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ORIGINAL RESEARCH

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Roles of skull base surgery and particle radiotherapy for orbital malignant tumors involving the skull base

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Abstract

Purpose: To investigate the oncological outcomes of orbital malignant tumors invading the skull base.

Methods: A retrospective analysis was conducted on 16 patients with orbital malignant tumors invading the skull base. Eleven patients were treated with skull base surgery, four patients were treated with particle therapies, and one patient was treated with chemoradiotherapy (CRT) as initial treatment.

Results: The most frequent histological type was adenoid cystic carcinoma in seven patients, followed by squamous cell carcinoma in two patients. Local recurrence occurred in two of the six surgically treated patients who did not receive postoperative radiotherapy (RT) or CRT. One of them was successfully salvaged by RT, and the other died of disease. With a median follow-up of 24 months, the 2-year overall, local control, and disease-free survival rates of all patients were 82.5%, 87.5%, and 59%, respectively.

Conclusions: Patients with positive surgical margins were at risk of local recurrence. Postoperative RT should be considered for all surgically treated patients.

Level of Evidence: 4.

KEYWORDS
orbital malignant tumors, particle radiotherapy, skull base surgery

1 | INTRODUCTION

The orbit is an anatomical cavity consisting of the conjunctiva, ocular bulb, optic nerve, extraocular muscles, lacrimal gland, and soft tissue. Its bony walls are composed of the maxilla, zygomatic bone, lacrimal bone, palatine bone, frontal bone, ethmoid bone, and sphenoid bone and are adjacent to critical organs such as the frontal lobe, internal carotid artery, and cavernous sinus. Malignant tumors can arise from their contents and present symptoms such as diplopia and exophthalmos,[1] but are often initially misdiagnosed due to their rarity. The most dominant subtype of orbital malignant tumors is malignant lymphoma,[1,2] followed by various histological types of primary cancers, such as squamous cell carcinoma (SCC) and adenoid cystic carcinoma (ACC), which occasionally invade the skull base. Treatment of

orbital malignant tumors poses unique challenges since the orbit is closely associated with an individual's quality of life and is anatomically complex. The goal of achieving local control must be weighed against the toxicities and long-term effects of treatments, which can result in significant morbidity, such as ipsilateral loss of vision and/or poor cosmetic impact.[3] Several recent studies have reported favorable oncological outcomes in patients with orbital malignant tumors treated with skull base surgery followed by adjuvant intensity-modulated radiotherapy (IMRT)[3-5] or particle radiotherapy.[6] However, the roles of skull base surgery and particle radiotherapy have not been fully investigated due to its rarity and variety of histological types. In this study, we reported our experience with patients with advanced orbital malignant tumors other than malignant lymphoma invading the skull base and evaluated the roles of these treatment modalities for advanced orbital cancers.

2 | METHODS

A retrospective analysis was performed on patients with orbital malignant tumors invading the skull base who were treated at Kobe University Hospital between 1993 and 2018. Six men and ten women were included in this analysis, with an average age of 53 (range, 10-74) years. Malignant tumors were located in the right orbit in four patients and in the left orbit in 12 patients. Patients were followed up for at least 24 months or until they died. Median follow-up period after treatment was 22 months (range: 1-99 M). Overall survival, disease free survival, and patterns of failure were evaluated. Local control was defined as free from disease in and around the periorbital tissues and postoperative bed. Regional control was defined as the absence of disease in draining regional lymphatics. Survival outcomes were calculated using the Kaplan-Meier method, with prognostic factors determined by the log-rank test. Statistical analyses were performed using JMP version 13 (SAS Institute, Cary, North Carolina). This retrospective study was approved by the institutional ethical committee of Kobe University Hospital (#B200049), and written informed consent was obtained at the time of initial treatment.

3 | RESULTS

3.1 | Clinical management

T classification was determined as T3 in three patients, T4a in one patient, T4b in six patients, and T4c in three patients according to the eighth Union for International Cancer Control tumor-node-metastasis classification.[7] Metastasis in the cervical lymph node was observed in two patients, and lung metastasis was present at the initial visit in one patient (Tables 1 and 2). The most frequent histological type was ACC in seven patients, followed by SCC in two patients (Table 2). Eleven patients were treated with skull base surgery,[8] four patients were treated with particle therapies (carbon beam with a total dose of 65-70.2 Gy [RBE] in three patients and a proton beam with a total dose of 65 Gy [RBE]), and one patient with a neuroendocrine tumor was treated with concomitant chemoradiotherapy (CCRT) with a total dose of 66 or 70 Gy and total cisplatin dose of 240 mg/m^2 as an initial treatment (Tables 3 and 4).

