



Intensity-modulated proton and carbon-ion radiation therapy in the management of major salivary gland carcinomas

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Background: Primary major salivary gland carcinomas (SGCs) present with diverse histological types that are known to be largely radioresistant with a high tendency to develop distant metastasis (DM). Photon-based radiotherapy (RT) is limited in terms of its therapeutic effect and toxicities. In view of the physical and biological advantages of intensity-modulated proton and/or carbon-ion radiation therapy, we aimed to evaluate the short-term therapeutic effect and toxicities in patients with major SGCs treated with this form of radiation therapy.

Methods: Between August 2015 and November 2019, a total of 55 consecutive and non-selected major SGC patients who received particle RT at the Shanghai Proton and Heavy Ion Center (SPHIC) were retrospectively analyzed. The 2-year overall survival (OS), progression-free survival (PFS), local-regional recurrence-free survival (LRRFS), and distant metastasis-free survival (DMFS) rates, as well as prognostic factors were analyzed. Additionally, acute and late toxicities were also analyzed.

Results: With a median follow-up time of 24 (range, 6–57) months, the 2-year OS, PFS, LRRFS, and DMFS rates were 91.6%, 78.6%, 94.2%, and 83.9%, respectively. At the time of this analysis, four patients had developed local or regional recurrence, and seven additional patients had developed DM. Three patients had died due to disease progression, and another patient with recurrence experienced a late Grade 5 event (hemorrhage) at 9 months after re-irradiation with carbon ion and subsequently died. Otherwise, none of the patients had grade 3 or higher treatment-induced acute or late adverse effects except one who developed grade 3 acute mucositis.

Conclusions: Overall, intensity-modulated proton and/or carbon-ion radiation therapy provided satisfactory therapeutic effectiveness in our major SGCs patients with a low incidence of acute and late toxicities.

Keywords: Proton; carbon ion; radiotherapy (RT); major salivary gland carcinomas (major SGCs)

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Introduction

Major salivary gland carcinomas (SGCs), including parotid, submandibular, and sublingual gland carcinoma, account for 3–6% of all head and neck cancers (1). Tumors of the major salivary glands are rare and heterogenous, including different histological types, such as mucoepidermoid carcinoma (MEC), adenoid cystic carcinoma (ACC), and salivary duct carcinoma, which are mostly considered radioresistant (2).

Surgery is the mainstay of management for resectable major SGCs (3,4). Postoperative radiotherapy (PORT) is often recommended in high-risk patients with adverse prognostic factors such as a positive surgical margin, high histological grade, tumor size and extension (i.e., pT3–4), lymph node involvement, or presence of perineural invasion (PNI). These prognosticators significantly influence tumor control and survival outcome and warrant adjuvant radiotherapy (RT) (5–9). Definitive RT is recommended for unresectable or inoperable major SGC patients (3,4). However, results from photon-based studies show that the 5-year local control (LC) rates are approximately 50% or less in inoperable salivary gland tumors (3), suggesting that conventional photon-based RT has limitations for the treatment of major SGCs. Neutron radiation appears to be the appropriate therapy for unresectable or inoperable cases with significantly improved LC, but the risk of severe toxicity is remarkably higher than that of photon-based RT (10–12).

There is an increasing interest in the use of particle (e.g., proton and carbon ion) beams in the treatment of SGCs (4,13,14). Particle beam radiotherapy (PBRT) provides favorable physical and biological advantages compared to photon-beam radiation, and has the potential to deliver a higher dose to the tumor region while sparing the normal structures adjacent to the target volume (15,16). Moreover, as a high linear energy transfer (LET) radiation, the relative biological effectiveness (RBE) of carbon ion beams is higher than that of proton and photon beams, indicating that SGCs, which are historically known to be radioresistant, may respond well to it. The use of intensity-modulated proton and/or carbon ion radiotherapy (IMPT or IMCT) in mixed cases with minor and major SGCs has shown a preliminary superiority in improving LC and reducing radiation-induced toxicities in some clinical studies (13,14,17–20). However, considering the differences in specific clinical presentations and the biological behavior of the tumor site of occurrence, the role of IMPT and/or

IMCT exclusively for major SGCs needs investigation.

The Shanghai Proton and Heavy Ion Center (SPHIC) initiated the clinical application of intensity-modulated PBRT using pencil beam scanning (PBS) technology in May of 2015. In this study, we report the outcomes of the use of IMPT and/or IMCT as the adjuvant or definitive treatment of the first cohort of patients with major SGCs. We present the following article in accordance with the STROBE reporting checklist (available at <https://atm.amegroups.com/article/view/10.21037/atm-20-7988/rc>).

