BMC Cancer

RESEARCH

Open Access

Long-term outcomes and prognostic factors of eye-preserving treatment with particle beam radiotherapy for orbital malignancies

Weixu Hu[1,4,5†], Qiong Cai[4,5,3†], Jing Gao[1,4,5], Jiyi Hu[1,4,5], Qingting Huang[1,4,5], Haojiong Zhang[2,4,5] and Lin Kong[1,4,5*]

Abstract

Background This retrospective study report the clinical experience of eye-preserving treatment follow by particle beam radiotherapy (IMPT or CIRT) for orbital malignancies. And to evaluate prognostic factors for orbital and lacrimal gland tumors.

Methods Sixty-two patients with orbital malignancies were identified in the records of a single center between 2015 and 2021. Sixty-one patients met inclusion criteria. All of the patients received eye-preserving treatment before PBRT. Majority of the patients (91.8%) were treatment with CIRT. Clinical data, treatment modality, local control, metastases and survivals and visual outcomes, as well as associated prognostic indicators were were assessed.

Results Sixty-one patients were followed with a median of 40.7 months (44.3 months for surviving patients). The 3- and 5-year DSS and LC rates were 88.1% and 69.9%, and the 3- and 5-year DMC rates were 77.5% and 74.2% for entire orbital malignancies. For lacrimal gland carcinoma, the 5-year DSS, LC, DMC, and PFS rates were 83.3%, 64.8%, 66.8%, and 53.4%. Tumor size, T stage, extraorbital invasion, and bone invasion influenced survivals. No grade 3 or higher acute toxicities were observed. A total of 8 patients experienced grade 3–4 visual impairment.

Conclusions Particle radiotherapy following eye-preserving treatment provided a favorable local control and survivals with moderate acute and late toxicities, even in patients with unresectable disease. Particle radiotherapy was a promising strategy for management of orbital tumors.

Keywords Orbital tumors, Lacrimal gland tumors, Proton beam radiation, Carbon ion beam radiation, Eye-preserving, Survival

†Weixu Hu and Qiong Cai contributed equally to this work.

*Correspondence:
Lin Kong
linkong1152@163.com
[1]Department of Radiation Oncology, Shanghai Proton and Heavy Ion Center, Fudan University Cancer Hospital, Shanghai 201315, China
[2]Department of Radiation Oncology, Shanghai Proton and Heavy Ion Center, Shanghai 201315, China
[3]Department of Research and Development, Shanghai Proton and Heavy Ion Center, 201315 Shanghai, China
[4]Shanghai Key Laboratory of radiation oncology, Shanghai 201315, China
[5]Shanghai Engineering Research Center of Proton and Heavy Ion Radiation Therapy, Shanghai 201315, China

Background

Primary malignant orbital tumors are rare and histologically diverse due to the orbit's complex anatomy, which include the globe, muscles, adipose tissue, blood vessels, lymphatics, and nerves. Lymphoma is the most common type. Lacrimal gland malignancies account for approximately 20% of orbital tumors, with adenoid cystic carcinoma (ACC) being the most prevalent subtype [1].

The management is challenging due to the critical structures and the limited space within the orbit, which complicates achieving both tumor control and vision preservation. Eye-sparing surgery (ESS) combined with adjuvant radiotherapy has become as the standard treatment approach, offering survival outcomes comparable to orbital exenteration (OE) [2–4].

Proton and heavy ion radiotherapy, leveraging the Bragg peak effect, allow precise tumor targeting while minimizing damage to normal tissues [5, 6]. Furthermore, carbon ions, as high-linear energy transfer (LET) radiation, possess greater biological efficacy compared to photons or protons [7–10], making them particularly effective in treating radioresistant tumors such as adenoid cystic carcinoma, malignant melanoma, and sarcomas. Particle radiotherapy (PBRT) has been increasingly used in head and neck malignancies [11].

This study reports updated results on the long-term efficacy and safety of proton beam (PBT) and carbon ion radiotherapy (CIRT) for malignant orbital tumors, analyzing prognostic factors for local control (LC), distant metastasis control (DMC), and disease-specific survival (DSS).

Methods

From November 2015 to November 2021, data from 62 consecutive patients with non-metastatic orbital malignancies were retrospectively reviewed. Excluding one patient whose pathological diagnosis changed mid-treatment. In our cohort, 4 patients underwent biopsy prior to particle radiotherapy, while the remaining 57 patients received eye-preserving surgery before particle radiotherapy. The study received approval from the Institutional Review Board (IRB) of our center. Prior to PBRT, all patients underwent a comprehensive assessment and imaging (MRI or CT) of the orbital region, with staging according to the AJCC 8th edition.

Patients were immobilized in a supine position using a dual-component polyurethane foam and head-neck-shoulder thermoplastic mask. Planning CT scan without contrast. MRI-CT fusion imaging guided target contouring. The gross tumor volume (GTV-p) was defined from imaging, with a 1–3 mm margin (dependent on OARs) added to create the high-risk clinical target volume (CTV-HR). The intermediate-risk CTV (CTV-IR) encompassed the tumor bed with a 1–3 mm margin and operative bed for cases with R1 or close surgical margins. The low-risk CTV (CTV-LR) included the orbital wall region within 1–1.5 cm of the primary tumor or its resection bed, and the periosteum. Orbital apex, superior and inferior orbital fissures, and foramen rotundum also included in CTV-LR in ACC, SCC, adenocarcinoma cases. Unless the cavernous sinus is involved, it is not routinely irradiated. All patients were treated using PTV-based planning, with a uniform expansion of 0.3 cm applied to the GTV/CTV to generate the planning target volume (PTV-G/PTV-C). Multiple-field optimization was employed for each plan. The PBRT dose was expressed in Gy-equivalents (GyE). Both intensity-modulated proton therapy (IMPT) and CIRT were delivered using pencil beam scanning (PBS) technology. All planning was optimized using the SyngoRT (V13B, Siemens, Germany) treatment planning system (TPS), and CIRT planning utilizes the Local Effect Model I (LEM I) for calculating the variable RBE of carbon ion beams.

DSS was defined as the time from diagnosis to death from disease or the last follow-up. LC and DMC were calculated from the date of diagnosis to recurrence or metastasis. Acute toxicities occurred within 90 days of PBRT initiation and late toxicities arose after 3 months. Survival curves were generated using the Kaplan-Meier method, and differences assessed with log-rank tests. Prognostic factors were evaluated through univariate and multivariate Cox regression analyses. All statistical analyses were performed using SPSS (Version 26.0) and R (Version 3.4.2).

Results

Characteristics of patients

Between 11/2015 and 11/2021, 61 eligible patients were treated at SPHIC. All patients underwent ESS or biopsy before PBRT. The median follow-up of all cohort was 40.7 months (range 7.7–91.8), and 44.3 months (range 11.6–91.8) for surviving patients.

Of the entire cohort, 36 patients (59%) had lacrimal malignancies. The median tumor diameter was 3 cm, and 82% had primary disease. macroscopic tumors were detected in 39 patients (63.9%) before PBRT.

ACC was the most common histology (28 patients, 45.9%) in lacrimal tumors, with 72.2% presenting with T2-stage disease. macroscopic tumors were detected in 23 patients (63.9%). In 7 patients (19.4%), the tumors extended beyond the orbit. Bone involvement in 44.4% of patients. Perineural invasion (PNI) occurred in 26 patients (72.2%). Detailed characteristics are summarized in Table 1.

