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Clinical study of 37 cases of orbital melanoma

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Abstract

Background To analyze the clinical features and prognosis of orbital melanoma.

Design Retrospective observational case series.

Methods A retrospective analysis of the electronic medical records, histopathology, imaging examinations, and follow-up information of 37 patients with orbital melanoma.

Results The most common primary site was the conjunctiva, with half of the patients presenting with orbital involvement at the initial visit. The most common symptoms were globe displacement due to intraorbital mass, causing swelling of the eyelids and blurred vision. All patients underwent mass excision surgery. Rates of intraorbital soft tissue infiltration, nerve invasion, and bone destruction were 48.6%, 18.9%, and 13.5%, respectively. Five patients (13.5%) have distant metastases to the liver, bones, lungs, skin, and parotid lymph nodes. The Median Survival Time of the 13 deceased patients was 132 ± 24.88 months, with a 5-year survival rate of 78.4%±7.3%. The presence of nerve invasion showed a significant correlation with prognosis ($P = 0.047 < 0.05$), while age, gender, eye involvement, bone destruction, and intraorbital soft tissue infiltration showed no significant correlation with prognosis ($P > 0.05$). The expression of Ki-67 was negatively correlated with patient survival time and rate, where higher Ki-67 expression was associated with shorter survival time (r^2=-0.267, r^2=-0.067).

Conclusions Treatment strategies for orbital melanoma should consider the tumor's invasive characteristics and Ki-67 expression levels to optimize treatment outcomes and improve patient survival rates. Furthermore, due to the significant impact of nerve involvement on prognosis, it is recommended that clinical focus on this factor be enhanced.

Keywords Orbit, Melanoma, Clinical presentation, Treatment, Prognosis

Introduction

Orbital melanoma is a rare and highly malignant tumor within the orbit, categorized as primary and secondary. Primary orbital melanoma (POM) is extremely rare, accounting for only 1% of all orbital tumors [1, 7, 12, 24]. Secondary orbital melanoma (SOM) represents 5–10% of all secondary malignant tumors in the orbit [3, 11, 21, 25, 27]. The origins of these melanomas include direct spread from orbital melanomas (such as uveal melanoma, conjunctival melanoma, and eyelid melanoma), direct extension from extrinsic orbital sites (such as meninges, lacrimal sac and paranasal sinuses), and less commonly, distant metastasis from cutaneous melanomas [16, 17,

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23, 26]. Magnetic resonance imaging (MRI) is an important method for diagnosing orbital melanoma. Due to the paramagnetic effect of melanin, MRI signals play a suggestive role in the diagnosis. This not only helps to identify the presence of a tumor but also helps to assess its extent and nature to provide a basis for the development of treatment options. This article analyzes and summarizes the clinical manifestations, treatment, prognosis, and influencing factors of orbital melanoma to provide valuable insights into its diagnosis and treatment.

Methods

Subjects

Thirty-seven patients with histologically confirmed malignant melanoma of the orbit were treated consecutively at the Department of Ophthalmic Oncology, Beijing Tongren Hospital, Capital Medical University, from August 2010 to April 2023. In this study, treatment choices were based on tumor characteristics (location, size, invasion level, and effect on surrounding tissues). Deeply invasive tumors often led to orbital content exenteration, while localized tumors with clear boundaries were treated with local extensive resection. Decisions also considered patient healt and age.

Clinical data

Collection of clinical parameters of the patients (such as gender, age of onset, eye involved, duration of disease, clinical manifestations, imaging findings, histopathology, treatment modalities, follow-up, prognosis, etc.). Analysis of the patients' imaging characteristics. For patients unable to undergo MRI due to systemic conditions or psychological factors or when involvement of the orbital bone is suspected, additional orbital CT scans are recommended. For those economically capable, a whole-body PET/CT scan is advised to determine the extent of tumor involvement.

Statistical analysis

The statistical data was analyzed utilizing SPSS 25.0 software (SPSS Inc., Chicago, IL). The data's normality was evaluated through the Kolmogorov-Smirnov test. Continuous variables that were normally distributed are expressed as mean ± standard deviation, while non-normally distributed variables are portrayed as median values. Kaplan-Meier survival analysis was performed with death as the endpoint, and differences in survival time between groups were assessed using the Log-rank test. $P < 0.05$ was deemed statistically significant.