Methods

Patients and pretreatment evaluation

Between August 2015 and November 2019, 55 consecutive and non-selected major SGC patients who received PBRT at the SPHIC were retrospectively analyzed. Pretreatment evaluation included a complete history and physical (H&P) examination, complete blood count (CBC), serum electrolyte panel, renal and hepatic function tests, and enhanced magnetic resonance imaging (MRI) or enhanced computed tomography (CT) (if MRI was contraindicated) of the head and neck region for all patients. Positron emission tomography (PET)/CT or chest CT, bone scan, and abdominal ultrasonography were employed to exclude distant metastasis (DM). All patients were staged based on the American Joint Committee on Cancer (AJCC) staging system and discussed in the institutional multidisciplinary tumor clinic to confirm the indication for PBRT prior to the registration and inclusion in the institutional tumor registry. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Institution Review Board (IRB) of the Shanghai Proton and Heavy Ion Center, Shanghai, China (No. 201022EXP-01). Individual consent for this retrospective analysis was waived.

Particle beam radiation therapy

All patients were immobilized with thermoplastic masks in the supine position. Plain CT for simulation with a 1.5-mm slice thickness from the vertex to the inferior margin of the clavicular heads was performed. MRI-CT fusion was applied for the target delineation. The gross tumor volume (GTV) was defined as the tumor discovered on clinical examination or imaging studies for patients without surgery or after incomplete surgical resection. Clinical target volume (CTV)

for boost (CTV-boost) was defined as the GTV with a 1–3 mm margin to deliver the prescribed dose to the tumor. The CTV included the CTV-boost or tumor bed (Patients with R0/R1 resection) and suspected subclinical extension based on the clinical high-risk estimation. The planning target volume (PTV) was created based on the CTV by adding 3 mm in the lateral direction for setup variability and 3–5 mm in the depth direction for range uncertainty, which was 3.5%.

Patients who had failed one previous course of photon-based radiation were required to provide their old treatment plans. Dose recovery from the previous RT doses was set at 70% (21). The dose constraints of the organs at risk (OARs) are based on TD5/5 described by Emami *et al.* except for the optic nerve (D20 <30 GyE), brain stem (Dmax <45 GyE), spinal cord (Dmax <30 GyE), and temporal lobes (V40 <7.66 cc; V50 <4.66 cc) which were based on the previous experience from the National Institute of Quantum and Radiation Science (NIQRS) of Japan (22,23).

PBRT was delivered utilizing the Siemens Syngo[®] planning system (VB13, Siemens health solution, Erlangen, Germany) with PBS technology. The beam arrangement varied based on the target volume geometry, and individual factors such as beam angles and/or patient positioning reproducibility were considered for optimal dosimetry. The planning for all patients used multi-field optimization (MFO) to maximize conformity and to reduce the dose to nearby OARs. The setup accuracy was verified with a daily orthogonal X-ray using bony landmarks as a reference, and verification CT scans were routinely performed on a weekly basis starting from the second week of PBRT to assess any anatomical changes. Recalculation was performed if clinically needed.

Follow-up

All patients were advised to adhere to our institutional standardized follow-up protocol after the completion of PBRT. The first follow-up visit was scheduled within 4–6 weeks after the completion of PBRT, then every 3 months during the first two years, every 6 months in the following 3 years, then annually thereafter. MRI of the head and neck area was arranged at each follow-up. PET/CT and other examinations including chest CT, bone scan, and abdominal ultrasonography were performed if clinically indicated.

Statistics

The duration of survival was calculated from the date of

diagnosis until the date of death or the last follow-up. The time to local, regional, or distant failure/progression was measured from the date of the initiation of PBRT until the documented date of failure/progression. Survival rates were calculated by the Kaplan-Meier method, while the Cox proportional hazard analysis method was performed to determine independent predictive factors. All analyses were performed using SPSS statistics software package (version 23.0, Chicago, IL, USA). Acute toxicities (occurring within 3 months after the initiation of PBRT) were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Event (CTC.AE version 4.03) and late toxicities (occurring >3 months after initiation of PBRT) were scored using the Radiotherapy Oncology Group (RTOG) late radiation morbidity scoring system.

Results

Patient characteristics

55 consecutive and non-selected major SGC patients who received PBRT at the SPHIC were analyzed between August 2015 and November 2019. The median follow-up was 24 (range, 6–57) months for the entire cohort. Primary sites of the tumors included the parotid gland (n=37), submandibular gland (n=17), and sublingual gland (n=1). Histologic types included ACC (n=23), adenocarcinoma (n=9), MEC (n=7), lymphoepithelial carcinoma (n=4), salivary duct carcinoma (n=2), rhabdomyosarcoma (n=2), acinar cell carcinoma (n=2), and others (n=6). Forty-one patients presented with newly diagnosed major SGCs. The remaining 14 patients presented with local recurrence after previous treatment, including nine who received prior radiation therapy with or without surgery, and five who received surgery without previous radiation. The patients who received previous resection with R0 or R1 had indicators for adjuvant radiation such as the stage of the disease (T3–T4/N2–3), a positive surgical margin, PNI, or a high-grade pathology type. The characteristics of the patients are summarized in *Table 1*.