Particle radiotherapy modalities

In patients receiving PBRT, 91.8% were received CIRT alone, using 63-73.5 GyE in 18–22 fractions for primary

Table 1 Characteristics of patients

characteristic	No. of patients (%)
Median age (orbital tumor, range)	35 (14–74)
Median age (lacrimal tumor, range)	35 (16–74)
Sex (orbital tumor, *n* = 61)	
Male	33 (54.1)
Female	28 (45.9)
Sex (lacrimal tumor, *n* = 36)	
Male	20 (55.6)
Female	16 (44.4)
Tumor site	
Lacrimal gland	36 (59)
Lacrimal sac	10 (16.4)
Inside orbit	15 (24.6)
Tumor histology (orbital tumor, *n* = 61)	
Adenoid cystic carcinoma	28 (45.9)
Adenocarcinoma	8 (13.1)
Sarcoma	8 (13.1)
Chondrosarcoma	6 (9.8)
Squamous cells carcinoma	3 (4.9)
Myoepithelial carcinoma	4 (6.6)
Undifferentiated carcinoma	2 (3.3)
Melanoma	1 (1.6)
Mucoepidermoid carcinoma	1 (1.6)
Tumor histology (lacrimal tumor, *n* = 36)	
Adenoid cystic carcinoma	26 (72.2)
Adenocarcinoma	7 (19.4)
Myoepithelial carcinoma	3 (8.3)
T category (lacrimal tumor, *n* = 36)	
T1	3 (8.3)
T2	26 (72.2)
T3	2 (5.6)
T4	5 (13.9)
Median Tumor diameter (orbital tumor range, cm)	3 (1.1–7.5)
Median Tumor diameter (lacrimal tumor range, cm)	3 (1.2–4.3)
Extension beyond orbit (orbital tumor, *n* = 61)	
Yes	13 (21,3)
No	48 (78.7)
Extension beyond orbit (lacrimal tumor, *n* = 36)	
Yes	7 (19.4)
No	29 (80.6)
Bone involvement (lacrimal tumor, *n* = 36)	
No	18 (50.0)
Yes	16 (44.4)
Unknow	2 (5.6)
Perineural invasion (lacrimal tumor, *n* = 36)	
Yes	26 (72.2)
No	4 (11.1)
Unknow	6 (16.7)
Tumor status (orbital tumor, *n* = 61)	
Primary	50 (82.0)
Recurrence	11 (18.0)
Tumor status (lacrimal tumor, *n* = 36)	
Primary	30 (83.3)

Table 1 (continued)

characteristic	No. of patients (%)
Recurrence	6 (16.7)
Radiation course (orbital tumor, *n* = 61)	
First course	58 (95.1)
Re-irradiation	3 (4.9)
Radiation course (lacrimal tumor, *n* = 36)	
First course	35 (97.2)
Re-irradiation	1 (2.8)
Margin status (orbital tumor, *n* = 61)	
R0	5 (8.2)
R1/close margin	17 (27.9)
R2/biopsy	39 (63.9)
Margin status (lacrimal tumor, *n* = 36)	
R0	3 (8.3)
R1/close margin	10 (27.8)
R2/biopsy	23 (63.9)
Radiotherapy technique (orbital tumor, *n* = 61)	
Proton	1 (1.6)
Carbon Ion	56 (91.8)
Proton & Carbon	4 (6.6)
Concurrent chemotherapy (orbital tumor)	
Yes	5 (8.2)
No	56 (91.8)

or residual tumors and 54–60 GyE in 18–20 fractions for low-risk regions. Four patients received both IMPT and CIRT, with IMPT 56 GyE in 28 fractions to low-risk regions followed by a 15 GyE CIRT boost in 3 fractions for gross tumors. One patient who achieved R0 resection received IMPT alone (56 GyE in 28 fractions). Elective nodal irradiation was not performed. Figure 1 illustrates the target delineation for ACC.

Survival outcomes and prognostic factors

For the entire group, the 3- and 5-year DSS rates were 88.1%, LC rates were 69.9%, DMC rates were 77.5%, and 74.2%, and PFS rates were 58.1% and 55.2%, respectively (Fig. 2). The tumor size was a critical prognostic factor. Tumors ≥ 4 cm was associated with poorer DSS, DMC rates, but not LC rate (Fig. 3AB, Table 2). Extraorbital extension significantly associated with worse DSS in univariate analysis and a higher risk of DM in multivariate analysis (Fig. 3C; Table 2). Patients with recurrent disease and those undergoing re-irradiation had lower 5-year DSS (Fig. 3D). Multivariate analysis (Table 2) identified melanoma patients, elderly, and females had a higher DM risk, while intraorbital malignancies had a lower PFS rate.

A subgroup analysis of patients with lacrimal tumors showed 5-year DSS, LC, DMC, and PFS rates of 83.3%, 64.8%, 66.8%, and 53.4%, respectively (Fig. 4). ACC, the most common type (72.2%), with 5-year DSS, LC, DMC, PFS rates were 89.3%, 60.1%, 66.3%, 52.9%. Univariate analysis indicated worse DSS in adenocarcinoma patients, but this requires further validation due to the small sample size. Patients with T1/T2 disease had significantly better outcomes. However, LC rates between early and advanced stages were not significantly different (5-year LC rates: 67% vs. 56.3%) (Fig. 5A-D). Tumors > 3 cm had a higher risk of metastasis and progression. When tumors ≥ 4 cm not only showed worse DSS and DMC, but also a lower LC rate(Fig. 5E-H). Multivariate analysis confirmed that larger tumors were associated with a higher rate of disease progression (Table 3). Bone involvement was also a negative prognostic factor associated with lower LC, DMC, and PFS rates in both univariate and multivariate analyses, although DSS was not significantly affected (Fig. 5I-L; Table 3). Extraorbital extension was correlated to worse DSS, DMC, and PFS, though LC rate was unaffected (Fig. 5M-P). PNI was observed in 72.2% of patients, with those without PNI showing worse DSS, although LC, DMC and PFS rates was unaffected. Given that the 4 patients without PNI had other poor prognostic factors (2 had bone invasion and 2 had T4-stage disease), this finding may be subject to bias. Additionally, Recurrent disease was associated with lower 5-year DSS and DMC rates.

Patterns of failure

Sisteen patients (26.2%) experienced local recurrence, with 6 also presenting DM, and 10 were single relapse. Seven recurrences occurred within the CTV-HR, three at the margin of the GTV or tumor bed or within the