Result

General characteristics

From August 2010 to April 2023, a total of 37 patients with orbital melanoma were enrolled, with an average age of 55 years (range 28–75); among them, 11 were male and 26 were female, all presenting with unilateral eye involvement. Of the cases, only 4 (10.8%) had POM, while 12 cases (32.4%) were secondary to conjunctival melanoma, 11 cases (29.7%) were secondary to Uveal melanoma, 8 cases (21.6%) were secondary to eyelid melanoma, and 2 cases (5.4%) were secondary to lacrimal sac melanoma. The most common initial symptom in all 37 patients with orbital melanoma was proptosis due to an intraorbital mass leading to blurred vision, with a few patients experiencing bloody discharge, eye redness, itching, and other local irritative symptoms. The fundamental clinical features of the 37 patients are shown in Table 1.

Imaging features

There were 32 patients with MRI descriptions, and a detailed analysis of the MRI findings revealed different

Table 1 Fundamental features of the 37 subjects

Characteristic	Total ($N=37$)					
Primary site, (%)						
Conjunctiva	12 (32.43%)					
Uvea	11 (29.73%)					
Eyelid	8 (21.62%)					
Lacrimal gland	2 (5.41%)					
Orbital	4 (10.81%)					
Median age (range)						
	28–79	48–61	41–75	28–79	30–56	59–71
sex, n(%)						
Male	11	4	3	6		2
Female	26	7	9	2	2	2
Separation						
Left	18	4	7	3	2	2
Right	19	7	5	5		2

Table 2 Imaging features of orbital melanoma on T1/T2MRI sequences

Morphology	T1	T2	DWI	CE-MRI
Mass shadow	Isosignal	Isosignal	N/A	N/A
Mass shadow	Isosignal	slightly high signal	High signal intensity	Mild heterogeneous enhancement
Nodular mass	Short	Short	N/A	Enhancement
Nodular mass	Heterogeneous Isointense Short	Heterogeneous Isointense Short	N/A	Mild heterogeneous enhancement
Mass shadow	slightly prolonged	Isointense	Low signal intensity	Mild to moderate enhancement
Mass shadow	Short	Long	N/A	Heterogeneous enhancement
Mass shadow	Isosignal	Isosignal	N/A	Heterogeneous enhancement
Irregular mass	Heterogeneous	Heterogeneous	N/A	Heterogeneous enhancement
Strip	N/A	Isosignal	N/A	No enhancement
Mass shadow	Heterogeneous	Heterogeneous	High signal intensity	N/A
Semi-elliptical	Slightly shortened	Isosignal	Iso-signal intensity	Homogeneous moderate enhancement
Nodular	Isosignal	Iso-long	Heterogeneous high signal intensity	Heterogeneous enhancement
Ellipsoid	Short	Short	N/A	Mild to moderate enhancement
Broad-based polypoid	Short	Short	N/A	Enhancement

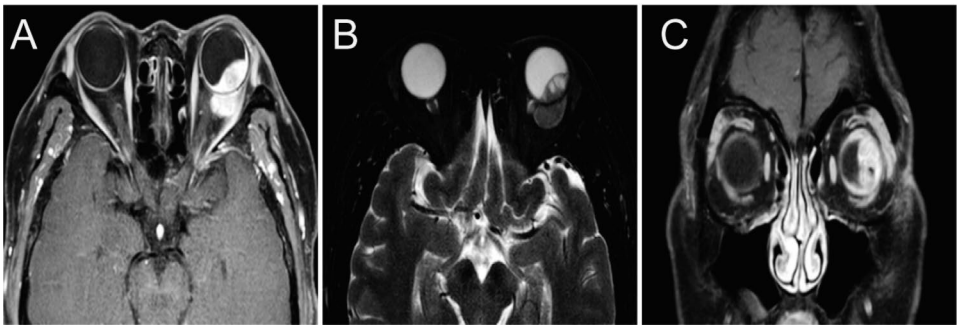

Fig. 1 **A-C**: Imaging changes of orbital melanoma (**A**) Horizontal T1WI enhanced scan image. (**B**) Horizontal T2WI scan image. (**C**) The enhancement scan shows uneven enhancement