PBRT

All patients received either IMPT (n=8), IMCT (n=37), or IMPT combined with IMCT (n=10) using PBS technology. The nine patients with local recurrence after previous RT were re-irradiated with IMCT (54–63 GyE/18–20 fractions). The remaining five patients with recurrence

Table 1 Characteristics of the patients, their disease, and treatments

Characteristic	No. of patients (%)
Median age [range], years	41 [14–92]
Gender	
Male	33 (60.0)
Female	22 (40.0)
Disease status	
Primary	41 (74.5)
Recurrence	14 (25.5)
RT parameters	
Initial treatment	46 (83.6)
Re-radiotherapy	9 (16.4)
Primary site	
Parotid gland	37 (67.3)
Submandibular gland	18 (32.7)
Histology	
Adenoid cystic carcinoma	23 (41.8)
Adenocarcinoma	9 (16.4)
Mucoepidermoid carcinoma	7 (12.7)
Lymphoepithelial carcinoma	4 (7.3)
Salivary duct carcinoma	2 (3.6)
Rhabdomyosarcoma	2 (3.6)
Acinic cell carcinoma	2 (3.6)
Others	6 (10.9)
Surgery status	
R0	17 (30.9)
R1	10 (18.2)
R2	17 (30.9)
No surgery	11 (20.0)
Clinical T classification	
T0	1 (1.8)
T1	9 (16.4)
T2	18 (32.7)
T3	10 (18.2)
T4	17 (30.9)

Table 1 (continued)**Table 1** (continued)

Characteristic	No. of patients (%)
Clinical N classification	
N0	46 (83.6)
N1	5 (9.1)
N2	4 (7.3)
Stage	
I	8 (14.5)
II	15 (27.3)
III	11 (20.0)
IV	21 (38.2)
Radiotherapy technique	
IMPT	8 (14.5)
IMCT	37 (67.3)
IMPT + IMCT	10 (18.2)

IMPT, intensity-modulated proton radiotherapy; IMCT, intensity-modulated carbon-ion radiotherapy.

received, either adjuvantly or definitively, RT naïve with IMPT (66 GyE/33 fractions, n=1) or IMCT (63–69 GyE/18–23 fractions, n=2; 70 GyE/20 fractions, n=2). Fifteen patients with newly diagnosed SGC who achieved R0 resection received IMPT (54–60 GyE/27–30 fractions, n=7) or IMCT (60 GyE/20 fractions, n=8), respectively. Ten patients completed a combination of IMPT and IMCT boost, and another 16 newly diagnosed patients completed IMCT according to our standard institutional protocols. The details of the dose/fractionation schemes are detailed in *Table 2*.

Survival outcomes

Within the median follow-up time of 24 (range, 6–57) months, four patients had died: Two newly diagnosed patients died of lung and bone metastasis 23 and 25 months after a combination of IMPT and IMCT boost, respectively; one re-irradiated patient died of local recurrence 24 months after re-irradiation with IMCT; another patient with recurrence died of grade 5 hemorrhage 9 months after re-irradiation with carbon ion. In addition, four patients developed local or regional recurrence after

Table 2 Fractionations of the IMPT/IMCT treatment scheme

Fractionation	Total dose (GyE)	Fraction (Fx)	No. of patients
IMPT			
66 GyE/33 Fx	66	33	1
60 GyE/30 Fx	60	30	3
56 GyE/28 Fx	56	28	3
54 GyE/27 Fx	54	27	1
IMPT + IMCT			
56 GyE/28 Fx + 18 GyE/6 Fx	74	34	1
56 GyE/28 Fx + 17.5 GyE/5 Fx	73.5	33	4
56 GyE/28 Fx + 15 GyE/5 Fx	71	33	5
IMCT			
70 GyE/20 Fx	70	20	8
69 GyE/23 Fx	69	23	1
66.5 GyE/19 Fx	66.5	19	1
66 GyE/22 Fx	66	22	1
63 GyE/21 Fx	63	21	4
63 GyE/18 Fx	63	18	9
60 GyE/20 Fx	60	20	12
54 GyE/18 Fx	54	18	1

IMPT, intensity-modulated proton radiotherapy; IMCT, intensity-modulated carbon-ion radiotherapy.

IMCT or a combination of IMPT and IMCT boost, and seven additional patients developed lung, bone, or brain metastases after PBRT. The 2-year overall survival (OS), progression-free survival (PFS), local-regional recurrence-free survival (LRRFS), and distant metastasis-free survival (DMFS) rates were 91.6%, 78.6%, 94.2%, and 83.9%, respectively, for the entire cohort (*Figure 1*).