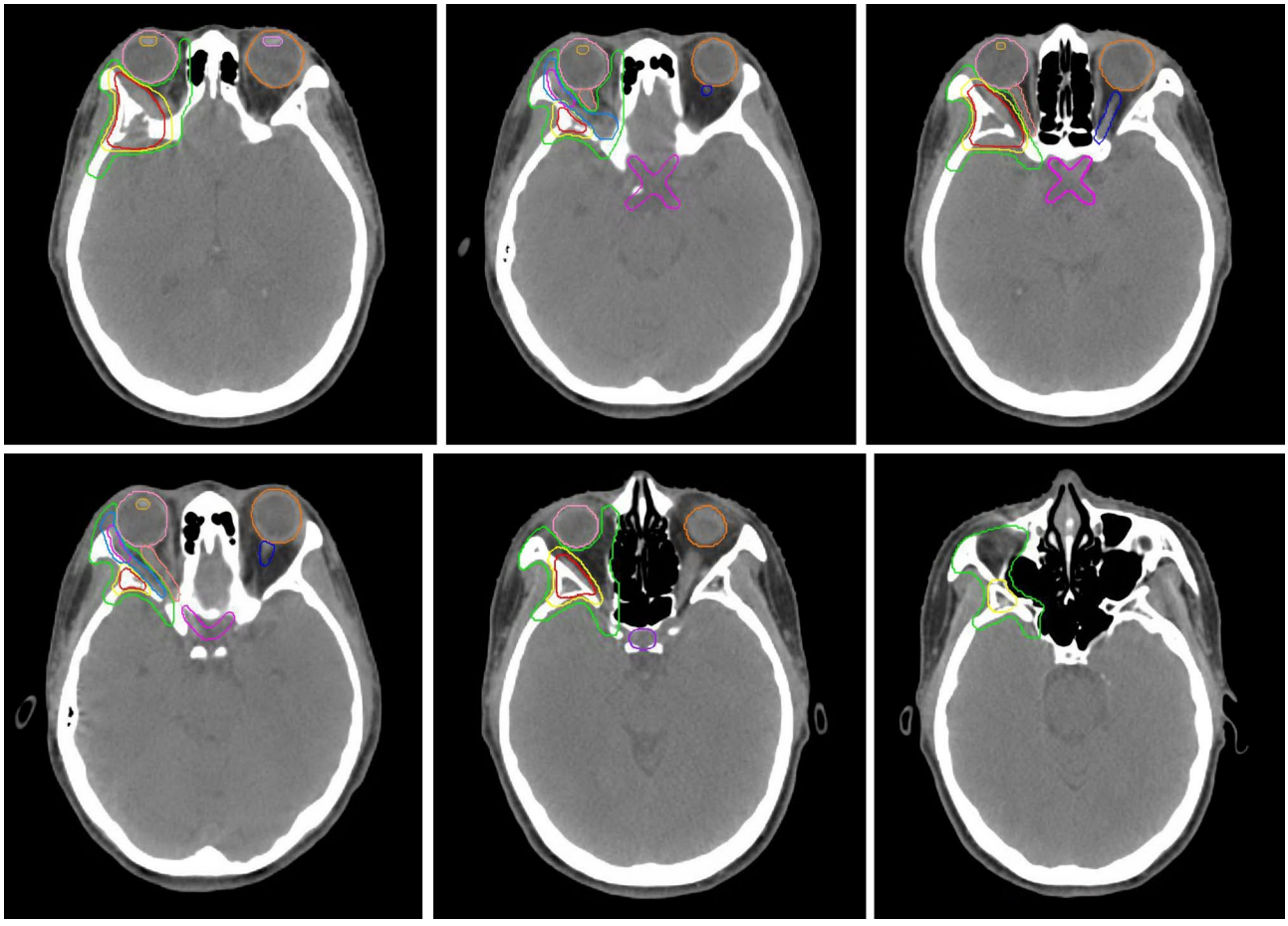

Fig. 1 For patients with R2 resection or biopsy, the CTV-HR (yellow line) encompassed GTV (red line) with a margin. For R1 or close margin cases, the tumor bed (pink line) and operative bed were included in the CTV-IR (blue line). For R0 cases, only CTV-LR (green line) was treated. Unless the cavernous sinus is involved, it is not routinely irradiated

CTV-IR. Of the 6 local recurrence outside the CTV, most involved inferior or medial orbital wall, or the orbital parietal bone, with none in the cavernous sinus.

A total of 13 patients experienced DM, the most common site was lung (4 patients), followed by skeletal (3 patients), brain (2 patients), parotid gland (2 patients), liver (1 patient), cerebral falx (1 patient), Frontal meninges (1 patient). No patients experienced regional lymph node recurrence.

Toxicity

Acute and late toxicities were detailed in Table 4. Normal function of the contralateral eye was preserved in all patients. No grade 3 or higher acute toxicities were observed, with most patients developing grade 1 toxicities. Two patients experienced grade 2 conjunctival congestion, which fully resolved within a month post-treatment. Late toxicities were observed in 24 patients including two cases of cataracts (1 grade 1, 1 grade 2), two cases of grade 3 glaucoma, and three cases of retinopathy (2 grade 2, 1 grade 3). Three patients developed brain injury one year post-treatment.

Regarding visual status. Three patients developed grade 1 visual impairment during acute phase. Two of these patients received CIRT (63GyE/18Fx and 70GyE/20Fx). One maintained grade 1 decreased vision at last follow-up of 6 years, while the other progressed to grade 3 two years post-treatment. The third patient, re-irradiation with CIRT (70GyE/20Fx) experienced worsening vision and eventually vision loss 4 months post-treatment. In the late phase, 13 patients experienced vision decline. Five patients had grade 1–2 deceased vision, while 8 had grade 3 or 4 (CIRT dose of 60-70GyE/18-20Fx). The median time to serve decreased vision (grade 3/4) was 11.5 months (4–24 months).

Discussion

Our retrospective study analyzed 61 patients with malignant orbital tumors treated with ESS or biopsy followed by PBRT. With a median follow-up of 40.7 months (44.3 months for surviving patients), the 3- and 5-year DSS and

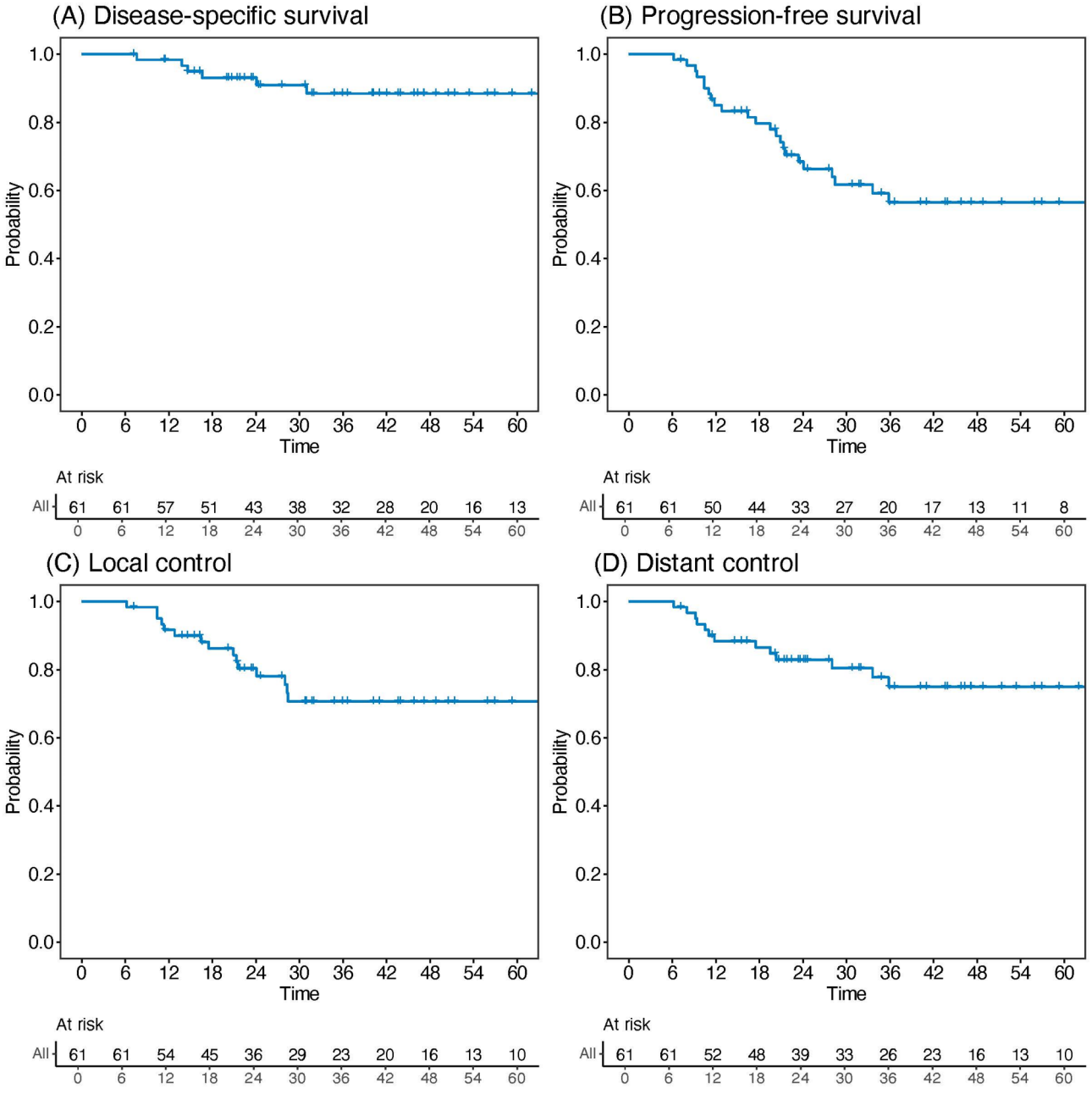

Fig. 2 The survival curves of DSS **(A)**, PFS **(B)**, LC **(C)**, and DMC **(D)** rates for the orbital malignancies

