year period was intended to determine the clinical indications for the procedure and to review the clinical outcomes when histopathologic margins were reportedly clear, looking specifically at factors affected local and systemic recurrence and mortality.

METHODS

A medical record search was conducted for all patients undergoing exenteration surgery at Sydney Eye Hospital, Sydney, NSW, Australia, from 1990 to 2004. The following parameters were extracted from patient records: age at first presentation, duration of treatment, treatment modalities prior to exenteration, laterality, tumor size and location, biopsy result, type of surgery, and type of socket reconstruction.

In cases of cutaneous malignancy, clinically clear skin margins and orbital apex tissues were sampled and submitted for frozen section examination at the time of surgery. Histopatho-

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TABLE 1. *Indications for exenteration according to the site of primary neoplasm, and histhopathologic diagnosis (n = 38).*

Site of primary neoplasm	No. of cases (%)	Histopathologic Diagnoses (number of cases)
Eyelid malignancy	19 (50%)	BCC (9), SCC (6), SGC (4)
Ocular surface malignancy (cornea and conjunctiva)	12 (31.5%)	SCC (9), MM (2), SGC (1)
Intraocular malignancy	3 (7.8%)	MM (3)
Lacrimal gland malignancy	1 (2.6%)	Pleomorphic adenocarcinoma
Lacrimal sac malignancy	1 (2.6%)	BCC
Orbital infections	2 (5.3%)	†MRSA socket infection (1), mucormycosis (1)

BCC = Basal cell carcinoma, SCC = Squamous cell carcinoma, SGC = Sebaceous gland carcinoma, MM = Malignant melanoma, †MRSA = Methicillan-resistant Staphylococcus aureus.

logic examination of exenteration specimens was performed by a sampling sectioning process. The histopathology results included the adequacy of surgical margins in the exenteration specimen. In cases of histopathologically incomplete excision, patients were offered additional surgery or radiotherapy.

Postoperative complications—and the development of local tumor recurrence, perineural spread, or systemic metastasis—were reviewed through hospital and treating-physician files.

Statistical analysis included independent samples *t* test for the comparison between BCC and SCC eyelid tumor presentation and operation age. The Kaplan-Mayer survival analysis was used to calculate the cumulative survival rate after orbital exenteration.

RESULTS

Thirty-eight patients underwent exenteration during the study period. There were 26 men and 12 women. The mean age of patients at the time of first presentation was 67.7 years (range, 35–93 years) and the mean age at the time of exenteration was 69.9 years (range, 36–93 years). Twenty exenterations involved the right side; 18, the left. The median follow-up period following exenteration was 48 months (range, 30–160 months).

The indications for exenteration were life-threatening orbital malignancy in 36 cases and life-threatening orbital infection in 2 cases. The specific conditions were: eyelid malignancies in 19 cases (50%; 9 BCC, 6 SCC, 4 sebaceous gland carcinoma [SGC]); ocular surface malignancy (cornea and conjunctiva) in 12 cases (31.5%); uveal malignant melanoma in 3 cases (7.8%); lacrimal gland and lacrimal sac malignancy, 1 case each (5.3%); and orbital infections, 2 cases (5.3%) (Table 1, T1 http://links.lww.com/A150). The pathologic diagnoses of all cases of exenteration, the age and gender distribution, and the delay between presentation of tumor and exenteration are summarized in Table 2 (http://links.lww.com/A151). The eyelids were the most common site for the primary neoplasm, and SCC was the most common histopathologic diagnosis. In the interval between presentation and exenteration, the following procedures were performed for different cases: enucleation (4 cases), radiotherapy (3 cases), and cryotherapy, radiation plaque therapy, and evisceration (1 case each). T2

Perineural invasion was found in 7 exenteration specimens, 4 of them having a primary eyelid skin cancer (3 SCC and 1 BCC). In cases in which surgical margins were histopathologically positive for malignancy, additional surgery was performed and/or adjuvant orbital radiotherapy was given. Specialist oncology management was provided if distant metastasis was discovered at presentation or during follow-up.

