ORIGINAL ARTICLE

Survival Analysis and Prognostic Factors for Peri-ocular Malignancies in Malaysia

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ABSTRACT

Introduction: This study aims to determine the prognostic factors and survival outcomes of patients that underwent this surgery. **Method:** A retrospective review of 43 patients who underwent exenteration for periocular malignancies over a 14-year period was carried out. Patient demographics, tumour histology, treatment details, surgical margins' status and post-operative survival were recorded. The survival outcome examined was the overall survival (OS) rate. Cox regression and Kaplan-Meier analysis were used to evaluate post-exenteration survival. **Results:** In total, 20 females and 23 males with a median age of 62 ± 17.3 years were identified. The most common indication for exenteration was basal cell carcinoma (20.9%), followed by squamous cell carcinoma (18.6%), adenocystic carcinoma (14%), malignant melanoma (14%) and sebaceous gland carcinoma (11.6%). The independent predictors for worse OS on multivariate analysis were Chinese ethnicity (adjusted hazard ratio [aHR] 4.95, p =0.017), sebaceous gland carcinoma (aHR 57.61 p=0.006), adenocystic carcinoma (aHR 45.87, p=0.008), clear surgical margins (aHR 5.41, p=0.025), receiving only chemotherapy (aHR 169.13, p=0.004), and receiving both adjuvant chemotherapy and radiotherapy (aHR 41.51, p=0.010). **Conclusion:** We recommend targeted public health initiatives for Chinese patients due to their increased mortality risk from peri-ocular malignancies. In addition, we advise comprehensive adjuvant therapy for all patients regardless of whether a clear surgical margin is achieved. Basal cell carcinoma and adenocystic carcinoma may also benefit from genetic research. We advocate more training for ophthalmologists to identify periocular malignancies earlier for better treatment options and increased chances of survival.
Malaysian Journal of Medicine and Health Sciences (2024) 20(1):60-69. doi:10.47836/mjmhs.20.1.9

Keywords: Orbital exenteration, peri-ocular malignancy; adjuvant, overall survival

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INTRODUCTION

The first orbital exenteration procedure was carried out in 1884 by a German ophthalmologist Ernst Fuchs; it involved the removal of the entire contents of the eye socket, including the eye, eyelids and surrounding tissue (1). This radical surgery is still widely used to treat orbital malignancies and severe infections of the eye or orbit that antibiotics cannot control. A substantial risk of consequences exists with major procedures like this, including bleeding, infection, injury to the surrounding tissues, and alterations to the patient's look and functionality. Therefore, it is typically reserved for patients who have exhausted all other forms of treatment options and for whom the procedure's benefits outweigh the risks.

After exenteration, the orbit may be left to heal innately through granulation. Alternatively, split skin grafts or rotational flaps from the forehead or face may be used to reconstruct the orbital cavity. Adjuvant therapy is

commonly added to the operation to eliminate any leftover cancer cells and stop recurrences; it can take the form of radiotherapy, chemotherapy, or a combination of the two. In order to improve survival by treating the micrometastases early and reducing the likelihood of recurrence, this neo-adjuvant therapy may also be given before the surgery (2).

Numerous studies have examined the connection between ethnicity, demography, sun exposure and the risk of developing orbital cancer (3, 4). Well-known instances of malignancies associated with ethnicity include basal cell carcinoma (BCC), squamous cell carcinoma (SCC) and sebaceous gland carcinoma (SGC). BCC is the most prevalent periorbital malignancy among Caucasians. It has been linked to recreational sun exposure as a major risk factor, as Caucasians tend to sunburn rather than suntan when on vacation (5). SCC has similarly been intimately linked to UV radiation from the sun and other sources. Populations living near the equator are more vulnerable to experiencing it, and for every 10 degrees of latitude, its prevalence decreases by 49% (6). The Indian subcontinent's most common indication for exenteration is SGC (7, 8). Genetic biomarkers such as vimentin, programmed death ligand-1 and -2, and the PCDH15 gene mutation have been implicated to its development (9, 10).

Information regarding the impact of the orbital exenteration on Malaysia's multi-ethnic society is still unknown. This study aimed to review the clinicopathological characteristics and outcomes of those who received this procedure in Malaysia. The data from this study will be utilised to identify individuals at risk and improve the current treatment approach, enabling the development of a strategy to increase patient survival.