signal patterns and contrast enhancement responses, uncovering the lesions' tissue characteristics and vascular activity. The MRI showed orbital space-occupying lesions in 5 cases, nodular signal shadows in 3 cases, patchy signal shadows in 4 cases, round signal shadows in 3 cases, and orbital exenteration broad-based mushroom-shaped signal shadows in 2 cases. The lesions in 4 cases appeared slightly longer T1 and slightly longer T2 signal shadows, with significant enhancement after contrast. In 4 cases, the lesion sites showed short T1 and short T2 signals, with uneven enhancement seen on imaging. In 2 cases, the lesion sites exhibited mixed T1 and T2 signal shadows with uneven enhancement on scanning. Short T1 and extended T2 signal shadows, with uneven amplification upon scanning, were seen in two cases. Two cases had long T1 and equal T2 signals, with mild enhancement after contrast. Some lesions appeared as slightly extended T1 and equal T2 signal shadows, showing low signal on diffusion-weighted imaging (DWI) and high signal on ADC map, further indicating the possibility of a tumor. Some areas of the lesions did not enhance after contrast, possibly due to necrosis or low perfusion within the cancer (Table 2). The involvement and consequences of the lesions included affecting the lacrimal gland and extraocular muscles, resulting in changes in eye position and morphology. Some patients experienced compression of the optic nerve and eyelid thickening, leading to visual impairment and restricted eye function. Additionally, some patients' lesions extended to the orbital apex, indicating posterior progression of the lesions, impacting more periocular structures. (Fig. 1.A-C).

Pathological diagnosis

Pathological diagnosis revealed that in 18 cases (48.6%), infiltration of orbital soft tissues occurred, with 7 cases (18.9%) involving the optic nerve, with the primary site being uveal melanoma in 5 (71.4%) of these patients, 5 cases (13.5%) showing destruction of the orbital wall bone, and 2 cases (5.4%) demonstrating lymphocytic infiltration. The main infiltration sites in orbital soft tissues include fibrous connective tissue, fatty tissue, striated muscle, levator palpebrae superioris muscle, and extraocular muscles.

Pathological histology and immunohistochemical staining

Pathological histology staining revealed diffuse growth of malignant melanoma cells, with poor cell adhesion, some cells containing melanin, significant cellular pleomorphism, prominent nucleoli, rough nuclear chromatin, and a high nuclear-to-cytoplasmic ratio, and numerous visible mitoses (Fig. 2.A-D). S-100 was positively expressed in 34 cases, negatively expressed in 2 cases, and unknown in 1 case. HBM45 was positively expressed in 32 cases and negatively expressed in 5 cases. Meland-A was positively expressed in 31 cases, with 6 instances negative. Vimentin was positive in 28 cases, with 9 instances unknown. The average expression level of Ki-67 was 49.7%, cell proliferation activity was relatively high. Mean Ki-67 values were 28.5% for primary uveal melanoma, 26.5% for eyelid melanoma, 24.8% for conjunctival melanoma, 12.5% for lacrimal sac, and 7.5% for POM. Orbital melanomas originating from uveal melanomas exhibit the highest Ki-67 index, and a higher Ki-67 index is generally associated with a poorer prognosis. Therefore, these findings may suggest that primary uveal melanoma may have a higher risk of aggressiveness and poorer prognosis than other types of orbital melanoma. (Fig. 2.E-I).

Mass character

The swelling showed a wide variety of traits, ranging from soft to hard texture, and colour ranging from greyish-black, black, greyish-white, greyish-brown, purplish-red to brownish-black. Most of the swellings were solid, while some showed tough, smooth, or brittle, date-like or fish-like features. There are various cell types, mainly including spindle cell type, epithelioid type, small round cell malignancy, and atypical melanocytes. In addition, a mixture of spindle and epithelioid cell types is also seen.