Predictive factors for OS, PFS, LRRFS, DMFS

The differences in the survival probabilities were compared by the log-rank test in terms of age, gender, disease status (newly diagnosed *vs.* recurrent), RT parameter (RT naïve *vs.* re-RT), surgery status (R0–1 *vs.* R2 + no surgery, and N/A), primary site (parotid gland *vs.* others), histology (ACC *vs.* others), T classification (T0–2 *vs.* T3–4), N classification (N0 *vs.* N1–2), and stage (I–II *vs.* III–IV) (*Table 3*). Univariate analysis showed that OS was associated with surgery status ($P=0.018$), and PFS was associated with the surgery status ($P=0.005$), T classification ($P=0.001$),

and stage ($P=0.002$) (*Figure 2*). The results also showed statistically significant differences in disease status ($P=0.020$), RT parameters ($P=0.045$), surgery status ($P=0.021$), and T classification ($P=0.051$) for LRRFS (*Figure 3*). In addition, DMFS was significantly associated with the T classification ($P=0.006$), N classification ($P=0.030$), and stage ($P=0.015$) (*Figure 4*).

Multivariate analysis using Cox regression identified the predictive factors with a P value of 0.5 or less from the univariate analyses for PFS and DMFS (*Table 4*). Multivariate analysis illustrated that surgery status was an independent prognostic factor for PFS. No significant prognostic factor was identified for DMFS in the multivariate analysis.

Acute and late toxicities

The most commonly observed acute adverse effects included grade 1 or 2 mucositis, dermatitis, and xerostomia: Four patients experienced acute grade 2 mucositis, four

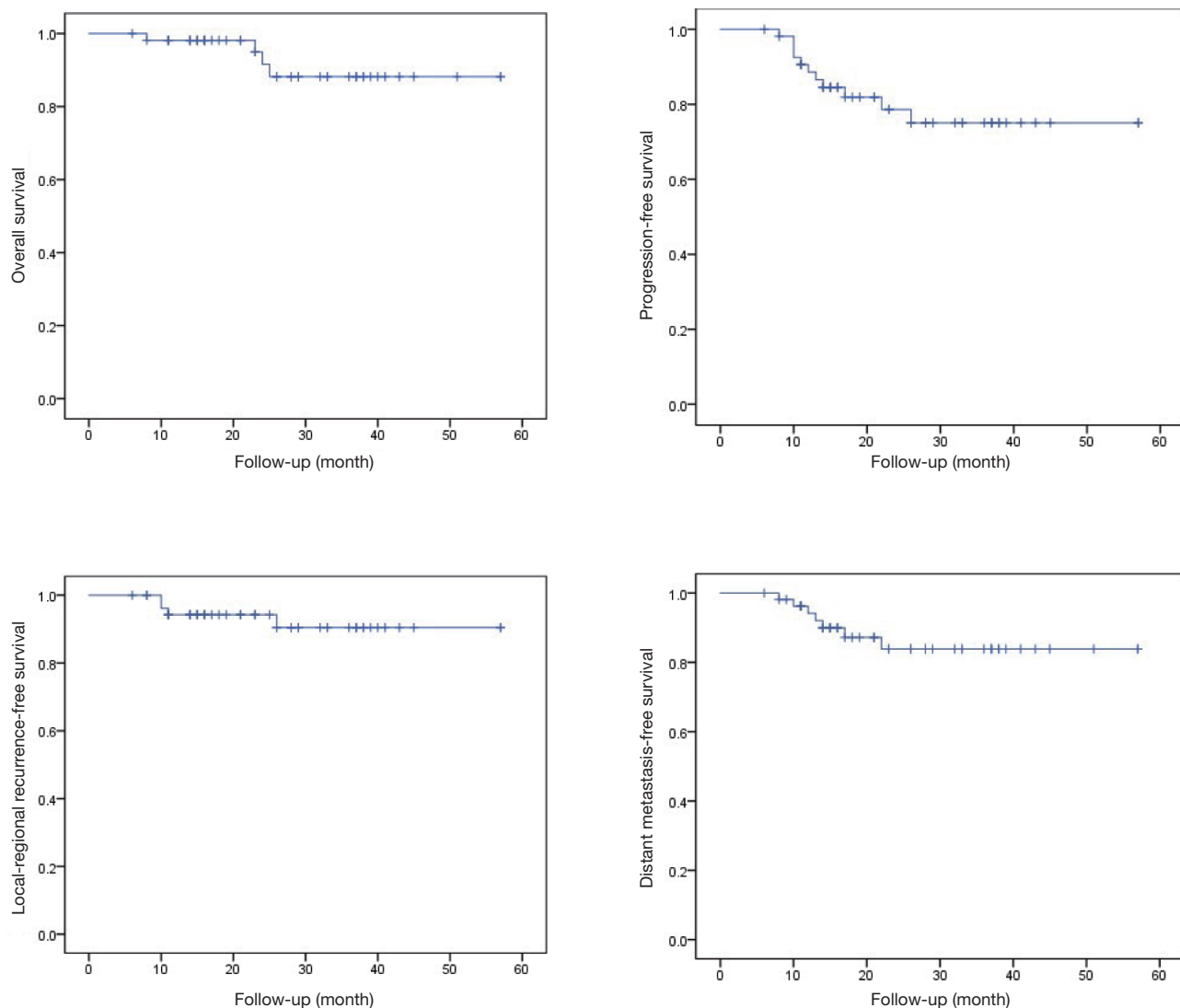


Figure 1 OS, PFS, LRRFS, and DMFS curves of the entire cohort. OS, overall survival; PFS, progression-free survival; LRRFS, local-regional recurrence-free survival; DMFS, distant metastasis-free survival.

patients experienced an acute grade 2 dermatitis, and one patient had grade 3 mucositis. No grade 4 or 5 acute toxicities were observed. The most common late side effects included grade 1 xerostomia, hearing impairment, tinnitus, and dysphagia. One patient with recurrent disease died due to hemorrhage at 9 months after re-irradiation with a minimal IMCT dose (54 Gy RBE in 18 fractions) (*Table 5*).