MATERIALS AND METHODS

Serdang Hospital is Malaysia's premier oculoplastic institution and accepts referrals from East and West Malaysia. The inclusion criteria for this study included any type of orbital cancer, whether primary or secondary. From the patients' medical records, information was obtained about their demographics, clinical characteristics, surgical management, histology results, and treatment outcome. The type of orbital surgery performed was evaluated using the Kesting orbital exenteration grading system, which assigns grades based on the extent of the orbital wall defect; with grade 1 being the least invasive and grade IV being radical surgery which included an orbital exenteration with a penetrating orbito-maxillary defect (11). Tumour invasiveness was determined by intra-operative bone erosion and histological perineural infiltration. Regional metastasis describes the spread of cancer cells into nearby lymph nodes or surrounding organs like the sinus or the brain. The histology report contained details about the type and size of the tumour. Uncommon histological diagnosis was categorised under others for statistical analysis, which consisted of 6 cases of primary malignancies and 3 cases of secondary malignancies. These primary malignancies consisted of two cases of baso-squamous carcinoma, one rhabdomyosarcoma, one malignant fibrous histiocytoma, one malignant epithelial tumour and one angiosarcoma. Whilst spindle cell sarcoma, a neuroendocrine tumour and systemic lymphoma comprised the three cases of secondary orbital malignancies. Additional details regarding the type of reconstruction done and the adjuvant therapy received were also retrieved from the medical records.

Patients who were lost to follow-up were traced by phone. While for those who were not contactable, the National Registration Department was then contacted for information on their survival and the circumstances of their death. Survival status was assessed from the surgery date until death or the last telephone interview on 30 April 2021, whichever happened first. Patients were regarded as censored cases if they were still alive at the time of the last known follow-up. Since many patients were referred from distant hospitals and subsequently received post-operative treatment and monitoring locally, our study could not evaluate disease-free survival.

Data were analysed using the Statistical Package for Social Sciences (SPSS version 27). Descriptive statistics for the categorial variables was displayed as frequency and percentage [n(%)]. Continuous variables which were normally distributed were presented as mean and standard deviation (SD), while skewed data were presented as median and interquartile range (IQR). The Kaplan-Meier curves were generated and compared using the log-rank test. Potential prognostic factors were also analysed using the Cox proportional hazard model. Predictors with $p < 0.25$ on univariate Cox analysis were included for further analysis in the multivariate Cox regression, and the adjusted hazard ratio (HR) was calculated. The significance level was set at $p < 0.05$.

This study was registered under the Malaysian National Medical Research Registry (NMRR) with the identification number NMRR-18-863-41267.

RESULTS

Patient characteristics

A total of 44 patients underwent orbital exenteration in Serdang Hospital during the study period from 1 January 2008 to 30 April 2021. One patient with recalcitrant mucormycosis that also underwent this surgery was left out of the analysis. The patients ages ranged from 20 years to 85 years old, with a median age of 62 years (IQR=25) Malays made up the majority of cases (60.5%), followed by Chinese (32.6%), Indians (4.7%), and indigenous ethnicity (2.3%), as shown in Table I. The gender distribution was almost equal, with 23