TABLE 1 Characteristics of patients with malignant orbital tumors

Characteristics		No. of patients (%)
Age (median)	10-74 (53)	
Sex	Male	6 (37.5)
	Female	10 (62.5)
Clinical T stage	T3	3 (18.75)
	T4a	3 (18.75)
	T4b	7 (43.75)
	T4c	3 (18.75)
Clinical N stage	N0	14 (87.5)
	N1	2 (12.5)
Clinical M stage	M0	15 (93.75)
	M1	1 (6.25)
Histology	Adenoid cystic carcinoma	7 (43.75)
	Squamous cell carcinoma	2 (12.5)
	Adenocarcinoma	1 (6.25)
	Sebaceous carcinoma	1 (6.25)
	Syringomatous carcinoma	1 (6.25)
	Leiomyosarcoma	1 (6.25)
	Myoepithelial carcinoma	1 (6.25)
	Carcinoma, NOS	1 (6.25)
	Neuroendocrine tumor	1 (6.25)

Among the 11 patients treated with skull base surgery, the surgical margin was pathologically positive in four patients. Three of them received postoperative IMRT with a total dose of 66 to 69.96 Gy, and one of them received cisplatin (CDDP)-based triweekly CCRT with a total dose of 69.96 Gy and a total dose of 240 mg/m^2 body surface area of CDDP. Postoperative radiotherapy was also performed in one patient with a negative surgical margin. The other six patients were followed up without postoperative treatment. Local recurrence was not observed in the patient who received postoperative radiotherapy with a negative surgical margin but occurred in two out of six patients without postoperative radiotherapy. One patient was successfully salvaged by IMRT, but another patient died of disease. Two patients developed lung metastases and died of disease.

Of the four patients treated with particle therapies (proton or carbon), three developed distant metastases and died of disease. Multiple lymph node metastases were also observed in one of these three patients. Of note, in two out of the three patients, positron emission tomography-computed tomography (PET-CT) revealed loss of accumulation, but "tumor shadow" remained even after the treatment, suggesting residual disease at the primary site.

Overall, three out of four patients died of distant metastasis, and the other one died of locoregional recurrence. The 2-year overall, local control, and disease-free survival rates of all patients were 82.5%,

TABLE 2 Clinical tumor-node-metastasis staging for all patients

Sub site	Histology	No.	T3	T4a	T4b	T4c	Treatment
Lacrimal gland	Adenoid cystic carcinoma	7		3	3	1	S4, PRT3
	Adenocarcinoma	1				1	PRT1
	Myoepithelial carcinoma	1			1		S1
	Carcinoma, NOS	1				1	S1
Eyelid	Squamous cell carcinoma	2	1		1		S2
	Sebaceous carcinoma	1			1		S1
	Syringomatous carcinoma	1			1		S1
	Neuroendocrine tumor	1					CRT1
Orbital	Leiomyosarcoma	1	1				S1
	Total	16	3	3	7	3	S11, PRT4, CRT1

Abbreviations: CRT, chemoradiotherapy; PRT, particle radiotherapy; RT, radiotherapy; S, surgery.

TABLE 3 Outcome of patients who underwent surgery

Surgical margin	No. of pts.	Adjuvant treatment	No. of pts.	Recurrence	No. of pts.	Salvage therapy	Histology	No. of pts.	Outcome
Positive	4	RT	3	None	1	None	Adenoid cystic carcinoma	1	NED
				Lung	1	None	Adenoid cystic carcinoma	1	AWD
				Local bone	1	None	Adenoid cystic carcinoma	1	DOD
		CRT	1	None	1	None	Carcinoma, NOS	1	NED
Negative	7	RT	1	Lung Kidney	1	None	Squamous cell carcinoma	1	DOD
		None	6	None	4	None	Leiomyosarcoma	1	NED
							Sebaceous carcinoma	1	NED
							Adenoid cystic carcinoma	1	NED
							Squamous cell carcinoma	1	NED
				Local	2	RT	Myoepithelial carcinoma	1	NED
						None	Syringomatous carcinoma	1	DOD

Abbreviations: AWD, alive with disease; CRT, chemoradiotherapy; DOD, died of disease; pts, patients; RT, radiotherapy; NED, no evidence of disease.