Discussion

This study presents 55 consecutive and non-selected patients with major salivary gland malignancies who

received adjuvant or radical IMPT and/or IMCT at the SPHIC. With a median follow-up time of 24 (range, 6–57) months, the 2-year OS, PFS, LRRFS and DMFS rates were 91.6%, 78.6%, 94.2%, and 83.9%, respectively. At the time of this analysis, four patients had developed local or regional recurrence, and seven patients had developed DM. Three patients had died due to disease progression. Another patient with recurrence died following a late grade 5 hemorrhage after re-irradiation with carbon ion beams. Otherwise, none of the patients experienced grade 3 or higher treatment-induced acute or late adverse effects except for 1 (2%) who developed grade 3 acute

Table 3 Univariate analysis for the 2-year OS, PFS, LRRFS, DMFS

Factor	2 y OS	P value	2 y PFS	P value	2 y LRRFS	P value	2 y DMFS	P value
Age		0.078		0.074		0.286		0.182
≤41	1		0.855		0.964		0.885	
>41	0.855		0.703		0.917		0.778	
Gender		0.460		0.580		0.765		0.411
Male	0.855		0.864		0.933		0.782	
Female	1		0.720		0.955		0.905	
Disease status		0.433		0.381		0.020		0.482
Primary	0.952		0.784		0.975		0.804	
Recurrent	0.836		0.774		0.833		0.929	
RT parameters		0.167		0.234		0.045		0.904
Initial treatment	0.958		0.809		0.978		0.827	
Re-radiotherapy	0.762		0.635		0.714		0.889	
Surgery status		0.018		0.005		0.021		0.102
R0 + R1	1.0		0.900		1.0		0.900	
R2 + no surgery	0.808		0.681		0.880		0.784	
Primary site		0.621		0.951		0.131		0.219
Parotid gland	0.941		0.820		0.914		0.901	
Others	0.866		0.741		1.0		0.741	
Histology		0.123		0.715		0.092		0.239
ACC	0.870		0.792		1.0		0.684	
Others	0.944		0.786		0.900		0.852	
T classification		0.418		0.001		0.051		0.006
T0–2	0.962		1.0		1.0		1.0	
T3–4	0.882		0.597		0.889		0.688	
N classification		0.327		0.182		0.519		0.030
N0	0.907		0.808		0.936		0.867	
N1–2	1.0		0.600		1.0		0.600	
Stage		0.512		0.002		0.080		0.015
I–II	0.957		1.0		1.0		1.0	
III–IV	0.889		0.633		0.900		0.717	

OS, overall survival; PFS, progression-free survival; LRRFS, local-regional recurrence-free survival; DMFS, distant metastasis-free survival; ACC, adenoid cystic carcinoma.

mucositis.

The results for patients with unresectable diseases treated with photon-based RT have shown that the role of conventional RT in the management of SGCs is limited

(24–26). In a study of 64 patients with inoperable tumors, Mendenhall *et al.* reported that the 5-year OS and 5-year LC were approximately 50% and 42%, respectively (26). Spratt *et al.* also demonstrated that the 2-/5-year OS and