The most frequently performed procedure was a conventional total exenteration with sacrifice of the eyelids (26 cases). Eight cases had some type of subtotal exenteration with eyelid sparing, and 4 cases had an extended exenteration. The surgical procedures performed are summarized in Table 3 (http://links.lww.com/A152). T3

To reconstruct the socket, a dermis-fat graft was implanted in a primary or secondary procedure in 11 cases, a split-thickness skin graft was used in 2 cases, and a full-thickness skin graft was applied in 1 case. The remaining orbits were allowed to granulate spontaneously. The average healing time was 5 months (range, 4–6 months) for spontaneous granulation, and 6 weeks (range, 4–8 weeks) for dermis-fat grafts.

At last follow-up, 5 of the patients were wearing an oculofacial prosthesis, either integrated or spectacle-mounted. Time to fitting the prosthesis was usually 6 months following the

TABLE 2. *Age and sex distribution, and the location of tumor for the different pathologic diagnoses (n=38)*

Diagnosis	Average age ± SD at presentation (yrs)	Average age ± SD at exenteration (yrs)	Sex distribution	Location (MC/LC = medial/lateral canthus)
Ocular surface SCC (n = 9)	67.7 ± 12.8	68.1 ± 12.6	6 men, 3 women	
Periocular SCC (n = 6)	56.7 ± 17.1	57.3 ± 17.8	6 men	2 MC, 2 LC, 2 lower lid
BCC (n = 10)	68.5 ± 14.7	72.4 ± 11.5	8 men, 2 women	6 MC
MM (n = 5)	76.5 ± 9.7	81.5 ± 8	2 men, 3 women	3 uveal, 2 conjunctival
SGC (n = 5)	73 ± 3.2	73.8 ± 2.2	3 men, 2 women	4 eyelids, 1 conjunctival
Pleomorphic adenocarcinoma (n = 1)	48	48	1 woman	Lacrimal gland
Orbital infections (n = 2)	75.5 ± 3.5	76.5 ± 4.9	1 man, 1 woman	1 MRSA socket infection, 1 mucormycosis

BCC = Basal cell carcinoma, SCC = Squamous cell carcinoma, SGC = Sebaceous gland carcinoma, MM = Malignant melanoma, †MRSA = Methicillin-Resistant Staphylococcus aureus.

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TABLE 3. *Type of exenteration procedure according to the primary diagnosis, and additional surgery*

Diagnosis	Type of exenteration			Reconstruction
	Total	Subtotal	extended	
Eyelid malignancies (n = 19)	15	2 (eyelid sparing)	2	Split-thickness skin graft - 1 Dermis-fat graft - 5
Ocular surface malignancy (cornea and conjunctiva)(n = 12)	7	5 (eyelid sparing)		Dermis-fat graft - 4
Intraocular malignancy (n = 3)	3			Split-thickness skin graft - 1 Dermis-fat graft -1
Lacrimal gland malignancy (n = 1)			1	
Lacrimal sac malignancy (n = 1)	1			Dermis-fat graft -1
Orbital infections (n = 2)		1	1	

BCC = Basal cell carcinoma, SCC = Squamous cell carcinoma, SGC = Sebaceous gland carcinoma, MM = Malignant melanoma. †MRSA = Methicillin-Resistant Staphylococcus aureus.

exenteration. Those patients who had dermis-fat grafts or underwent subtotal exenteration were less likely to wear an eye patch ($p < 0.05$).

Histopathologic examination of the exenteration specimens revealed clear margins in 24 cases (63%) and positive margins in 14 cases (37%). Of the latter, 5 patients had SCC and 3 had BCC.

Nine recurrences (23.7%), 3 local and 6 systemic, were seen during the follow-up period. Seven of the 9 recurrent cases had been reported to have clear margins on histopathologic examination. The median time from exenteration to the detection of systemic recurrence was 3.1 years (range, 2.5 months to 7 years). Local recurrences presented an average of 8 months (range, 2–15 months) postoperatively. A detailed analysis of cases with systemic or local recurrences occurred is outlined in Table 4.

Early complications included: early wound dehiscence (1 patient with choroidal melanoma), nonhealing granulating socket (1 patient with eyelid SCC), and socket hemorrhage (1 patient with SGC). Late complications included partial socket necrosis in a patient with SGC 7 months after surgery and xanthogranulomatous inflammation 6 years after exenteration in a patient with BCC. Seven patients (18.4%) died of the disease during the follow-up period (Fig., Table 4). Two patients died from unrelated medical causes.