LC rates were 88.1% and 69.9%, respectively, and the 3- and 5-year DMC rates were 77.5% and 74.2%. For lacrimal gland carcinoma, the 5-year DSS, LC, DMC, and PFS rates were 83.3%, 64.8%, 66.8%, and 53.4%. Tumor size, T stage, extraorbital invasion, and bone invasion influenced survival, as detailed in the following sections.

A multidisciplinary approach involving ESS and postoperative radiotherapy is gaining favor for malignant orbital tumors [2–4, 12–15]. In 2019, studies by Jie Yang et al. [16] and Hung JY et al. [17] on lacrimal ACC treated with photon radiotherapy after ESS reported a 5-year LC rate of 20%, with 50–70% local recurrence. PBRT, with its superior dose distribution and biological effectiveness, has since been increasingly adopted. For patients with biopsy or residual disease, higher doses can enhance local control. Paul Lesueur et al. [18] reported 5-year OS and LC rates of 78% and 60% for PBT, exceeding photon therapy outcomes.

Carbon ion radiation (CIRT) offers superior dose distribution and higher biological efficacy, though reports on its use for malignant orbital tumors are limited. In 2019, we reported early outcomes, and this study

Table 2 Prognostic factors of orbital malignancies (multivariate analysis)

Factors		Disease specific survival		Local control		Distance metastasis control		Progression-free survival	
	N	*p*	OR	*p*	OR	*p*	OR	*p*	OR
Age									
≤35	30	Reference		Reference		Reference		Reference	
>35	31	0.942	15.26	0.639	0.77	0.056	4.936	0.339	1.552
Gender									
Male	33	Reference		Reference		Reference		Reference	
Female	28	0.94	23.56	0.274	1.875	0.008	21.064	0.092	2.356
Tumor site									
Lacrimal gland	36	Reference		Reference		Reference		Reference	
Lacrimal sac	10	0.987	0	0.438	0.526	0.06	0.1	0.282	0.509
Inside orbit	15	0.839	1.546	0.088	0.149	0.97	0	0.029	0.153
Tumor histology									
Epithelial	46	Reference		Reference		Reference		Reference	
Sarcoma	14	0.969	0	0.139	4.0	0.973	0	0.547	1.58
Melanoma	1	0.999	30.51	0.989	0	0.021	83.51	0.2222	5.01
Tumor status									
Primary	50	Reference		Reference		Reference		Reference	
Recurrence	11	0.283	9.542	0.832	0.795	0.489	0.445	0.6647	0.694
Radiation course									
First course	58	Reference		Reference		Reference		Reference	
Re-irradiation	3	0.712	0.476	0.531	2.543	0.878	0.783	0.343	2.946
Margin status									
R0 + R1/close margin	22	Reference		Reference		Reference		Reference	
R2/biopsy	39	0.86	0.737	0.141	2.861	0.734	0.776	0.585	11.342
Median Tumor diameter*									
<4 cm	49	Reference		Reference		Reference		Reference	
≥ 4 cm	11	0.048	28.01	0.161	2.768	0.001	25.4406	0.041	3.532
Extension beyond orbit									
No	48	Reference		Reference		Reference		Reference	
Yes	13	0.946	61.91	0.56	1.598	0.046	9.744	0.187	2.319

* One patient primary tumor diameter was unknow

extends the follow-up to a median of 40.7 months [19]. The 3- and 5-year DSS rates were 88.1%, while the LC rates were 69.9%. DMC rates were 77.5% and 74.2%, with PFS rates of 58.1% and 55.2%, respectively. For patients without macroscopic tumor disease (36.1%), the 5-year LC and DSS rates were 82.9% and 86.1%. Patients with macroscopic tumors (63.9%) received high-dose radiotherapy (CIRT of 70–72 GyE/18–20 fractions or IMPT 56 GyE/28 fractions combined with CIRT 15 GyE/5 fractions), with 5-year LC and DSS rates of 64.1% and 71.8%. However, both univariate and multivariate analyses showed the presence of macroscopic tumors did not a significant prognostic factor for survivals. Therefore, high-dose PBRT may contribute to disease control. Tumor size ≥ 4 cm increased DM incidence and reduced DSS rates, however there was no significant impact on LC rates. These findings may underscore adequate dosing to the macroscopic tumor is critical for local control. In univariate analysis, extraorbital invasion decreased 5-year DSS rates (61.9% vs. 97.7%), but no significant differences in LC or DM rates, and multivariate analysis also showed a significantly increased risk of DM, which may partially explain the lower DSS rate. In a retrospective study, Randa Tao et al. [20] included multiple types such as ACC, SCC, and adenocarcinoma and found that the pathological type did not affect OS. In our study, we categorized all patients into three groups: epithelial tumors, sarcomas, and melanoma. Multivariate analysis indicated a higher risk of DM in melanoma. Given the limited sample size, this conclusion may be biased. Generally, the efficacy of treatment for recurrent or re-irradiated diseases is unsatisfactory. In our cohort, recurrence or re-irradiation was associated with lower DSS in univariate analysis. Intraorbital tumors showed a tendency for disease progression in multivariate analysis, but pathological type may influence outcomes (93.3% of these patients had sarcomas or chondrosarcomas), this conclusion requiring further validation.

Lacrimal tumors made up 59% of the cohort. The 5-year DSS, LC, DMC, and PFS rates were 83.3%, 64.8%,