Table I: Patient Data

Age range (year)	*Tumour origin*	*Race*	*Histological diagnosis*	*Surgery-Type*	*Reconstruction*	*Adjuvant*	*Metastasis.*	*Survival (months)*
20-29	**Lacrimal gland/Orbit**	**M**	**ACC**	**I**	**SSG**	**Yes**	**Nil**	**23 months***
	Lacrimal gland/Orbit	M	ACC	I	SSG	Yes	Nil	Alive
	Lacrimal gland/Orbit	M	ACC	I	None	Yes	Nil	Alive
30-39	**Lacrimal gland/Orbit**	**M**	**ACC**	**I**	**SSG**	**Yes**	**Nil**	**34 months***
	Lacrimal Gland/Orbit	**I**	**ACC**	**I**	**None**	**Yes**	**Yes**	**15 months***
	Orbit	M	Rhabdomyosarcoma	IV	None	Yes	Nil	Alive
	Orbit	**C**	**Spindle cell sarcoma**	**I**	**None**	**Yes**	**Yes**	**34 months****
40-49	**Lid**	**M**	**SGC**	I	**None**	**Yes**	**Nil**	**23 months***
	Lid	M	BCC	IV	None	Nil	Nil	Alive
	Cheek/Maxillary sinus/ Orbit	M	BCC	IV	None	Yes	Yes	Alive
	Orbit	M	Malignant fibrous histiocytoma	I	None	Yes	Nil	Alive
50-59	Lid	M	BCC	IV	None	Yes	Nil	Alive
	Lid	C	BCC	I	SSG	Yes	Nil	Alive
	Lid	**O**	**SGC**	**I**	**SSG**	**Yes**	**Nil**	**5 months***
	Lid	M	SGC	I	None	Yes	Nil	Alive
	Conjunctiva	**C**	**CMM**	**I**	**SSG**	**Yes**	**Nil**	**30 months***
	Maxillary sinus/Orbit	M	SCC	IV	None	Yes	Nil	Alive
	Orbit	**C**	**Neuroendocrine tumour**	**IIa**	**None**	**Yes**	**Yes**	**3 months****
60-69	**Lid**	**M**	**BSC**	**IV**	**None**	**Yes**	**Nil**	**38 months***
	Lid	C	SCC	IV	None	Yes	Yes	Alive
	Lid	M	SCC	I	SSG	Yes	Nil	Alive
	Conjunctiva	C	SCC	I	None	Nil	Nil	Alive
	Conjunctiva	M	CMM	I	None	Yes	Nil	Alive
	Conjunctiva	**M**	**CMM**	**I**	**None**	**Yes**	**Nil**	**33 months***
	Maxillary sinus/Orbit	M	Malignant epithelial tumour	I	None	Yes	Nil	Alive
	Orbit	C	Angiosarcoma	I	SSG	Yes	Nil	Alive
70-79	Lid	M	BCC	IIa	None	Yes	Nil	Alive
	Lid	M	BCC	I	SSG	Nil	Nil	Alive
	Lid	**M**	**BCC**	**IV**	**None**	**Yes**	**Nil**	**37 months /old age**
	Lid	M	BCC	I	None	Nil	Nil	Alive
	Lid	**C**	**BCC**	**I**	**None**	**Yes**	**Nil**	**35 months***
	Lid	**C**	**BSC**	**I**	**None**	**Nil**	**Nil**	**41 months / old age**
	Lid	**C**	**SGC**	**IV**	**None**	**Yes**	**Nil**	**12 months***
	Lid	**C**	**SGC**	**I**	**SSG**	**Yes**	**Yes**	**3 months***
	Lid	**M**	**SCC**	**I**	**SSG**	**Yes**	**Yes**	**33 months***
	Conjunctiva	C	CMM	IIa	None	Yes	Nil	Alive
	Conjunctiva	M	CMM	I	None	Yes	Nil	Alive
	Conjunctiva	C	SCC	I	SSG	Yes	Nil	Alive
	Conjunctiva	M	SCC	I	None	Nil	Nil	Alive
	Lacrimal gland/Orbit	M	ACC	I	SSG	Yes	Nil	Alive
80-89	Lid	M	SCC	I	None	Yes	Nil	Alive
	Conjunctiva	I	SCC	I	None	Nil	Nil	Alive
	Conjunctiva	**C**	**CMM**	**I**	**None**	**Yes**	**Yes**	**34 months / old age**
	Orbit	**M**	**Lymphoma**	**I**	**None**	**Yes**	**Yes**	**13 months****

*Duration of survival owing to the advancement of the orbital malignancy ** Duration of survival owing to secondary malignancy into the orbit.
OE: Orbital exenteration; M: Malay; C: Chinese; I: Indian; BCC: Basal cell carcinoma; SCC: Squamous cell carcinoma; BSC: Basosquamous cell carcinoma; ACC: Adenoid cystic carcinoma; CMM: Conjunctival malignant melanoma; SSG: Split skin graft; AT: Adjuvant therapy; Mets: Metastasis

males and 20 females. The majority of patients worked in blue-collared jobs (55.8%), followed by homemakers (23.3%) and white-collared employees (20.9%). All the male patients except for three, were smokers. The majority of patients (51.1%) did not have any medical co-morbidities. However, a third (32.6%) had two or more medical co-morbidities, the most prevalent of which were hypertension and diabetes.

The most common presenting symptom was a presence of a mass in 33 patients (76.7%), followed by reduced vision (41.9%), proptosis (25.6%), congestion of the conjunctiva (23.2%) and pain (14%). In almost 4 out of 5 patients, the tumour size was more than 20 mm. However, at the time of exenteration, the majority of patients (60.5%) had a visual acuity of 6/60 or better, and 8 patients (18.6%) had vision that was nearly normal (better than 6/12).

Histopathological diagnosis

In our facility, orbital exenteration was performed on twelve different histological types of orbital cancers. The demographic characteristics, histological diagnosis and surgical outcome for each patient are presented in Table II. The most common site for exenteration-indicating cancers was the eyelid (41.9%), followed by the intra-orbital (34.9%) and conjunctival malignancies (23.3%). While the most common indication for exenteration based on histological diagnosis was BCC (9, 20.9%), followed by SCC (8, 18.6%), adenocystic carcinoma (6, 14%), malignant melanoma (6, 14%) and sebaceous gland carcinoma (5, 11.6%). The nine uncommon histological diagnoses (20.9%) were categorised under others have already been described above. Most patients had localised malignancies (74.4%), while regional metastasis with lymph node involvement was seen in 4.7% of cases. Of concern, is the fact that one in five patients (20.9%) presented with distant metastases at presentation. Tumour invasiveness, which involved either bony erosion or perineural infiltration, was seen in most patients (60.5%).