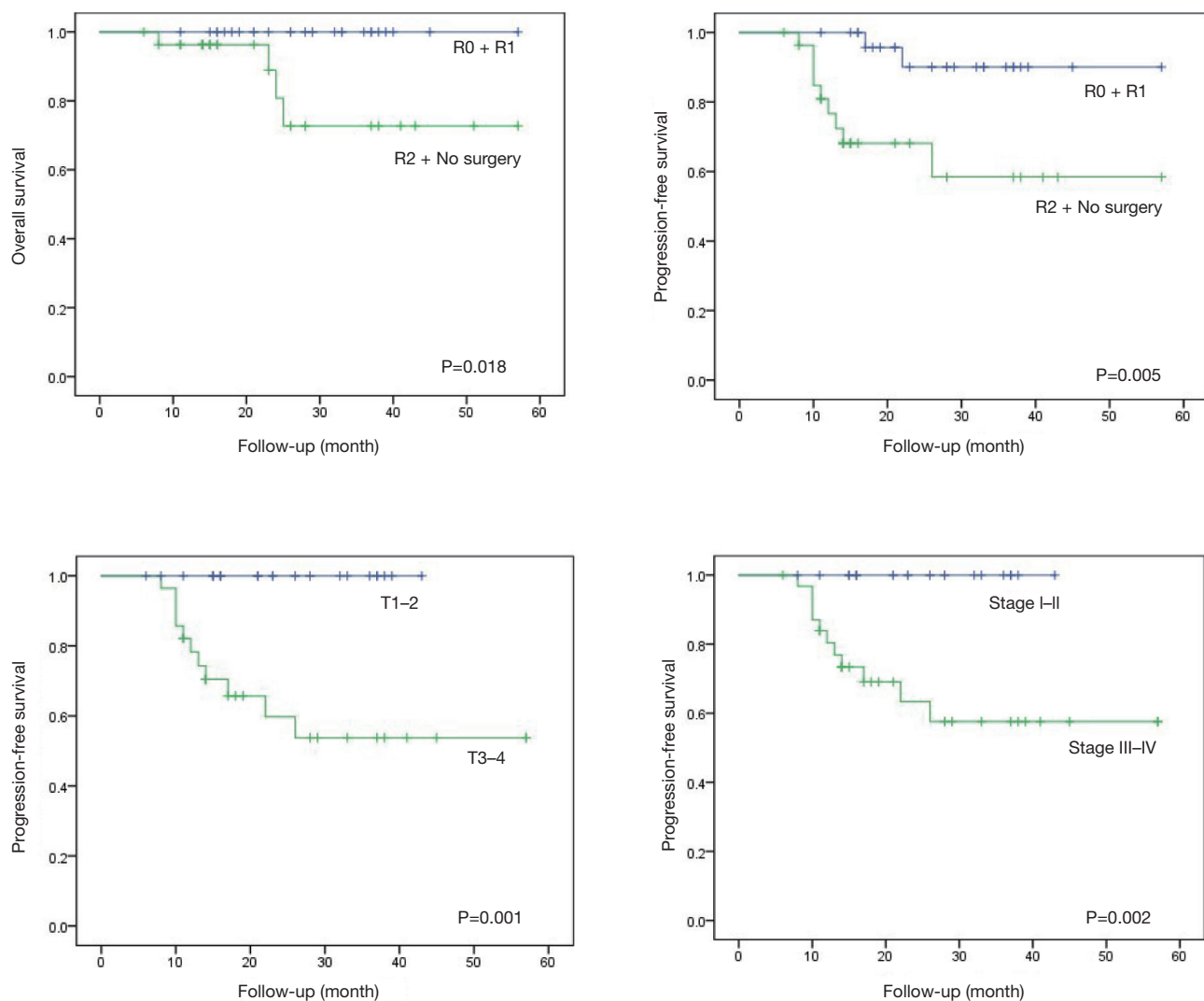


Figure 2 OS curves according to surgery status. PFS curves showing surgery status with R2 and no surgery, T3–4, and stage III–IV diseases had a worse PFS. OS, overall survival; PFS, progression-free survival.

LC were only 50%/29% and 69%/55%, respectively, in a retrospective study of 27 patients with unresectable salivary gland tumors treated with photon-based RT (25). Conversely, fast neutron RT has provided somewhat more favorable outcomes for those relatively radioresistant tumors compared to photon-based RT (10,12,27). Timoshchuk *et al.* reported a favorable 2-/5-year LC rate of 88%/78% and a 2-/5-year OS rate of 82%/62% using radical neutron RT in treating 145 patients with malignant salivary gland tumors (27), suggesting that neutron, as a high LET radiation, appears to be beneficial in improving OS and LC. However, the incidence of acute and late toxicities caused by

neutrons was relatively high. Davis *et al.* showed that acute xerostomia and mucositis were observed in 89% and 88% of patients, respectively, during neutron treatment, and 56%, 52%, and 74% of patients who received a telephone survey experienced late toxicities of trismus, dysphagia, and saliva decrease, respectively (12). Although the above published clinical studies often contain heterogenous characteristics of patients and diseases (e.g., primary site, tumor pathology, and stages), these results demonstrate that radical RT with either photon or neutron is still limited in terms of its therapeutic effect or toxicities in treating unresectable major SGCs.