Prognosis

All 37 patients underwent surgical resection; 28 cases underwent exenteration of the orbit, while 9 cases had partial excision. The average follow-up time was 66.14 ± 46.716 months (range 4-165 months). A total of 24 patients (64.8%) were alive without disease (AOD), 3 cases (8.1%) died from other causes (DOC), and 10 cases (27%) died from melanoma (DWD). There were 5 cases (13.5%) with distant metastasis to the liver, bones, lungs, and skin. One case (2.7%) had metastasis to the parotid lymph node. The Median Survival Time of the 13 deceased patients was 132 ± 24.88 months, with a 5-year overall survival rate of 78.4%±7.3% (Fig 3 A). Logistic regression analysis revealed a significant correlation between patients with neural invasion and prognosis ($P = 0.047 < 0.05$). In contrast, we conducted a survival analysis of orbital melanoma patients using the Cox proportional hazards model based on different primary sites and assessed the impact of factors such as age, gender, bone destruction, optic nerve infiltration, and soft tissue infiltration on patient prognosis. However, our results showed that *P*-values for all variables were greater than 0.05, suggesting that these factors did not exhibit independent prognostic value in our study sample. The expression of Ki-67 was negatively correlated with patient survival time and rate; higher Ki-67 expression was associated with shorter survival time (r^2=-0.267, r^2=-0.067) (Fig. 3.B).

13 cases of known deceased patients diagnosed with orbit melanoma died on average 61.92 ± 51.75 months (range 4-151 months) after diagnosis. Survival rates varied based on the primary tumor origin, with those initially involving the orbit having the best survival rates and those from the uvea having the worst (Fig. 3C). Among 37 patients, the time interval from the primary tumor to orbital disease ranged from 0 to 60 months, with 19 cases (51.3%) showing orbital involvement at the first presentation (Fig. 3.D). There was no correlation between disease-free interval in the orbit and overall survival (r squared = 0.037).

Discussion

Malignant melanoma originating in the eye and adnexa is an extremely dangerous and uncommon orbital tumor, primarily secondary, with primary cases being sporadic. Regarding the origin of POM, there are currently two main theories: one suggests it may arise from melanocytes of neural crest origin migrating along specific nerve pathways to the orbit [1, 6, 9, 10, 13, 16, 17, 23]; while the other proposes it may stem from an abnormal aggregation of melanocytes within the orbit [1, 2, 20, 23]. SOM has a more complex origin, primarily caused by invasion or metastasis to the orbit from melanomas in other locations such as the choroid, conjunctiva, skin, or meninges [18, 21]. This study retrospectively analyzed the clinical, pathological, imaging, and prognostic characteristics of 37 patients diagnosed with orbital melanoma through histopathological examination.

Patients ranged from 28 to 75 (mean age of 55), with middle-aged and older patients making up the majority. Adetunji reported a higher incidence of orbital melanoma in men than in women among 88 patients [1]. The male-to-female ratio in this study was 26:11, a difference that may reflect variations in sample selection, geographic regions, and genetic backgrounds. Further research may be necessary to explore the potential reasons underlying these differences to understand their impact on the disease better. The rates of infiltration into peripheral tissues, involvement of the optic nerve, and occurrence of bone destruction were 48.6%, 18.9%, and 13.5%, respectively, with no significant correlation to patient prognosis ($P > 0.05$). The rates of infiltration into peripheral tissues, and occurrence of bone destruction