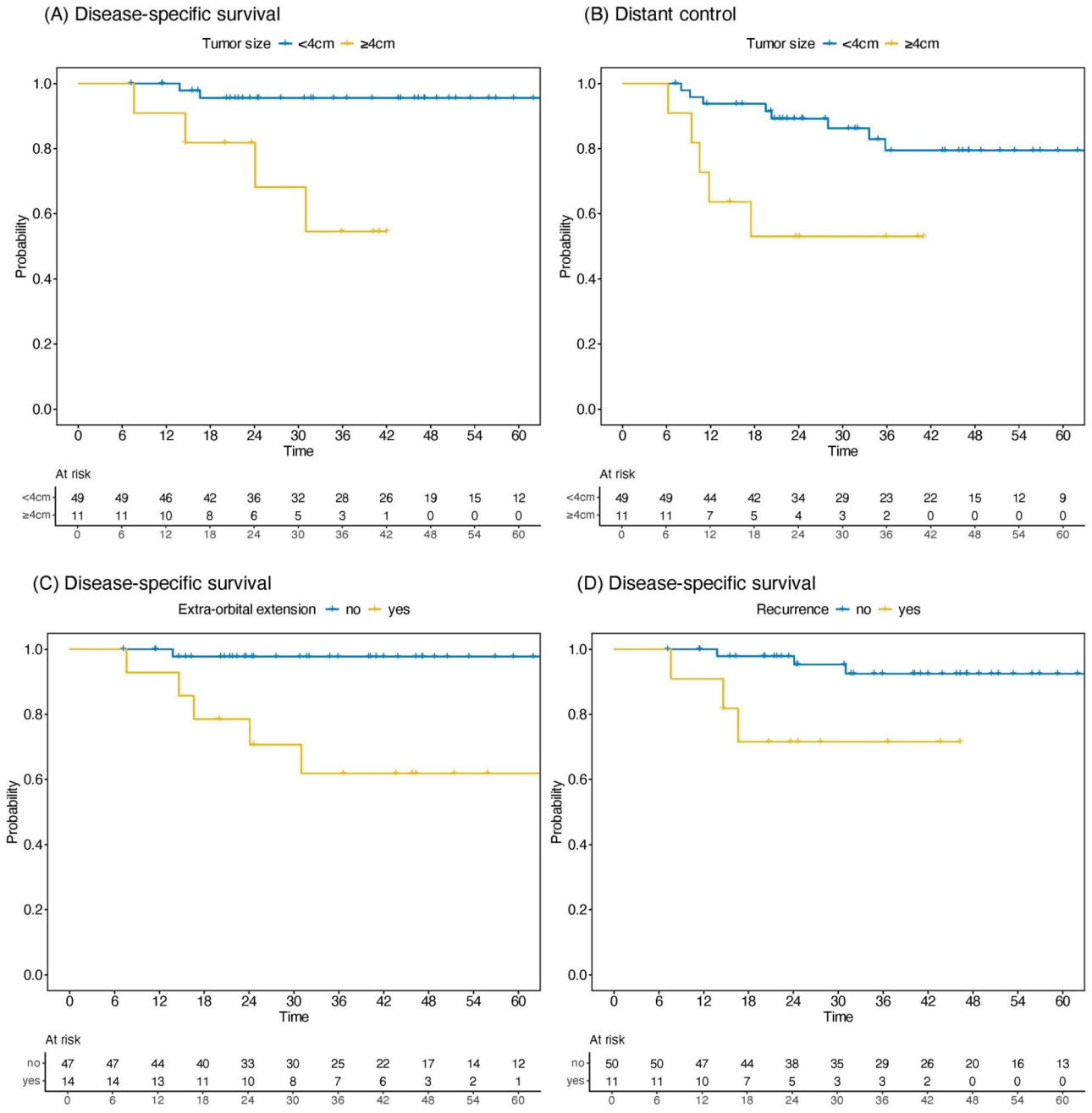

Fig. 3 The survival curves compare the DSS **(A)** and DMC **(B)** rates of patients with larger tumor. Tumors size ≥ 4 cm was significantly decreased DM control ($p = 0.014$) and DSS ($p = 0.001$) rates. Survival curves compare the DSS **(C)** rate of patients with extraorbital disease. Extraorbital extension significantly decreased DSS ($p = 0.001$) rate. Survival curves compare the DSS (D) rate of patients with recurrent disease. Recurrent disease significantly decreased DSS ($p = 0.014$) rate

66.8%, and 53.4%, respectively. Previous studies reported 5-year OS rate of photon radiotherapy after ESS ranging from 37 to 65% [3, 4]. While a study by Ford JR et al. [2], with 49% of patients received PBT showed 5-year DSS and LC rates of 81% and 71%. Sati Akbaba et al. [21] reported outcomes of combination of photon and CIRT, with 5-year OS and LC rates of 68% and 44%. Japanese researchers use CIRT alone for locally advanced lacrimal tumors, with 5-year OS, LC, and DFS rates of 65%, 62%, and 34% [22]. In our cohort, 36.1% had R0-R1 margins with 5-year DSS, LC and DMC rates of 72.7%, 80.8% and 76.9%. For patients with macroscopic tumors (63.9%), the 5-year DSS, LC, DMC, and PFS rates were 87%, 58.2%, 63%, and 48.4%. Although no significant differences in survivals between patients with or without macroscopic

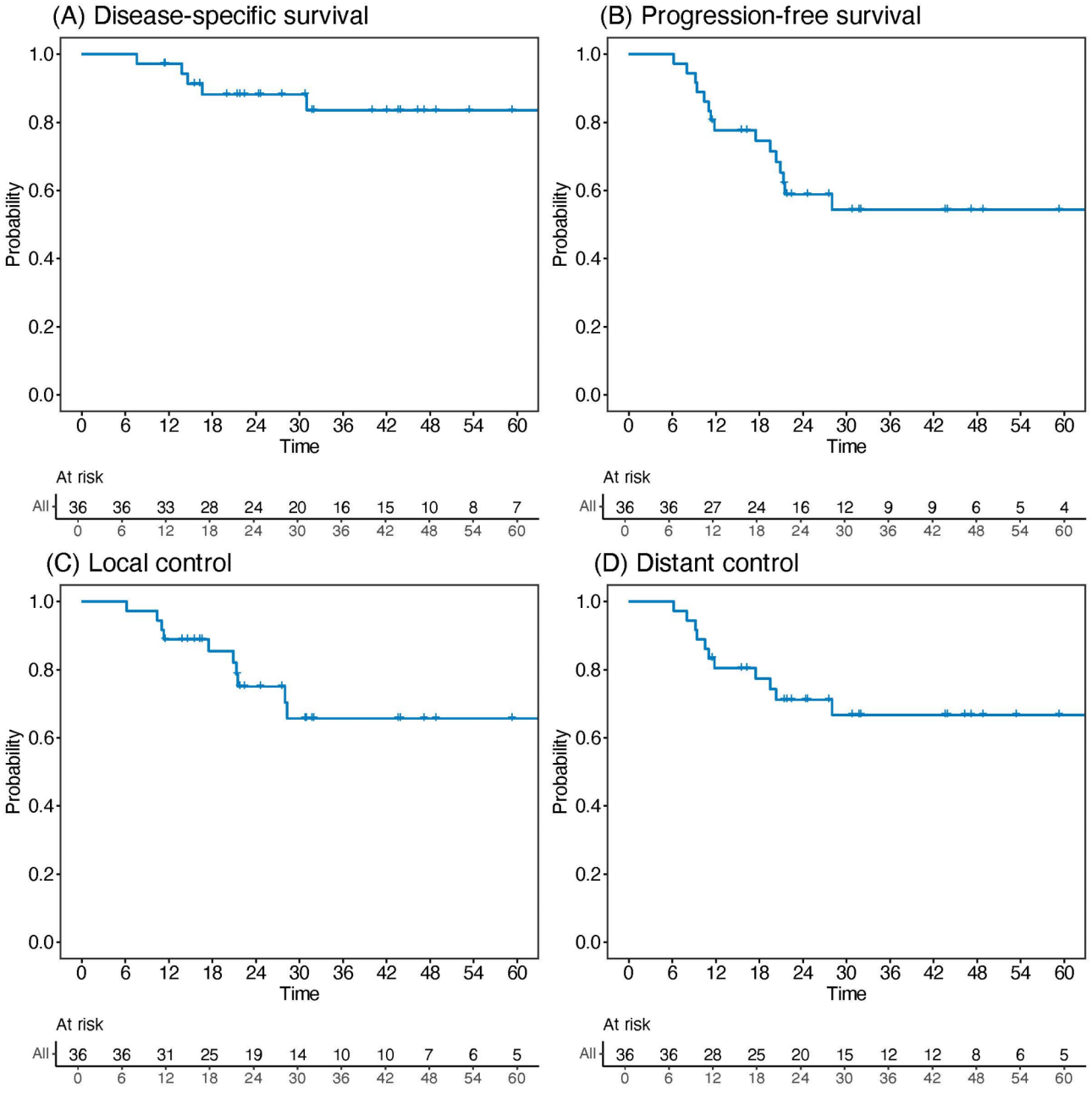

Fig. 4 The survival curves of DSS **(A)**, PFS **(B)**, LC **(C)**, and DMC **(D)** rates for the lacrimal tumors

tumors, we advocate high-dose treatment for those with macroscopic tumors.