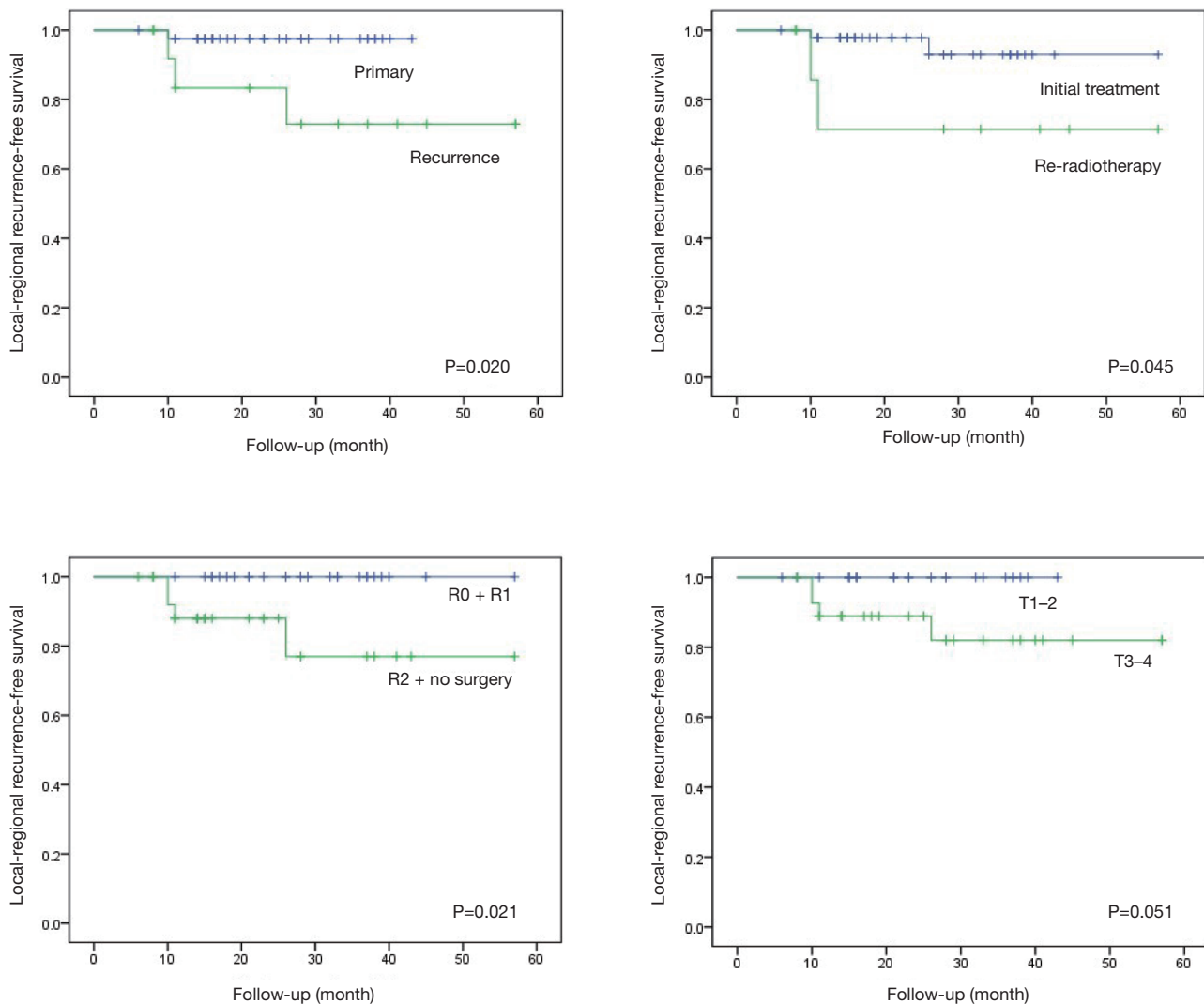


Figure 3 Local-regional recurrence-free survival curves according to disease status, radiotherapy (RT) parameter, surgery status, and T classification.

With respect to resectable diseases, surgery with adjuvant RT is recommended for patients at high risk of local-regional recurrence (6-9,28-30). In a retrospective study reported by Al-Mamgani *et al.*, 186 patients with parotid gland carcinoma received postoperative photon RT. After a median follow-up of 58 months, the 5-year OS and LC were 68% and 89%, respectively (9). Chung *et al.* reported that the 5-year OS and LC outcomes were 76% and 97%, respectively, for patients treated with postoperative photon RT for cancers excluding ACC of the major salivary glands (30). Lee *et al.* demonstrated that the 5-year OS of adjuvant

photon RT for 1,313 patients with major salivary ACC was 82.4% (28). These studies indicated that postoperative radiation therapy for major SGCs was associated with an improved therapeutic effect. Our study showed similar findings, and our multivariate analysis showed surgery status was an independent prognostic factor for PFS. However, side effects induced by photon-based PORT may severely compromise the quality of life (QoL) of patients who achieve long-term survival and tumor control. Hosni *et al.* observed that grade 3 late toxicities occurred in nine patients after adjuvant photon RT, including osteoradionecrosis in four cases, neck fibrosis in three cases, trismus in one