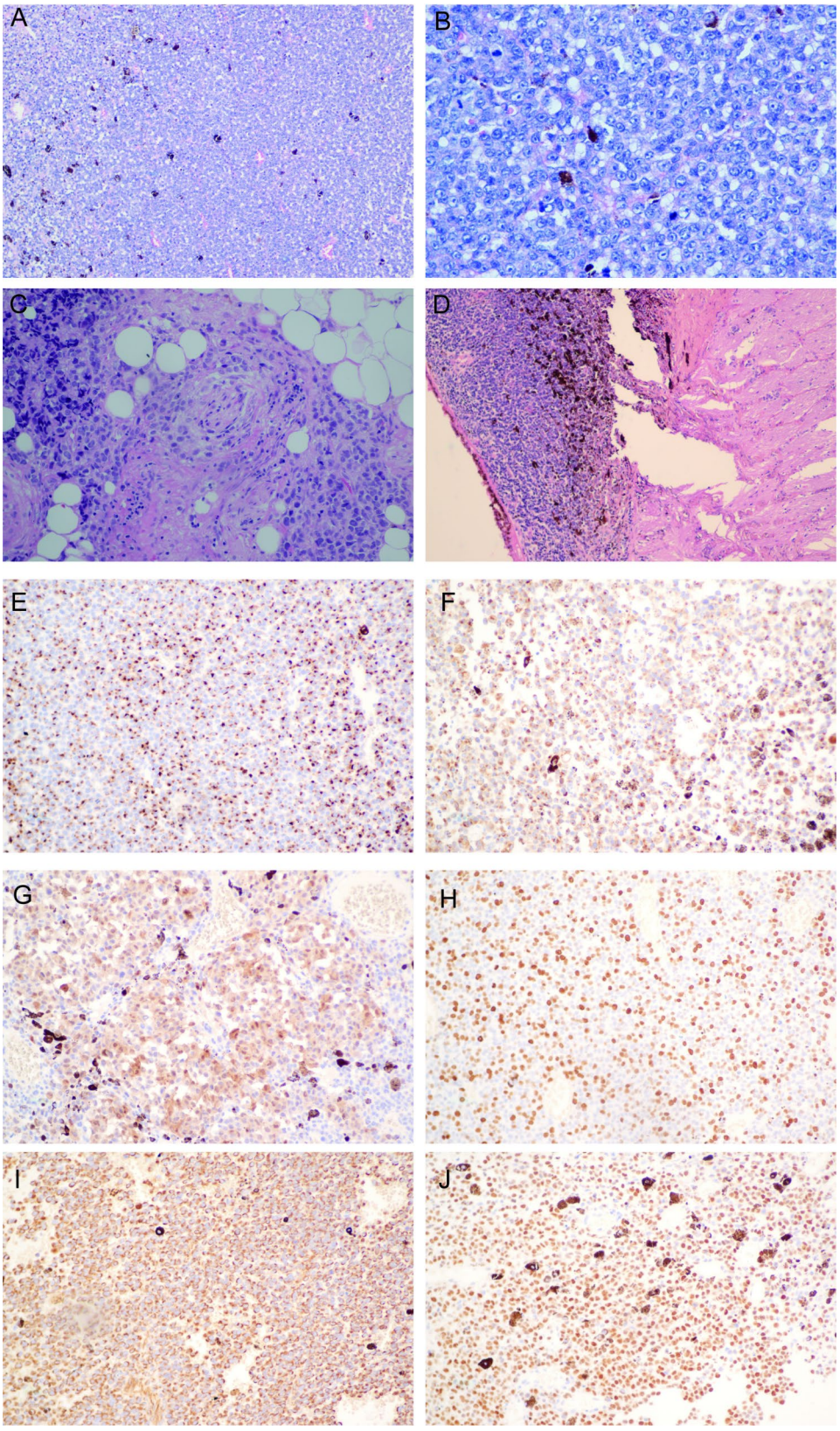

Fig. 2 **A-D**: Histopathological changes of orbital melanoma (Primary tumor location: choroid) (**A**) He-100X, (**B**) He-400x, (**C**) He-200X Nerve invasion, (**D**) He-40X Lamina cribrosa invasion. **G-I**: Immunohistochemical Staining of Orbital Melanoma. (**E**) HBM45(+) (**F**) Meland-A (+), (**G**) S-100 (+), (**H**) Ki-67 (+), (**I**) Vimentin (+), (**J**) CyclinD1 (+)