ACC was the most common histological type in lacrimal tumor, accounting for 72.2%, consistent with data from MD Anderson [2], Moorfields Eye Hospital [4], Samsung Medical Center [23], and Heidelberg Ion-Beam Therapy Center [21]. Due to its radioresistance, local recurrence of photon radiotherapy is around 50% [16, 17]. Studies by Natalie Wolkow et al. [24] and Paul Lesueur et al. [18] on lacrimal ACC treated with photon and PBT or PBT alone reported lower local recurrence rates of 22% and 20%, with 5-year LC and OS rates of 60% and 78%. Sati Akbaba et al. [21] reported 5-year LC and OS rate of 21% and 71% for lacrimal ACC treated with photon and CIRT or CIRT alone. Among our patients with lacrimal ACC, 65.4% had macroscopic tumor disease, and 5-year DSS, LC, DMC, and PFS rates of 89.3%, 60.1%, 66.3%, and 52.9%, respectively. These outcomes suggest PBRT may offer a survival advantage over photon radiotherapy for ACC, supporting its prioritization in treatment. Our univariate analysis showed a worse DSS rate for adenocarcinoma compared to ACC, but with

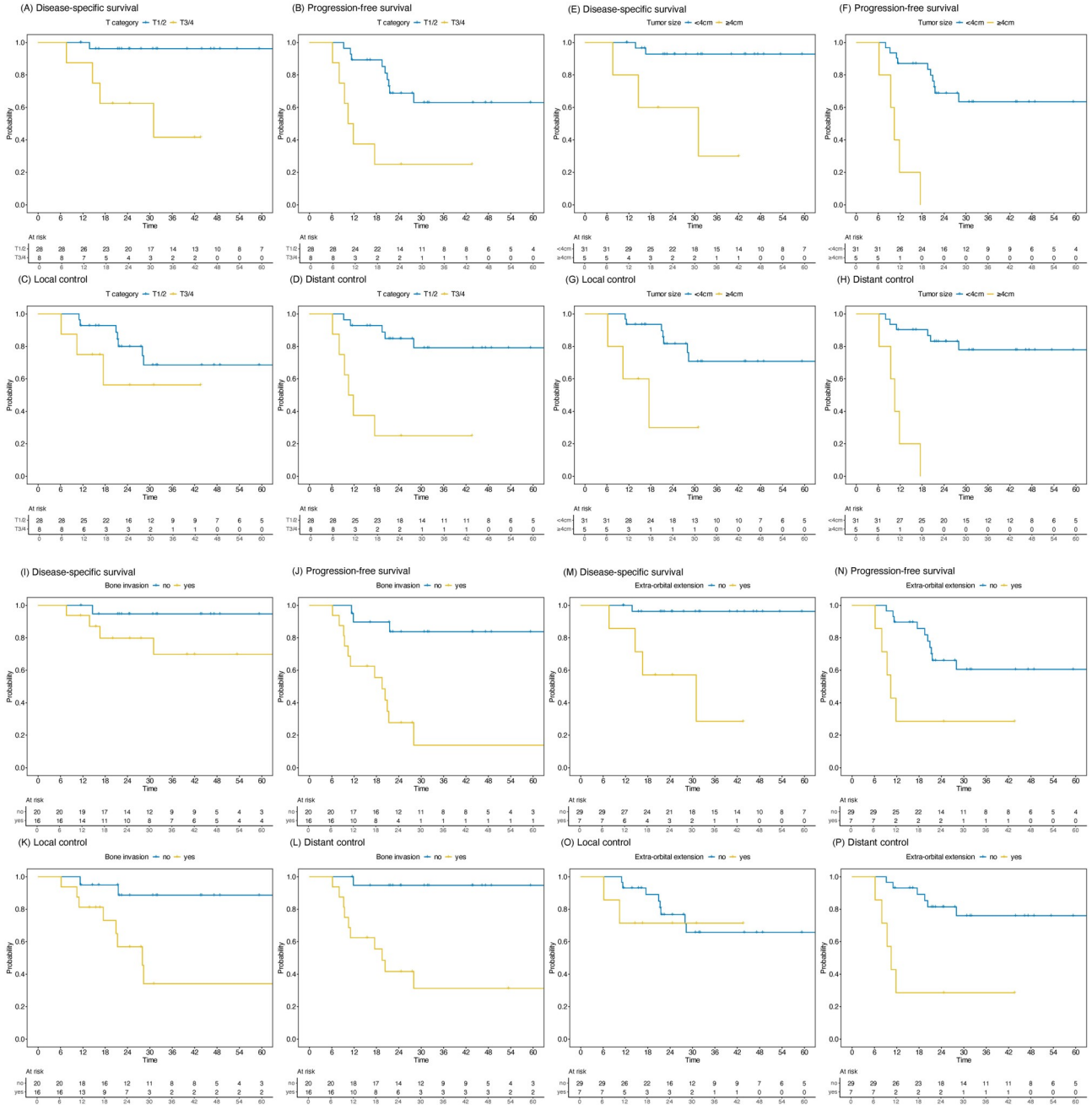

Fig. 5 The survival curves compare the DSS **(A)**, PFS **(B)**, LC **(C)**, and DMC **(D)** rates of patients with advanced T category. Advanced T category was significantly decreased DSS ($p = 0.001$), PFS ($p = 0.004$) and DMC ($p = 0$) rates, but not LC ($p = 0.258$) rate. Survival curves compare the DSS **(E)**, PFS **(F)**, LC **(G)**, and DMC **(H)** rates of patients with large tumors. Tumors size ≥ 4 cm was significantly decreased DSS ($p = 0.001$), PFS ($p = 0$), LC ($p = 0.008$) and DMC ($p = 0$) rates. Survival curves compare the DSS **(I)**, PFS **(J)**, LC **(K)**, and DMC **(L)** rates of patients with bone involvement. Bone involvement significantly decreased PFS ($p = 0$), LC ($p = 0.04$) and DMC ($p = 0$) rates, but not DSS ($p = 0.081$) rate. Survival curves compare the DSS **(M)**, PFS **(N)**, LC **(O)**, and DMC **(P)** rates of patients with extraorbital disease. Extraorbital extension significantly decreased DSS ($p = 0$), PFS ($p = 0.012$) and DMC ($p = 0.001$) rates, but not LC ($p = 0.669$) rate

only 7 cases of adenocarcinoma, this requires validation with a larger sample.