TABLE 4 Outcome of patients who received radiotherapy

Treatment	Recurrence	No. of pts.	Salvage treatment	No. of pts.	Histology	Outcome
Particle radiotherapy (n = 4)	None	1	None	1	Adenoid cystic carcinoma	NED
	Neck	1	S + RT	1	Adenocarcinoma	AWD
	Bone	1	RT	1	Adenoid cystic carcinoma	DOD
	Brain, lung	1	RT + CT	1	Adenoid cystic carcinoma	DOD
CRT (n = 1)	Neck	1	RT	1	Neuroendocrine tumor	NED

Abbreviations: AWD, alive with disease; CRT, chemoradiotherapy; CT, chemotherapy; DOD, died of disease; NED, no evidence of disease; pts, patients; RT, radiotherapy; S, surgery.

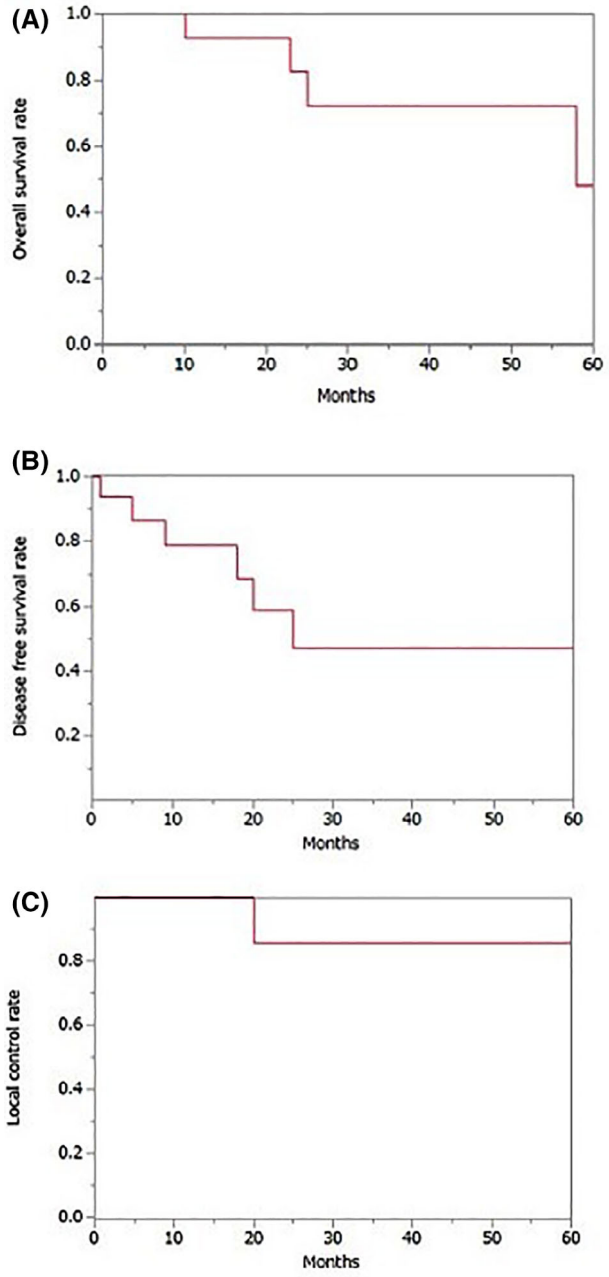

FIGURE 1 Survival curves of orbital cancer patients. (A) Overall survival, (B) Disease-free survival, and (C) Local control rate

87.5%, and 59%, respectively with a median follow-up of 24 months (Figure 1).

4 | DISCUSSION

Orbital malignancies other than malignant lymphoma are extremely rare, and reports on the oncological outcomes of locally advanced orbital malignant tumors are limited. Although orbital preservation is ideal, treatment of advanced cancers invading the skull base should be determined by the radical cure of the disease. We conducted a retrospective review of advanced orbital malignant tumors with skull base invasion to develop optimal treatment strategies for advanced orbital cancers.

In most of the previous reports on orbital malignant tumors, the majority of the patients were in the early stages, and most of them were treated with orbital resection. Aggressive orbital malignant tumors are also treated with orbital exenteration because of the complexity of the surrounding anatomy.[3,9,10] In recent years, a multidisciplinary orbit-sparing treatment approach is generally recommended when feasible to preserve some extent of visual function while maintaining high rates of local control.[9] In a study of 29 locally advanced orbital malignant tumors, favorable oncological outcomes with a 5-year survival rate of 60% and 5-year local control rate of 83% were achieved by applying postoperative IMRT following orbital debridement.[3] Wolkow et al have reported globe-preserving surgery followed by proton beam radiation. Although surgical procedures in their study included subtotal, gross, and piecemeal resections, favorable long-term survival with variable periods of useful vision was reported compared to other recent reports.[5]

In the present study, all tumors invaded the skull base and orbital contents, such as the optic nerve and/or extraocular muscles. Thus, en bloc radical resection consisting of orbital exenteration with extensive skull bone removal in combination with extracranial and intracranial approaches followed by simultaneous free flap reconstruction was performed in all surgically treated patients. Although the number of patients was limited and observation periods were relatively short, oncological results were relatively more favorable compared with previous reports despite the far-advanced cancers in this series, suggesting the significant impact of skull base surgery on the treatment for far-advanced orbital cancer.