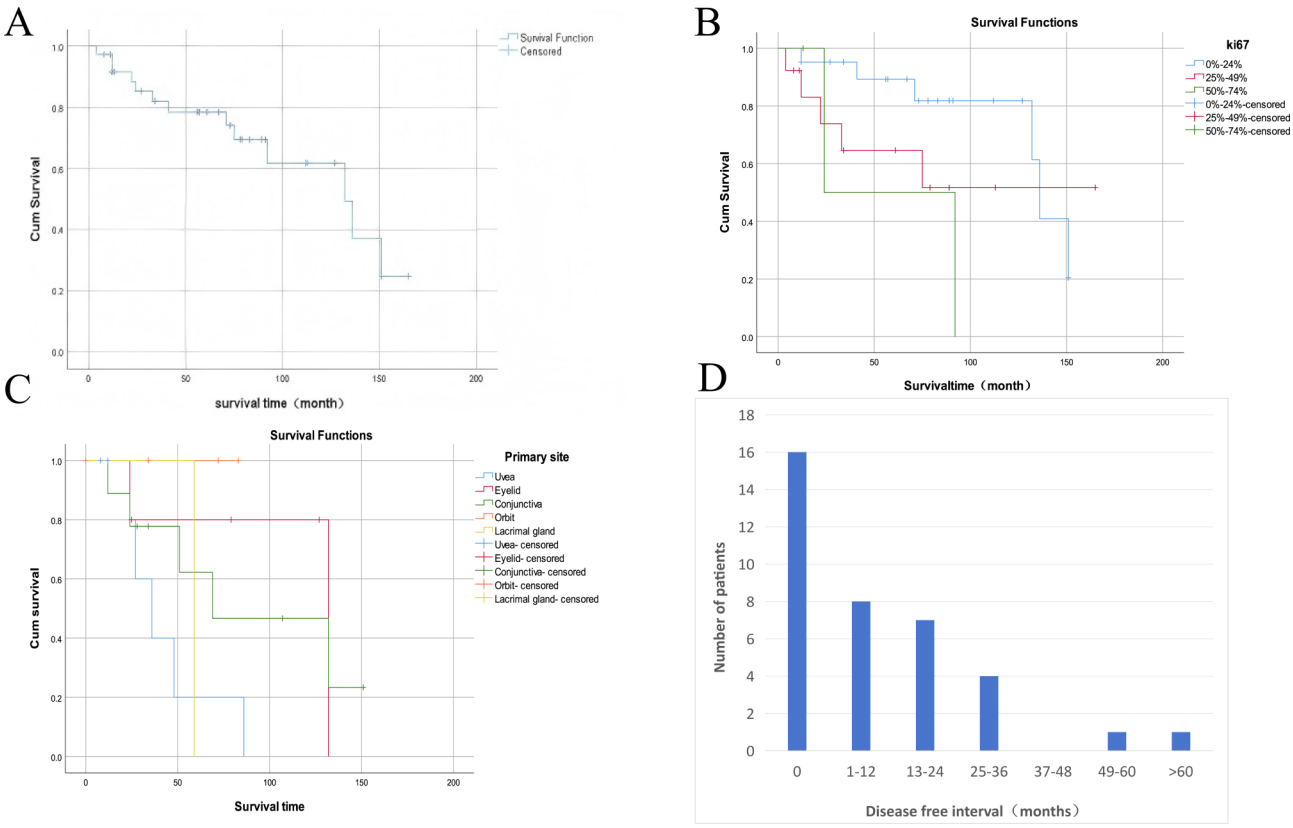

Fig. 3 **A.** Kaplan-Meier survival analysis of 37 patients. The 5-year survival rate was 78.4%±7.3%. **B.** Kaplan-Meier Survival Analysis of 37 Patients (According to ki-67 Expression). **C.** Kaplan-Meier Survival Analysis of 37 Patients (According to Primary Tumor Origin). **D.** The time interval between the diagnosis of primary melanoma and the appearance of orbital disease in 37 patients

were 48.6%, and 13.5%, respectively, with no significant correlation to patient prognosis ($P > 0.05$).

Melanoma diagnosis by histological investigation is considered the gold standard, while imaging studies serve as essential adjuncts to the diagnostic process. MRI reveals that due to the paramagnetic properties of melanin, on T1-weighted images, the tumor usually shows a high signal intensity, and on T2-weighted images, a low signal intensity with a characteristic display rate of 72–95% [6]. Analysis of patient MRI findings indicates that the imaging characteristics of orbital melanoma are diverse and complex, encompassing a variety of neoplastic and non-neoplastic changes. Histological examination shows that tumor cells are arranged in sheets or nests, with variable cell sizes, significant atypia, and spindle or epithelioid morphology [17]. Immunohistochemical staining demonstrates positive expression of S-100, HMB-45, Melan-A, and other melanocytic markers in the most tumor cells [7, 10, 13–15]. In this study, the positive expression rates were 91.8% for S-100, 86.4% for HMB-45, and 83.7% for Melan-A.