Multiple studies have shown that advanced T-stage is linked to poorer OS [17, 25–27] and higher DM rates [2, 16, 25, 27]. In our univariate analysis, T3/4 disease correlated with increased DM and reduced DSS, though LC rates were unaffected. Since T-stage is associated with tumor size, bone invasion, and extraconal extension, we analyzed these factors individually. Tumor size ≥ 3 cm was associated with a higher risk of DM, although LC rate remained unaffected. When the tumors ≥ 4 cm, not only an increased risk of DM and reduced DSS, but also

Table 3 Prognostic factors of lacrimal gland tumor (multivariate analysis)

Factors		Disease specific survival		Local control		Distance metastasis control		Progression-free survival	
	N	*p*	OR	*p*	OR	*p*	OR	*p*	OR
Age									
≤35	17	Reference		Reference		Reference		Reference	
>35	19	0.291	297.65	0.902	0.884	0.539	3.687	0.26	2.58
Gender									
Male	20	Reference		Reference		Reference		Reference	
Female	16	0.35	126.92	0.915	0.899	0.106	117.23	0.881	1.15
Tumor histology									
Adenoid cystic carcinoma	26	Reference		Reference		Reference		Reference	
Adenocarcinoma	7	0.165	157.03	0.82	0.712	0.103	81.63	0.633	1.652
Myoepithelial carcinoma	3	0.855	0.282	0.979	0	0.976	0	0.985	0
T category									
T1-2	29	Reference		Reference		Reference		Reference	
T3-4	7	0.955	0.001	0.949	0	0.922	0	0.19	0.041
Tumor status									
Primary	30	Reference		Reference		Reference		Reference	
Recurrence	6	0.893	0.311	0.193	30.183	0.953	158.1	0.317	7.044
Margin status									
R0 + R1/close margin	13	Reference		Reference		Reference		Reference	
R2/biopsy	23	0.974	0.875	0.968	0.957	0.776	1.804	0.426	0.506
Median Tumor diameter									
<4 cm	18	Reference		Reference		Reference		Reference	
≥4 cm	18	0.168	51.98	0.944	111.38	0.909	157.66	0.016	120.55
Bone involvement*									
No	18	Reference		Reference		Reference		Reference	
Yes	16	0.555	3.515	0.025	8.465	0.909	147.76	0.003	20.485
Extension beyond orbit									
No	29	Reference		Reference		Reference		Reference	
Yes	7	0.914	832.06	0.582	0.238	0.095	55.26	0.809	1.654

* Two patients bone involvement status were unknow

reduced LC rates. Multivariate analysis confirmed larger tumors were more prone to disease progression. Skinner HD et al. [27] also reported the incidence of DM was higher when tumors ≥ 3.5 cm. The lacrimal gland is firmly anchored to the orbital periosteum and lacrimal tumors may directly invade the orbital bone. Bone invasion was reported common in tumors > 2 cm [28] and significantly reduced DSS rates [2]. Our analysis also showed bone invasion not only reduced LC rate but also increased metastasis risk. Therefore, High-dose irradiation is recommended for bone-involved areas. The study by Noh JM et al. [26] found that the 5-year survivals were poor in lacrimal ACC with extraorbital extension. Similarly in our study, extraorbital invasion linked to reduced DSS and higher DM rates, though LC was unaffected.

Although some reported PNI as a negative factor for survivals [2, 27], others suggested it has no significant impact [16, 21, 23]. Our analysis showed better DSS rate in patients with PNI, likely due to bias. Since all 4 PNI-negative patients had adverse factors like bone invasion, T4 stage, or re-irradiation. Thus, we excluded PNI from our multivariate analysis.

Despite advancements in ocular preservation through ESS and adjuvant radiotherapy, managing radiation-induced toxicities remains challenging. In a study by Holliday EB et al. [29], after a median dose of 60 GyE, 35% of patients experienced Grade 3 acute dermatitis, and 30% developed chronic Grade 3 toxicities. Paul Lesueur et al. [18] reported no Grade 3 or higher acute toxicities with 73.8 GyE of PBT, but chronic toxicities included brain injury (27%), hyperprolactinemia (40%), and rare cases of cataracts, keratitis, and osteitis. Japanese study [22] on high-dose CIRT did not result in Grade 3 or higher acute toxicities, however significant late toxicities were observed such as Grade 4 optic nerve injury (36.4%), brain injury (6%), and Grade 3 keratitis (9%). In our center, most toxicities were mild, such as Grade 1 edema, epiphora, dry eye, or conjunctivitis. Among late toxicities, aside from vision deterioration, the common symptom was Grade 1 dry eye (9.8%) and brain injury (4.9%). Regarding visual outcomes, three patients (4.9%)

Table 4 Characteristics of toxicities

	Acute Toxicities				Late Toxicities							
	Grade 1		Grade 2		Grade 1		Grade 2		Grade 3		Grade 4	
Adverse reaction	***N***	**%**	***N***	**%**	***N***	**%**	***N***	**%**	***N***	**%**	***N***	**%**
Epiphora	4	6.6	0		3	4.9	0		0		0	
Dry eyes	2	3.3	0		6	9.8	0		0		0	
Conjunctival congestion	4	6.6	2	3.3	0		0		0		0	
Periorbital edema	13	21.3	0		0		0		0		0	
Decreased vision	3	4.9	0		3	4.9	2	3.3	3	4.9	5	8.2
Cataract	0		0		1	1.6	1	1.6	0		0	
Glaucoma	0		0		0		0		2	3.3	0	
Retinopathy	0		0		0		2	3.3	1	1.6	0	
Brain injury	0		0		3	4.9	0		0		0	

experienced Grade 1 vision impairment during the acute phase. Vision decline occurred in 10 patients during the late phase. Four patients experienced vision deterioration 4 to 7 months post-treatment, two patients around 1 year, and two patients at 2 years. Grade 3–4 vision loss emerging at a median of 11.5 months post-treatment.

Our study has several limitations. The low incidence of orbital tumors and varying biological behaviors of different pathological types introduce bias. Future studies should aim to increase the number of patients and analyze specific pathological types for greater accuracy. Additionally, no cases of cavernous sinus recurrence were observed. Therefore, for patients with lesions confined to the orbit without involvement of the orbital apex or cavernous sinus, the cavernous sinus will not be included in CTVs, though this warrants further study and longer follow-up. Lastly, currently studies are single-institution and focus on either proton or CIRT. In the future, prospective randomized studies are needed to optimize treatment strategies.

Conclusion

Despite the retrospective nature and modest number of patients, we can still come to the conclusion that proton and carbon ion beam radiation provided a favorable local control and survivals after eye-preserving treatment, and even in patients with unresectable disease. No severe acute PBRT induced toxicity was observed, and severe late toxicity was observed in < 15% of cases. Particle radiotherapy was a promising strategy for management of orbital tumors.

Abbreviations

IMPT	Intensity-modulated proton therapy
PBT	Proton beam therapy
CIRT	Carbon-ion radiotherapy
PBRT	Particle radiotherapy
PBS	Pencil beam scanning
ACC	Adenoid cystic carcinoma
SCC	Squamous cells carcinoma
ESS	Eye-sparing surgery
PNI	Perineural invasion
OE	Orbital exenteration
LET	High-linear energy transfer
LC	Local control
DMC	Distant metastasis control
DSS	Disease-specific survival
PFS	Progression free survival
DFS	Disease free survival
GTV	Gross tumor volume
CTV	Clinical target volume
PTV	Planning target volume

Author contributions

Weixu Hu and Qiong Cai contributed equally as co-first authors. Weixu Hu: design the study, collect data and analysis, interpretation, drafting, revising the article and final approval. Qiong Cai: collect data and analysis, drafting, revising the article and final approval. Jiyi Hu: data collection, data analysis, revision and final approval. Qingting Huang: collect data, drafting, revision and approve of the version. Jing Gao: collect data, revision and approve of the version. Haojiong Zhang: collect patient's data, and approve of the version.

Lin Kong: Conceptualization and design study, supervision, data analysis and results interpretation, revising the article, funding acquisition, final approval.

Funding
This work was supported by the Shanghai Municipal Commission of Health (Grants No. 202040280); Pudong New Area Science and Technology Development Fund (Grants No. PKJ2022-Y52); Key Research and Development Program of the Ministry of Science and Technology (Grants No. 2022YFC2401505).

Data availability
The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethical approval
This study was performed in line with the principles of the Declaration of Helsinki. This study has been granted an exemption form the requirement of written informed consent and human participants in this study were reviewed and approved by institutional review board (IRB) of Shanghai Proton and Heavy Ion Center (IRB No. 180910EXP-01).

Consent for publication
Not applicable.

Competing of interest
The authors declare there is no conflict of interest.