Treatment modalities

There were only three types of orbital exenteration procedures conducted, with type 1 (72%) surgeries being the most common, followed by type IV (20.9%) and type II (6.9%) surgeries. Oculoplastic surgeons performed every exenteration procedure at our institution, while otolaryngology specialists supported the type IV surgeries. In addition to the exenteration, four patients underwent concurrent procedures, comprising two radical neck lymph node dissections and two parotidectomies. A clear surgical margin was achieved in only 55.8% of the patients.

The majority of patients (72.1%) were left to heal naturally by granulation without a split-skin graft or flap. Only 12 patients (27.3%) had their orbits rebuilt utilising split skin grafts, with no rotational flaps documented.

Table II: Demographic characteristics of patients with periocular malignancies, 2008-2021

Variables	No (%)	Mortality (%)
	43	41.9
Gender		
Female	20 (46.5)	40.0
Male	23 (53.5)	43.5
Age		
< 60 years	18 (41.9)	44.4
≥ 60 years	25(58.1)	40.0
Ethnicity		
Malay	26 (60.5)	30.8
Chinese	14 (32.6)	57.1
Indian	2 (4.7)	50.0
Indigenous	1 (2.3)	100.0
Occupation		
Blue-collar	24 (55.8)	45.8
White-collar	9 (20.9)	33.3
Housemaker	10 (23.3)	40.0
History of smoking		
Yes	20 (46.5)	35.0
No	23 (53.5)	47.8
No. Medical comorbidities		
≤ 1	29 (67.4)	37.9
≥ 2	14 (32.6)	50.0
Histology:		
BCC	8 (18.6)	25.0
SCC	9 (20.9)	11.1
CMM	6 (14.0)	50.0
SGC	5 (11.6)	80.0
ACC	6 (14.0)	50.0
Others	9 (20.9)	55.6
Tumour origin		
Conjunctiva	10 (23.3)	30.0
Eyelid	18 (41.9)	50.0
Orbit	15 (34.9)	40.0
Duration of symptom		
≤ 12 months	22 (51.2)	31.8
> 12 months	21 (48.8)	52.4
Visual acuity		
≤ 6/60	17 (60.5)	50.0
> 6/60	26 (39.5)	29.4
Pain on presentation		
No	37 (86)	40.5
Yes	6 (14.0)	50.0
Mass on presentation		
No	10 (23.3)	40.0
Yes	33 (76.7)	42.4
Tumour size		
≤ 20 mm	9 (20.9)	33.3
> 20 mm	34 (79.1)	44.1
Tumour invasiveness		
Yes	23 (60.5)	30.4
No	15 (39.5)	53.3
Status of metastasis		
None	32 (74.4)	34.4
Lymph Nodes	2 (4.7)	50.0
Distant metastasis	9 (20.9)	66.7
Surgical margins		
Unclear	19 (44.2)	31.6
Clear	24 (55.8)	50.0
Adjuvant therapy		
None	6 (14.0)	16.7
Radiotherapy	15 (34.9)	20.0
Chemotherapy	5 (11.6)	60.0
Both	17 (39.5)	64.7
Recurrent disease		
No	23 (53.5)	13.0
Yes	20 (46.5)	75.0

The rate of surgical complications recorded was only 8 (18.6%); with infections being the most common issue (4 cases), followed by fistulas and delayed radiotherapy-induced wound healing with 2 cases respectively.

All patients underwent adjuvant therapy, with the exception of 6 patients who had BCC (4 cases) and SCC (2 cases) with tumour sizes of less than 20 mm and no signs of tumour invasion or regional metastasis. The patients who did not receive adjuvant therapy had an 83.3% 1-year survival rate, which quickly fell to 50% at 3-years, to only 16.7% at 5 years. No patients at our facility received neoadjuvant therapy. Regardless of the surgical margin obtained, most patients underwent adjuvant radiotherapy, chemotherapy, or both. Most patients (39.5%) were treated with both, followed by a third (34.9%) who received only radiotherapy. There were 5 patients (11.63%) who were given palliative care with only chemotherapy. Recurrences of the malignancy were seen in almost half the patients (46.5%), with a 90% mortality rate.