DISCUSSION

Exenteration is a radical and disfiguring operation and is infrequently performed. It may be the preferred first-line treatment in some clinical situations or performed to control relentlessly progressive conditions.[2,7,8] Over time, advances in new treatment modalities such as adjuvant chemotherapy and plaque radiotherapy have improved the surgical cure rate of aggressive malignancies.[7,9,10]

The success of the surgery has been reported to be dependent on obtaining tumor-free margins performed before distant metastasis.[11] We achieved tumor-free margins in 63% of cases, which is comparable with the

TABLE 4. *Detailed analysis of cases with systemic or local recurrence*

Postrecurrence Follow-up/Treatment	Exent-rec	Primary disease	Gender/side	Age (yrs)	Case No.
			Distant metastasis		
Radiotherapy, extended exenteration, later liver metastasis. Died of metastasis.	2.5 yrs	Uveal MM	F/L	78	1
2 more extended exenterations.	2 yrs	Limbal MM	F/L	89	2
Metastasis to LN and ant. chest wall: left parotidectomy, modified neck dissection. Died of metastasis.	3 yrs	LG pleomorphic adenocarcinoma	F/L	48	3
Palliation. Died after 7 years.	7 yrs	SGC-MC	M/R	75	4
Metastasis to submental and cervical LN: right neck dissection, radiotherapy. Died of metastasis.	2 yrs	SCC-LC	M/L	58	5
Cervical nodes metastasis, palliation. Died of metastasis.	2 yrs	SCC-LC	M/R	42	6
			Local recurrences		
Orbital recurrence, referred to palliation. Died.	15 mos	SCC-conjunctiva	M/R	88	7
Orbital recurrence, referred to palliation. Died of metastasis.	7 mos	SGC-LUL	F/L	71	8
Extended exenteration, partial ethmoidectomy.	2 mos	BCC-MC	M/R	48	9

Exent-Rec, exenteration-recurrence interval; F, female; M, male; L, left; R, right; MM, malignant melanoma; LG, ; LN, lymph nodes; ant., anterior; SGC, sebaceous gland carcinoma; MC, medial canthus; LC, lateral canthus; LUL, ; BCC, basal cell carcinoma; SCC, squamous cell carcinoma.

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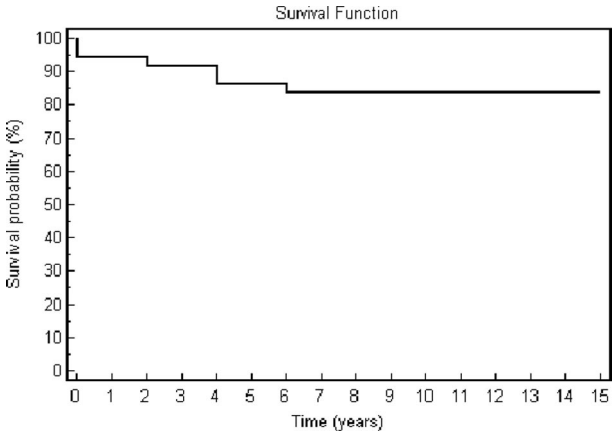

Cumulative survival plot for 38 patients who underwent orbital exenteration at Sydney Eye Hospital, 1990 to 2004.

recent series of Ben Simon et al.[11] (68%) and Goldberg et al.[8] (62%).

Radical surgery is only part of a wider management plan for these conditions. An essential part of the surgical decision-making process is the reconstruction and rehabilitation of the exenterated socket.[8,11,12] Frequent dressing changes, often for many months to complete epithelialization, long-term recurrence follow-up, and consideration of psychological effects should be included in the multidisciplinary care.

Several studies have suggested that the surgical planning should be individualized. Instead of performing a total exenteration for every progressive orbital process that invades the orbit, the following factors should be considered: location (i.e., availability of surgical planes), biologic behavior of the disease process, reconstructive and prosthetic options, and whether the primary goal of exenteration will be to achieve surgical cure or local tumor control.[8,13,14] Eight of our 38 cases were subtotal exenterations. It previously has been reported[4,8,15] that subtotal exenteration procedures result in faster healing with fewer complications, less frequently required dressing changes, and better overall aesthetic results. The recent trend is in favor of partial eyelid-sparing exenteration for most cases of malignant orbital tumors, and it may be used in more than half of the cases involving the eyelids and about 90% of tumors with conjunctival origin.[5,8,16] In our study, only 2 of 19 cases (10.5%) of eyelid malignancies but 5 of 7 cases (71.4%) of conjunctival origin had subtotal exenteration. This may reflect the historical nature of the current study, in which the transfer to an individualized approach was adopted earlier for conjunctival origin tumors, and only recently for eyelid malignancies cases. It is notable that those 2 cases of subtotal exenteration for eyelid malignancies were performed after the year 2000.