However, two of the six patients with negative surgical margins who did not have postoperative RT developed local recurrence. As Kobayashi et al have reported,[11] it is relatively difficult to ensure sufficient safety margins and evaluate the precise status of the surgical margins in skull base surgery due to its anatomical complexity. In addition, it has been well known that ACC often shows perineural invasion. Thus, the present results suggest that postoperative RT or chemoradiotherapy should be considered for all surgically treated patients regardless of the pathological status of the surgical margins.

Although the number of patients was small, the primary site was well controlled in all patients treated with particle therapy. Hu et al have reported that particle therapy following eye-sparing surgery provided effective local control with infrequent severe toxicities in patients with orbital malignancies.[12] They also reported severe late toxicities in <10% of the cases. Several reports from Japan have reported favorable oncological results with particle therapy alone, while visual acuity was impaired in the long term.[13-15] However, image assessment after particle therapy has some limitations. In particular, in cases where tumor shadows with internal necrosis are prolonged, it is often difficult to determine the presence or absence of viable cells (Figure 2). Tomura et al reported pitfalls of ^{18}F-FDG PET/CT for ACC imaging include inherently low ^{18}F-FDG uptake in ACCs.[16] The fact that two out of four patients treated with particle

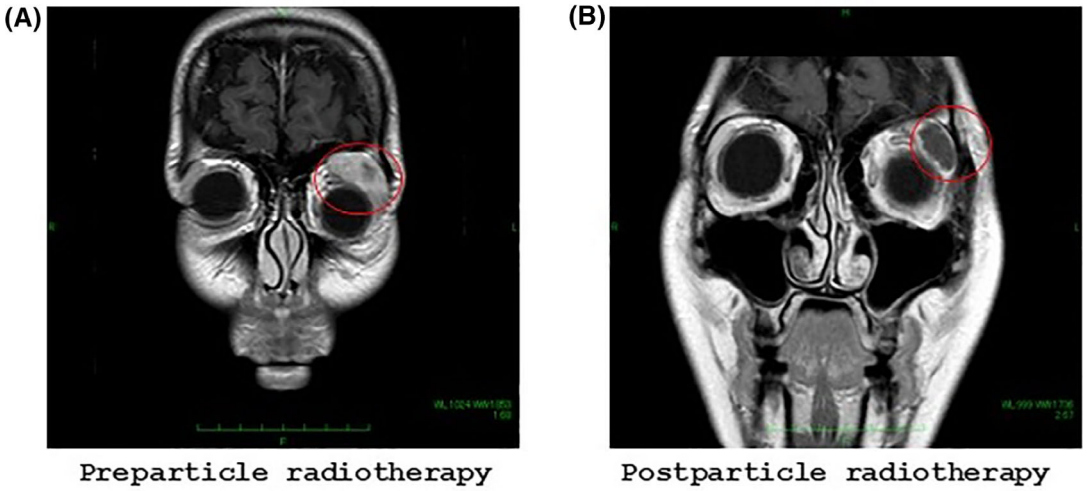

FIGURE 2 (A) Coronal magnetic resonance imaging view of preparticle radiotherapy with left lacrimal gland tumor. (B) Coronal magnetic resonance imaging view of postparticle radiotherapy with left lacrimal gland tumor

therapy developed distant metastases may suggest that subclinical tumor cells might remain in the primary site, while fluorine-18-deoxyglucose accumulation was not observed on PET-CT. All patients who treated with particle therapy rejected the surgery for cosmetic reasons. The short duration of available retrospective follow-up periods limits our evaluation of this study. These limitations of the study also need to be acknowledged.

5 | CONCLUSION

A clinical study was conducted on 16 orbital primary cancers with skull base extensions. Even patients with negative surgical margins were at a risk of local recurrence. Postoperative RT or CRT should be considered in all surgically treated patients, regardless of the pathological status of the surgical margins. Close follow-up for distant metastasis is mandatory in patients treated with particle therapy, even if no accumulation is observed on PET-CT.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

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