Outcome

The median overall survival (OS) time for our cohort was 5.8 years (95% CI, 55.954 to 84.88 months) , and over the 13-year research period, 18 patients (41.8%) passed away (Table III). At 1-year, the OS rate was 88%, followed by 76% at 3-years and 40% at 5-years. A 76-year-old BCC patient had the longest OS time of 9-years and had undergone Type 4 exenteration and parotidectomy, followed by radiotherapy and chemotherapy, before passing away from old age. In contrast, the shortest OS time was only three months; for a patient with neuroendocrine malignancy with a painful metastasis to the orbit.

BCC patients had the longest median OS time of 7.5 years (95% CI, 13.15 to 65.23 months), followed by SCC patients with 6.3 years (95% CI, 8.06 to 61.36 months), adenoid cystic carcinoma (ACC) patients with 3.8 years (95% CI, 8.86 to 27.62 months) , conjunctival malignant melanoma (CMM) patients with 3.1 years (95% CI, 2.67 to 31.56 months) and finally, SGC patients with 1.2 year (95% CI, 5.62 to 22.37 months). No patients with SGC had a 3-year survival rate. Figure 1(c) presents the Kaplan-Meier analysis of OS based on the histological diagnosis. The median OS time for patients presenting with less than 12 months duration of symptoms was 6.7 years (95% CI, 9.75 to 62.44 months) compared to 4.1 years for those presenting after 12 months; however, this was not statistically significant.

Figure 1(d) shows Kaplan-Meier analysis of OS stratified based on the surgical margin status. The clear margin was an independent predictor for mortality among our patients. The 5-year survival rate for patients with clear surgical margins was 12.5 months compared to 36.8 months for those with unclear margins; this was statistically significant ($p < 0.05$).

Table III: Factors related to the median overall survival (OS)

Characteristics	Median OS time (months)	Survival		
		1 Year (%)	3 Year (%)	5 Year (%)
Overall rate	69.9	88.0	76.0	40.0
Gender				
Female	73.1	95.0	65.0	20.0
Male	54.7	78.3	39.1	26.1
Age at diagnosis				
< 60 years	69.2	83.3	44.4	33.3
≥ 60 years	58.7	88.0	56.0	16.0
Ethnicity				
Malay	85.7	100.0	73.1	34.6
Chinese	32.2	64.3	21.4	7.1
Indian	21.0	100.0	0.0	0.0
Indigenous	6.0	0.0	0.0	0.0
Occupation				
Blue-collar	55.8	83.3	45.0	29.2
White-collar	48.8	77.8	55.6	11.1
Housemaker	71.9	100.0	60.0	20.0
History of smoking				
No	58.3	91.3	52.2	13.0
Yes	75.8	80.0	50.0	35.0
Medical co-morbidities				
≤ 1	73.2	82.8	55.2	21.4
≥ 2	54.4	92.9	42.9	24.1
Histological diagnosis				
BCC	91.1	87.5	75.0	37.5
SCC	75.6	88.9	55.6	22.2
CMM	37.2	83.3	33.3	0.0
SGC	14.6	60.0	0.0	0.0
ACC	45.5	100.0	50.0	33.3
Others	58.6	88.9	66.7	33.3
Tumour origin				
Conjunctiva	38.3	80.0	30.0	0.0
Eyelid	76.2	87.5	58.3	25.0
Orbit	52.2	88.9	55.6	44.4
Duration of symptoms				
≤ 12 months	80.9	90.9	59.1	31.8
> 12 months	49.3	1.0	42.9	14.3
Visual acuity				
≤ 6/60	66.6	92.3	61.5	23.1
> 6/60	64.4	76.5	35.3	23.5
Pain on presentation				
No	63.2	86.5	48.6	21.6
Yes	69.8	83.3	66.7	33.3
Mass on presentation				
No	66.9	80.0	70.0	40.0
Yes	67.4	87.9	45.5	18.2
Tumour size				
≤ 20 mm	71.4	77.8	33.3	11.1
> 20 mm	62.6	88.2	55.9	26.5*
Tumour invasiveness				
No	58.0	86.7	53.3	20.0
Yes	76.8	82.6	47.8	26.1*
Status of metastasis				
None	70.4	77.8	22.2	11.1
Regional nodal	52.0	87.5	59.4	25.0
Distant	37.6	100.0	50.0	50.0*
Surgical margins				
Unclear	82.3	89.5	63.2	36.8*
Clear	53.5	83.3	41.7	12.5
Adjuvant therapy				
None	73.0	83.3	50.0	16.7
Radiotherapy	84.9	81.8	27.3	9.0
Chemotherapy	15.4	93.3	86.7	46.7*
Both	53.2	88.2	29.4	11.8
Recurrent disease				
No	43.0	87.0	73.9	34.8
Yes	32.6	85.0	25.0	10.0