The preservation of orbital tissues also facilitates the completion of a primary reconstruction. However, when there is a need to sacrifice the globe, conjunctiva, or eyelids, the use of autogenous tissue to fill the posterior orbit is preferred because of the higher chance of extrusion and infection with alloplastic implant materials.[8,17]

The most common autogenous tissue used to fill the posterior orbit was dermis-fat graft harvested from the abdominal wall. This was performed in 11 of our patients as a primary or secondary procedure after obtaining histologic clearance. We found this procedure to be acceptable to the patient because there was no residual deep cavity, and the deformity appeared less significant. Those patients without dermis-fat graft or with partial-thickness graft were more likely to wear an eye patch. Dermis-fat grafts, like subtotal exenteration surgery, seem to optimize the aesthetic results. However, there were 2 complications associated with the use of dermis-fat graft: early wound dehiscence and infiltrating SCC of the socket. Dermis-fat graft has an important disadvantage, in that any residual tumor is hidden below the graft and can grow with no external sign. On the other hand, reconstruction of the exenteration cavity with a thin skin graft facilitates earlier detection of local recurrence.

In our study, the most common indication for performing an exenteration was secondary orbital spread of adnexal or ocular malignancies, seen in 34 of 38 cases. They originated in the eyelids (19 cases), on the ocular surface (12 cases), and in the globe (3 cases). Only 2 cases were performed for a primary orbital malignancy (1 in the lacrimal gland and 1 in the lacrimal sac). SCC was the most common etiology for exenteration, followed by BCC. It has been reported that some cases of periocular BCC and SCC have the potential to behave aggressively.[10,18] However, tumor-related death is rare in BCC with orbital invasion.[18] Of the 10 cases with periocular BCC we had, only 1 had local recurrence and there was no case with systemic recurrence or death.

There has been some variation in the main indications for exenteration reported in different series. Some series found eyelid BCC to be the most frequent malignant tumor leading to exenteration;[2,7,12] however, recent series have found SCC to be the most common.[11,19] This may reflect geographic differences in the prevalence of different ophthalmic malignancies, ethnic grouping of patients seen in different centers,[9] or earlier diagnosis and better treatment for BCC by the use of Mohs micrographic surgery.[20]

Exposure to ultraviolet radiation in a population largely composed of whites of Anglo-Saxon heritage is a major risk factor in Australia.[21] The rate of orbital invasion from cutaneous BCC and SCC has been documented to range from 0.8% to 8.2%.[22] Medial canthal location, late presentation, inadequate initial surgery, and insufficient follow-up are the main risk factors for the spread of BCC, leading ultimately to exenteration.[18,23,24] In our study, 6 of the 10 (60%) BCCs requiring exenteration originated in the medial canthal area, and 1 case of

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TABLE 5. *Type of exenteration procedure according to the primary diagnosis, and additional surgery*

Diagnosis	Average age ± SD at presentation (yrs)	Average age ± SD at exenteration (yrs)	Presentation to exenteration interval (months)
Ocular surface SCC (n = 9)	67.7 ± 12.8	68.1 ± 12.6	4
Periocular SCC (n = 6)	56.7 ± 17.1	57.3 ± 17.8	6
SGC (n = 5)	73 ± 3.2	73.8 ± 2.2	8
BCC (n = 10)	68.5 ± 14.7	72.4 ± 11.5	45
MM (n = 5)	76.5 ± 9.7	81.5 ± 8	48

BCC = Basal cell carcinoma, SCC = Squamous cell carcinoma, SGC = Sebaceous gland carcinoma, MM = Malignant melanoma, †MRSA = Methicillin-Resistant Staphylococcus aureus.