Received: 24 November 2024 / Accepted: 20 March 2025
Published online: 28 March 2025

References

1. Kim JS, Al-Lozi A, Leyngold IM. Malignant orbital tumors: current approach to diagnosis and management. Curr Ophthalmol Rep. 2021;9(1):16–24.
2. Ford JR, Rubin ML, Frank SJ, Ning J, Debnam JM, Bell D, El-Naggar A, Ferrarotto R, Esmaeli B. Prognostic factors for local recurrence and survival and impact of local treatments on survival in lacrimal gland carcinoma. Br J Ophthalmol. 2021;105(6):768–74.
3. Bonavolonta P, Esmaeli B, Donna P, Tranfa F, Iuliano A, Abbate V, Fossataro F, Attanasi F, Bonavolonta G. Outcomes after eye-sparing surgery vs orbital exenteration in patients with lacrimal gland carcinoma. Head Neck. 2020;42(5):988–93.
4. Rose GE, Gore SK, Plowman NP. Cranio-orbital resection does not appear to improve survival of patients with lacrimal gland carcinoma. Ophthalmic Plast Reconstr Surg. 2019;35(1):77–84.
5. van de Water TA, Bijl HP, Schilstra C, Pijls-Johannesma M, Langendijk JA. The potential benefit of radiotherapy with protons in head and neck cancer with respect to normal tissue sparing: a systematic review of literature. Oncologist. 2011;16(3):366–77.
6. Khan FM. The physics of radiation therapy. Lippincott Williams & Wilkins; 2009.
7. Hirohiko Tsujii TK, Masayuki Baba H, Tsuji H, Kato S, Kato S, Yamada. Shigeo Yasuda, Takeshi Yanagi, Hiroyuki Kato, Ryusuke Hara, Naotaka Yamamoto, Junetsu Mizoe: clinical advantages of carbon-ion radiotherapy. New J Phys 2008, 10.
8. Kanai T, Endo M, Minohara S, Miyahara N, Koyama-ito H, Tomura H, Matsufuji N, Futami Y, Fukumura A, Hiraoka T, et al. Biophysical characteristics of HIMAC clinical irradiation system for heavy-ion radiation therapy. Int J Radiat Oncol Biol Phys. 1999;44(1):201–10.
9. Elsasser T, Kramer M, Scholz M. Accuracy of the local effect model for the prediction of biologic effects of carbon ion beams in vitro and in vivo. Int J Radiat Oncol Biol Phys. 2008;71(3):866–72.
10. Jones B. A simpler energy transfer efficiency model to predict relative biological effect for protons and heavier ions. Front Oncol. 2015;5:184.
11. Karcioglu ZA, Hadjistilianou D, Rozans M, DeFrancesco S. Orbital rhabdomyosarcoma. Cancer Control. 2004;11(5):328–33.
12. Woo KI, Kim YD, Sa HS, Esmaeli B. Current treatment of lacrimal gland carcinoma. Curr Opin Ophthalmol. 2016;27(5):449–56.
13. Han J, Kim YD, Woo KI, Sobti D. Long-Term outcomes of Eye-Sparing surgery for adenoid cystic carcinoma of lacrimal gland. Ophthalmic Plast Reconstr Surg. 2018;34(1):74–8.
14. Esmaeli B, Yin VT, Hanna EY, Kies MS, William WN Jr., Bell D, Frank SJ. Eye-sparing multidisciplinary approach for the management of lacrimal gland carcinoma. Head Neck. 2016;38(8):1258–62.
15. Woo KI, Yeom A, Esmaeli B. Management of lacrimal gland carcinoma: lessons from the literature in the past 40 years. Ophthalmic Plast Reconstr Surg. 2016;32(1):1–10.
16. Yang J, Zhou C, Wang Y, Fan X, Jia R. Multimodal therapy in the management of lacrimal gland adenoid cystic carcinoma. BMC Ophthalmol. 2019;19(1):125.
17. Hung JY, Wei YH, Huang CH, Chen LW, Fuh CS, Liao SL. Survival outcomes of eye-sparing surgery for adenoid cystic carcinoma of lacrimal gland. Jpn J Ophthalmol. 2019;63(4):344–51.
18. Lesueur P, Rapeaud E, De Marzi L, Goudjil F, Levy C, Galatoire O, Jacomet PV, Dendale R, Calugaru V. Adenoid cystic carcinoma of the lacrimal gland: high dose adjuvant proton therapy to improve patients outcomes. Front Oncol. 2020;10:135.
19. Hu W, Hu J, Gao J, Yang J, Qiu X, Kong L, Lu JJ. Outcomes of orbital malignancies treated with eye-sparing surgery and adjuvant particle radiotherapy: a retrospective study. BMC Cancer. 2019;19(1):776.
20. Tao R, Ma D, Takiar V, Frank SJ, Fuller CD, Gunn GB, Beadle BM, Morrison WH, Rosenthal DI, Edson MA, et al. Orbital carcinomas treated with adjuvant intensity-modulated radiation therapy. Head Neck. 2016;38(Suppl 1):E580–587.
21. Akbaba S, Lang K, Held T, Herfarth K, Rieber J, Plinkert P, Auffarth GU, Rieken S, Debus J, Adeberg S. Carbon-ion radiotherapy in accelerated hypofractionated active raster-scanning technique for malignant lacrimal gland tumors: feasibility and safety. Cancer Manag Res. 2019;11:1155–66.
22. Hayashi K, Koto M, Ikawa H, Ogawa K, Kamada T. Efficacy and safety of carbon-ion radiotherapy for lacrimal gland carcinomas with extraorbital extension: a retrospective cohort study. Oncotarget. 2018;9(16):12932–40.
23. Woo KI, Sagiv O, Han J, Frank SJ, Kim YD, Esmaeli B. Eye-Preserving surgery followed by adjuvant radiotherapy for lacrimal gland carcinoma: outcomes in 37 patients. Ophthalmic Plast Reconstr Surg. 2018;34(6):570–4.
24. Wolkow N, Jakobiec FA, Lee H, Sutula FC. Long-term outcomes of Globe-Preserving surgery with proton beam radiation for adenoid cystic carcinoma of the lacrimal gland. Am J Ophthalmol. 2018;195:43–62.
25. Lin YH, Huang SM, Yap WK, Yang JW, Yeung L, Tsan DL, Chang JT, Chen LC. Outcomes in patients with lacrimal gland carcinoma treated with definitive radiotherapy or eye-sparing surgery followed by adjuvant radiotherapy. Radiat Oncol. 2020;15(1):156.
26. Noh JM, Lee E, Ahn YC, Oh D, Kim YD, Woo KI, Ko YH, Kim S. Clinical significance of post-surgical residual tumor burden and radiation therapy in treating patients with lacrimal adenoid cystic carcinoma. Oncotarget. 2016;7(37):60639–46.
27. Skinner HD, Garden AS, Rosenthal DI, Ang KK, Morrison WH, Esmaeli B, Pinnix CC, Frank SJ. Outcomes of malignant tumors of the lacrimal apparatus: the university of Texas MD Anderson cancer center experience. Cancer. 2011;117(12):2801–10.
28. Williams MD, Al-Zubidi N, Debnam JM, Shinder R, DeMonte F, Esmaeli B. Bone invasion by adenoid cystic carcinoma of the lacrimal gland: preoperative imaging assessment and surgical considerations. Ophthalmic Plast Reconstr Surg. 2010;26(6):403–8.
29. Holliday EB, Esmaeli B, Pinckard J, Garden AS, Rosenthal DI, Morrison WH, Kies MS, Gunn GB, Fuller CD, Phan J, et al. A multidisciplinary orbit-Sparing treatment approach that includes proton therapy for epithelial tumors of the orbit and ocular adnexa. Int J Radiat Oncol Biol Phys. 2016;95(1):344–52.

Publisher's note