BCC: Basal cell carcinoma, SCC: Squamous cell carcinoma, CMM: Conjunctival malignant melanoma, SGS: Sebaceous gland carcinoma, ACC: Adenocystic carcinoma

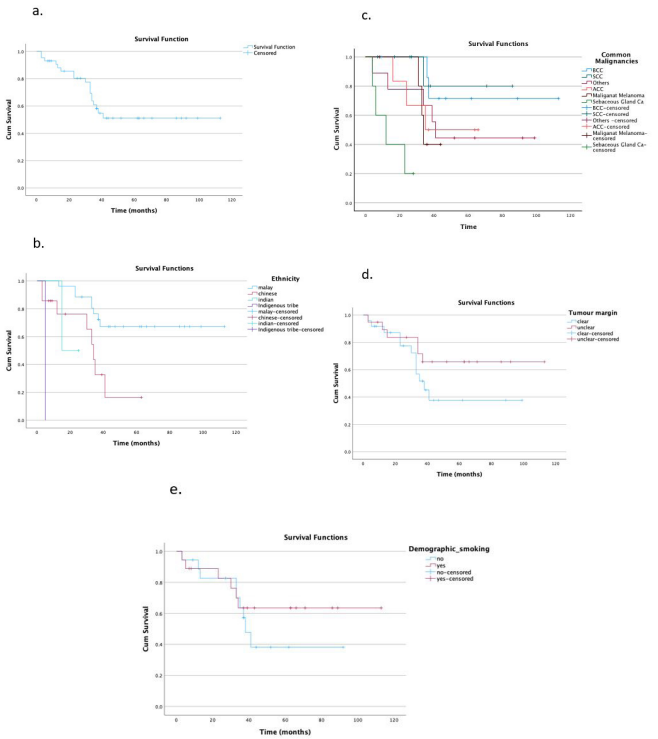

Figure 1: : Kaplan-Meier curve showing the estimated overall survival for a) all patients; (b) ethnicity; (c) smokers vs non-smokers; (d) categories for histological diagnosis of orbital malignancies; (e) surgical margin clear vs unclear

Univariate and multivariate analysis of the prognostic factors among patients with orbital malignancies

Chinese ethnicity, indigenous ethnicity, SGC on histology, distant metastases, chemotherapy-only treatment, and recurring disease were all significant factors in univariate analysis ($p < 0.05$). For further analysis, Cox proportionate hazard regression analysis was used to get the adjusted hazard ratio for each independent variable. All predictors with a p-value < 0.25 were included in the model and omitted one by one if it was not statistically significant. The predictors of OS were identified from the multivariate analysis is shown in Table 4. The OS rate was independently linked with Chinese ethnicity, a clean surgical margin, histological diagnosis of SGC, ACC, or other cancers, and treatment with adjuvant therapies or only chemotherapy alone in the final Cox model. These factors had a significant effect ($p < 0.05$) on a patient's survival. The Omnibus tests of model coefficients were $p < 0.001$ for the overall score via a backward procedure.

DISCUSSION

Our study showed an overall 5-year survival rate of 40% after exenteration, which aligns with regional survival rates of 41.2% in Thailand (12) and 33% in Taiwan (13). Compared to Caucasian Australians and Americans, who recorded 5-year survival rates of 58% to 92%, respectively (14, 15), Southeast Asians have a much lower survival rate. This disparity in the survival

Table IV: Univariate and Multivariate analysis for various factors related to overall survival (OS)

Variables	Univariate Cox		Multivariate Cox	
	Unadjusted HR (95% CI)	p-value	Adjusted HR (95%CI)	p-value
Gender				
Female	1			
Male	1.46 (0.57,3.71)	0.426		
Age at diagnosis				
≥ 60 years	1			
< 60 years	1.14 (0.48,2.89)	0.787		
Ethnicity				
Malay	1		1	
Chinese	4.22 (1.55,11.47)	0.005*	4.95 (1.34,18.33)	0.017*
Indian	6.37 (0.70,57.96)	0.100	11.78 (0.63,221.82)	0.100
Indigenous	47 (3.85,583.727)	0.003*	8.79 (0.42,183.63)	0.161
Occupation				
Blue-collar	1			
White collar	0.64 (0.18,2.30)	0.492		
Housemaker	0.70 (0.22,2.198)	0.540		
History of smoking				
Yes	1			
No	1.23 (0.48,3.18)	0.671		
Medical co-morbidities				
≤ 1	1			
≥ 2	1.41 (0.54,3.64)	0.481		
Histological diagnosis				
BCC	1		1	
SCC	0.70 (0.06,7.75)	0.771	1.51(0.09,25.67)	0.775
CMM	3.44 (0.57,20.99)	0.180	1.66 (0.26,10.63)	0.591
SGC	24.90 (3.53,175.24)	0.001*	57.61 (3.25,1021.04)	0.006*
ACC	2.63 (0.43,15.83)	0.290	45.87 (2.72,774.34)	0.008*
Others	2.49 (0.48,12.83)	0.276	13.80 (1.47,129.21)	0.021*
Tumour origin				
Conjunctiva	1			
Eyelid	1.26 (0.34,0.71)	0.731		
Orbit	0.86 (0.21,3.51)	0.837		
Duration of symptoms				
≤ 12 months	1			
> 12 months	1.77 (0.68,4.57)	0.239		
Visual acuity				
≤ 6/60	1			
> 6/60	0.83 (0.29,2.33)	0.716		
Pain on presentation				
No	1			
Yes	0.95 (0.27,3.28)	0.931		
Mass on presentation				
No	1			
Yes	1.39 (0.45,4.24)	0.565		
Tumour size				
> 20 mm	1			
≤ 20 mm	1.05 (0.30,3.65)	0.937		
Tumour invasiveness				
Yes	1			
No	1.54 (0.60,3.99)	0.370		