late presentation (11 years after local BCC excision) had local recurrence. In a large series reported from Australia, 84.4% of 64 patients with orbital invasion from periocular BCC had a recurrent or previously incompletely excised tumor, and the medial canthus was involved in 56.2%.[18]

Eyelid SCC is more aggressive than BCC and exhibits perineural invasion at an earlier stage,[25,26] therefore the chances of orbital invasion are higher, and may occur earlier than with BCC.[22] The aggressive nature of eyelid SCC also is evidenced in our study, as eyelid SCC exenteration was performed at a significantly younger age (57.3 ± 17.7 years) as compared with eyelid BCC (72.4 ± 11.5 years) (independent samples t test < 0.04). There was also a higher incidence of perineural invasion (50%) for SCC, and the time period between presentation and exenteration was less for SCC (5 months) than for BCC (3.9 years) (Table 5, http://links.lww.com/A153).

This finding of earlier indication for exenteration with eyelid SCC has not been reported previously. A male predominance was found in our study. This is in accordance with previous studies.[19] One factor accounting for this may be more sun exposure and subsequent actinic changes occurring in men from work or recreational activities.

SCC may be very difficult to control and eradicate completely even with exenteration. Recently, Malhotra et al.[20] in their study of a Mohs surgery database of Australian patients with periocular squamous intraepidermal carcinoma demonstrated significant subclinical tumor extension, with recurrence rates of 5% and 12% for treated primary and recurrent lesions, respectively.

SCC of the conjunctiva is regarded as a low-grade malignancy and intraocular invasion has been reported to be uncommon, with figures of 2% to 11%.[23–26] In a recent Australian study of SCC of the ocular surface, corneal and/or scleral invasion was found in 30%, orbital invasion was noted in 15%, and 23% required orbital exenteration.[25] Ocular surface squamous neoplasia is commonly seen in Australia[27,28] and 9 of our exenterated patients (24.3%) had a primary SCC of the ocular surface.

SGC was the indication for exenteration in 5 (13.5%) cases. In another recent series of exenterations reported from India, 26% (6/26) of cases had SGC. Its prevalence varies in different populations.[29] It is more common in the upper eyelid than the lower, possibly because there are more meibomian glands in the upper eyelid.[19,29] In a recent series, the superior tarsal and forniceal conjunctiva were involved in 100% of cases with intraepithelial spread, even when the tumor apparently had originated in the tarsus of the lower eyelid.[30] This may be explained either by a tumor of multicentric origin, or that mapping biopsies of the bulbar conjunctiva occasionally had missed the epithelial involvement because of "skip" areas.

Exenteration for SGC is controversial. Shields et al.[30] have shown that even if the tumor extends in the conjunctival stroma, surgical excision and the use of adjuvant therapy, rather than exenteration, may be considered.[30,31] In our study, the upper eyelid was involved in 3 of the 5 cases of SGC, and 2 patients with SGC developed metastases, which was the cause of death. However, the number of cases is too small to be statistically significant.

There were a total of 9 recurrences (23.6%), 3 local recurrences and 6 distant metastases, seen during the follow-up period (Table 1, http://links.lww.com./A150). Recurrence rates of 7% to 10% have been reported in cases of locally invasive tumors (such as BCC and SCC) when all the involved tissue was removed and clear margins were seen on histopathology.[2,11] However, exenteration for some orbital malignancies, particularly adenoid cystic carcinoma of the lacrimal gland[18] and uveal malignant melanoma with extrascleral extension,[8,11] does not necessarily lead to any increase in disease-free survival. Local recurrences presented earlier (average, 8 months) postoperatively compared with systemic recurrences (average, 3.1 years). It seems therefore that the first year is the most important period for follow-up of local recurrences. Systemic examination is needed for the longer follow-up.

Of the 7 patients (18.4%) who died as a direct result of the lesion, 6 had tumor metastases and 1 died from mucormycosis. A similar figure was found in a recent survey of exenteration cases in which 20.3% of the patients died as a direct result of the orbital tumor.[12]

To conclude, exenteration is still indicated for some cases of orbital disease, although the indications have narrowed over the last few decades as a result of earlier diagnosis and the development of alternative treatments. Eyelid SCC exenteration was performed

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at a significantly younger age than the other indications. The first year is the most important period for follow-up of local recurrences, but rigorous, lifelong follow-up of these patients for systemic examination is needed.

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