The prognosis of orbital melanoma is generally poor and influenced by complex prognostic factors. Rose treated 13 patients uniformly, yet their prognoses varied greatly [22]; Figueira et al. found, through histopathological examination, that the prognosis of this disease seems unrelated to the type of tumor cells but rather to the tumor cells' number of mitotic Fig. [7]. In this study, the Median Survival Time of the 13 deceased patients was 132 ± 24.88 months, with a 5-year survival rate. of 78.4% ± 7.3%. Logistic regression analysis revealed a significant correlation between the presence of neural infiltration in patients and their prognosis ($P = 0.047$), indicating neural infiltration may be an important factor affecting prognosis. However, factors such as age, gender, eye laterality, bone destruction, and peripheral tissue infiltration did not show a substantial association with the prognosis ($P > 0.05$), this may be due to the limited size of our sample and the possible presence of uncontrolled confounding variables, which may have contributed to the failure of the above factors to show significant prognostic value. In addition, different subtypes of orbital melanoma may have different biological behaviors, which may also affect the prognostic value of each factor. Furthermore, the expression level of Ki-67 protein was negatively correlated with patient survival time and rate (r^2=-0.267, r^2=-0.0.067), implying that patients with higher Ki-67 expression levels may face shorter survival

times, highlighting the potential value of Ki-67 in evaluating patient prognosis.

POM is rare for treating melanoma in the eye socket, leading to a lack of standardized treatment protocols. However, surgical excision remains the primary treatment method [4, 9, 14, 19]. According to existing literature, scholars hold different opinions on the choice of surgical procedure. Figueira suggest that direct excision of orbital contents results in higher disease-free survival rates than extensive local excision [7]. On the other hand, Rose et al. argue that local excision combined with adjuvant radiotherapy is this disease's primary treatment [22]. Chemotherapy, particularly dacarbazine, is thought to be the primary treatment option for SOM [8]. Over the past few years, the development of new immunotherapies, particularly the discovery of the immune checkpoints PD-1 and CTLA-4, has provided new treatment perspectives and may bring revolutionary changes in treatment in the coming years [5, 8]. A study of 37 patients with orbital melanoma revealed that all patients underwent surgical excision, indicating that excision is the primary and common treatment method. The choice of different surgical procedures (excision of orbital contents, local excision, tumor excision after enucleation) depends on the tumor's location, size, and spread. 64.8% of patients had disease-free survival at an average follow-up time of 66.14 months, demonstrating the positive impact of surgical excision on disease control. However, 27% of patients died from melanoma, indicating that the risk of death from the disease still exists even with treatment. Although the overall 5-year survival rate is relatively high (78.4%), there is still a proportion of patients who die or experience disease recurrence and metastasis, suggesting the need for close monitoring of patient post-treatment to identify and manage recurrence and metastasis early.

Regardless of the location or timing of the initial tumor in patients with a history of melanoma, the possibility of orbital recurrence should be carefully considered.

Although survival rates for orbital melanoma vary, further research into its causes is needed. Surgery is the primary treatment approach, but with the development of new immunotherapies, treatment strategies in the coming years may undergo significant changes. Emphasizing the importance of orbital melanoma, active treatment of primary cancers, and close collaboration between ophthalmologists and oncologists are crucial for ensuring comprehensive treatment and monitoring of the condition.

Abbreviations

MRI	Magnetic resonance imaging
AOD	Alive without disease
DOC	Died from other causes
DWD	Died from melanoma

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Not applicable.

Author contributions
All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by L, M andL. Land M wrote the first draft of the manuscript. L, L and R created the relevant tables and figures of this article. M, D and L finished the final review. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability
The datasets analysed during the current study are available in the Mendeley Date repository, doi: 10.17632/hrmf2rvrt2.2.

Declarations

Ethics approval and consent to participate
The name of the ethics committee: Ethics Committee of Beijing Tongren Hospital, Capital Medical University Ethics No. TREC2023-KY061.

Informed consent
has been obtained from all participants in the study.

Consent for publication
Not Applicable.

Competing interests
The authors declare no competing interests.

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