Table IV: Univariate and Multivariate analysis for various factors related to overall survival (OS) (Continued)

Variables	Univariate Cox		Multivariate Cox	
	Unadjusted HR (95% CI)	p-value	Adjusted HR (95%CI)	p-value
Status of metastasis				
None	1			
Lymph Nodes	1.76 (0.23,13.67)	0.589		
Distant metastasis	3.78 (1.35,10.53)	0.011*		
Surgical margins				
Unclear	1		1	
Clear	2.07 (0.77,5.54)	0.148	5.41(1.24-23.54)	0.025*
Adjuvant Therapy				
None	1		1	
Radiotherapy	0.80 (0.08,7.73)	0.848	3.08 (0.20,46.70)	0.417
Chemotherapy	18.02 (1.62,199.73)	0.018*	169.13 (5.38,5320.2)	0.004*
Both	4.88 (.62,38.29)	0.132	41.51 (2.42,712.80)	0.010*
Recurrent disease				
No	1			
Yes	9.92 (2.79,35.17)	<0.001*		

* p-value < 0.05
HR, hazard ratio; CI, confidence interval.
Univariate and multivariate analysis for orbital malignancies treated with curative intent. Covariates included those p<0.25 from univariate analysis. Omnibus tests of model coefficients were p<0.001 for the overall score via a backward procedure.

rate can be related to the difference in histological diagnosis between Caucasians and Asians. BCC is the most prevalent periocular malignancy in Caucasians, accounting for 90% of eyelid lesions (16), while it accounted for 20.9% in our study, similar to findings from India at 20% (17) and 46.7% in China (18). BCC has been shown to have the highest survival rate of any non-melanoma skin cancer, with a 2-year survival rate of 78% in the US (15), correspondingly, the 3-year survival rate for BCC in our study was 75%. BCC is a slow-growing, locally invasive cancer with high-risk features such as recurrent disease, medial canthal tumours, or morphea form subtypes (15, 19). BCC is typically associated with prolonged sun exposure (20), however, the majority of the BCC patients (62%) in our study were white-collared workers and homemakers. Indoor workers in Malaysia have been shown to lack sun exposure (21), increasing the need to investigate additional probable causes of BCC in our region. The fact that nearly all of the patients in our cohort were of Malay ethnicity (78%) provides a hint as to possible genetic associations for this disorder.

Another orbital malignancy that may benefit from genetic exploration is adenocystic carcinoma (ACC). It was the only lacrimal gland malignancy that underwent exenteration in our study. Once again, most patients were of Malay ethnicity (5/6, 83%), with a median age of only 28 years. This is significantly younger than the median age of 50 years, reported in the US (22), and roughly on par with the median age of 39 years in China (23). Our 5-year survival rate for patients with ACC was only 33%, compared to China's 58% (24). Therefore, ACC malignancies appear more aggressive in Malaysia, with a high Malay ethnic predominance. Whole exome sequencing may be instrumental for this malignancy, which may allow for identification of at-risk individuals, early detection and intervention. It may also be beneficial to search for NOTCH1 and NOTCH2 mutations, which have been linked to functionally severe head/neck ACC (25).

In our cohort, SGC had the poorest prognosis; it is a known aggressive cancer with high mortality and increased risk of metastasis and recurrence (26). The median OS time for our patients was only 14.6 months (95% CI, 5.62 to 22.37 months), with no 3-year survival rate. This tumour is India's most common indication for orbital exenteration and has a higher preponderance for females (8). However, none of our patients was of Indian ethnicity, nor did they show any gender bias. All our patients presented six months after the onset of their symptoms with tumour sizes between 17 mm - 40 mm with positive regional lymph nodes, and a history of previously being treated for recurring chalazion. It has been determined that symptoms of more than six months, tumours larger than 10mm, orbital invasion or pagetoid histology are all high-risk indicators for SGC (20). Highlighting the need for local ophthalmologists to have more training to recognise eyelid tumours and the potential use of artificial intelligence to help detect these dangerous tumours (27). In India, the overall 5-year Kaplan-Meier estimate was 20% for patients with systemic metastasis and 26% for patients with regional lymph node metastases, which is significantly higher than our local findings. This suggests that early diagnosis and treatment may improve the prognosis for our patients.

Our study also identified patients of Chinese ethnicity as a poor prognostic factor in the overall survival (OS) rate. The median OS time for the Malay ethnicity was 85.7 months compared to only 32.2 months among the Chinese. Sub-group analysis also revealed that 78% of Chinese patients presented in either stage 3 or 4, compared to only 42% among the Malays. The barriers to early presentation for orbital malignancies have not been explored in Malaysia. However, it has been shown that Chinese patients with colorectal cancers had the lowest survival rate in Malaysia (28). They tended to present later with more advanced stages than Malays (29, 30) due to low levels of awareness of colorectal cancer (30). The level of knowledge, attitude and practices regarding orbital malignancies have not been explored in Malaysia; if misinformation or a lack of awareness is found to be the cause of late presentation among patients of Chinese ethnicity, then a targeted health education programme should be implemented for this high-risk group, emphasising the advantages of early detection as well as the identification of symptoms and risk factors.

A clean surgical margin was attained in 55.8% (n=24) of our patients, which was comparable to reports of 48% from the US (31) and 64.1% from Australia (32). Almost half (10/24, 41%) of these patients had metastasis; seven regional lymph nodes and three distant metastasis. Therefore, these patients required both radio- and chemotherapy. There were three patients treated with only radiotherapy, and six patients with clear margins that were refrained from further intervention. Alarmingly, however, only 12.5% of patients with clear surgical margins survived at five years compared to 36.8% of individuals with unclear surgical margins. Therefore, while a clear surgical margin may indicate local tumour control, micrometastasis has already occurred (33, 34). Patients with clear margins and the appearance of local control for periocular malignancies have been reported to have local recurrences and even presented with distant metastases later (32, 35). It has also been demonstrated that there is no statistically significant difference in the overall survival of patients with a clear or unclear surgical margin (12, 31). It is worth noting that patients with unclear surgical margins have been shown to have an increased surgical cure rate when treated with adjuvant radiation, chemotherapy, or a combination of the two (36, 37). Therefore, there is a clear benefit for intensive adjuvant therapy for patients deemed to be low-risk with clear margins. The unfavourable outcomes of our patients with clear surgical margins support the notion that they should be treated aggressively in the same way as patients with uncertain surgical margins.

An interesting finding in our study was that smokers had a lower mortality risk on univariate analysis; however, this was not statistically significant on multivariate analysis. The 5-year survival rate for smokers was 35% compared to only 13% for non-smokers. This protective effect of smoking has been reported in ocular melanoma, in which smokers had a higher recurrence-free survival (38). It has been hypothesised that long-term nicotine use had accumulated in the melanocytes shielding the skin against inflammation and UV light (39). Future, larger cohort studies are needed to confirm this potentially positive connection between nicotine and the survival outcomes among individuals with orbital cancers.

A limitation of this study is the retrospective design involving a single centre with a small sample size. This research also lacked information on disease-free survival as most of the patients had follow-up post-exenteration in their local ophthalmology clinics. Details on the chemotherapy and radiotherapy regimes was also lacking as the treatment was carried out in another hospital. This study's strength, however, came from the multiethnic cohort and the location of Malaysia's top orbital malignancy referral centre.

CONCLUSION

We were able to identify high-risk groups, such as Chinese ethnicity, that may benefit from focused public healthcare initiatives to increase awareness of periocular malignancies. We were also able to determine specific cancers, such as BCC and ACC, that may benefit from genetic research since it may provide crucial details about cancer's genesis, which can guide treatment choices and enhance patient outcomes. We recommend comprehensive adjuvant therapy for all periocular malignancies to improve the survival of patients with periocular malignancies, irrespective of the type of malignancy and the surgical margin status. We also advocate life-long monitoring of patients post-exenteration, with particular attention after the 3rd year, as regional and distant metastasis may occur years after obtaining effective control locally.

ACKNOWLEDGEMENT

This is a self-funded study. The Ministry of Health (MoH) permits the use of secondary data as long as it has been anonymised. The data were de-identified before analysis

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