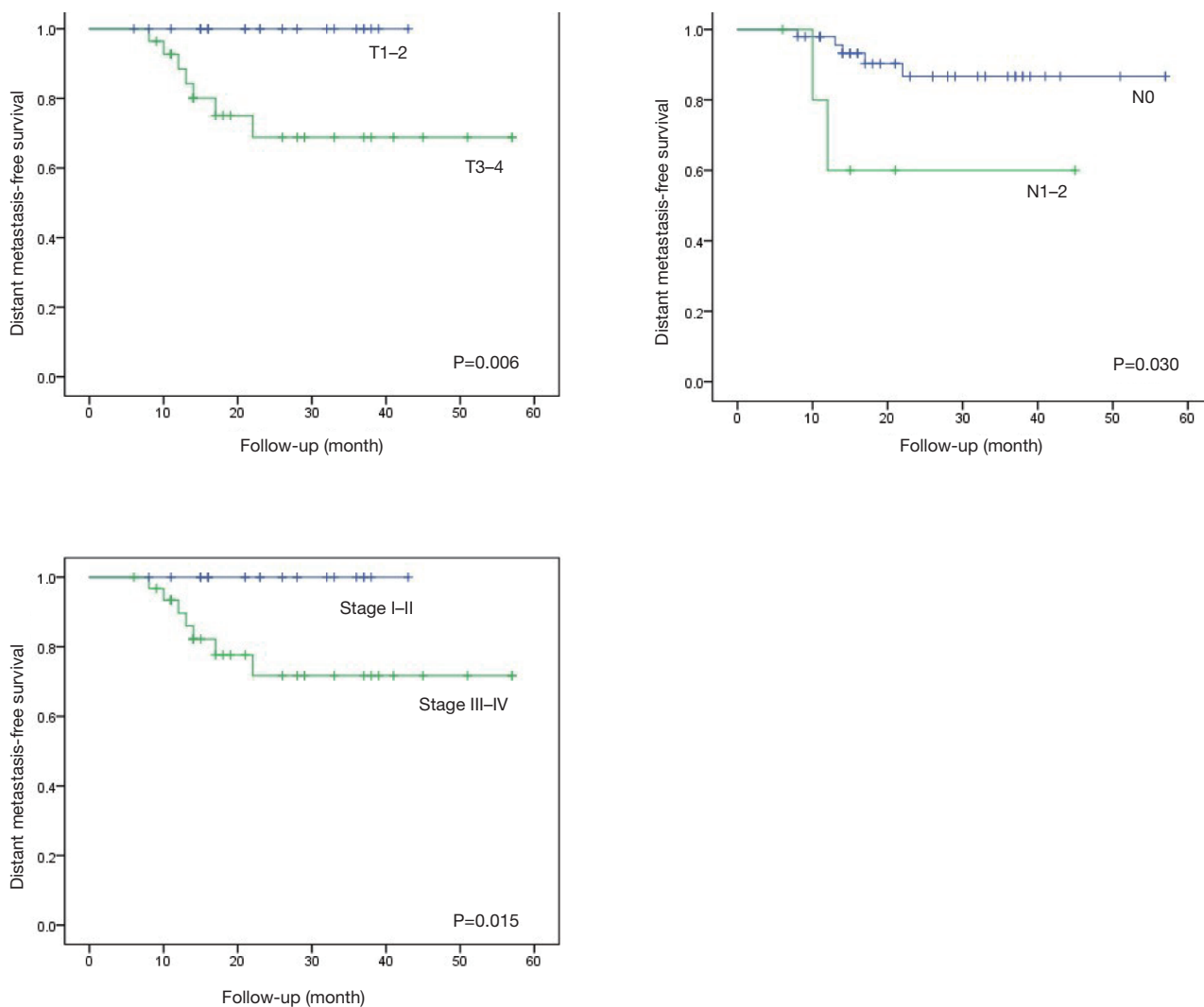


Figure 4 Distant metastasis-free survival curves show that T3–4, N1–2, and stage III–IV diseases had worse DMFS. DMFS, distant metastasis-free survival.

case, and dysphagia in one case (7). Swisher-McClure *et al.* demonstrated that the incidence of grade 2/3 acute mucositis and dysphagia was 91% and 27%, respectively, in pediatric patients with parotid gland carcinoma after radical surgery irradiated with adjuvant RT (18). Obviously, RT technology with improved tolerability is more favorable for patients with high risk pathological factors.

Proton and carbon ion beams can provide a more focused dose distribution due to their physical characteristics; therefore, a higher dosage can be delivered to the tumor volume while sparing the adjacent normal organs (15). Moreover, the high RBE of carbon ion has the advantage of destroying these tumors, which were thought to be

radioresistant. In a retrospective multicenter study of 69 patients with major SGCs who received carbon-ion radiotherapy (CIRT), Hayashi *et al.* demonstrated that CIRT can result in good survival and LC rate. The 3-year OS and LC rates were 94% and 81%, respectively (31). Sulaiman *et al.* also reported 2-year OS and LC rates of 94% and 88%, respectively, for ACC of the head and neck (including 35 cases of major salivary gland ACC) utilizing CIRT (14). Koto *et al.* adopted definitive CIRT for 46 patients with locally advanced parotid gland carcinomas and reported 5-year LC and OS rates of 74.5% and 70.1%, respectively (32). Therefore, combined with the results of our study, the therapeutic effect of PBRT for the

Table 4 Cox proportional hazard regression analysis for 2-year PFS and DMFS

Factors	PFS		DMFS	
	P	HR (95% CI)	P	HR (95% CI)
Age	0.30	2.29 (0.48–10.93)	0.58	1.69 (0.07–10.72)
Gender	–	–	0.87	0.86 (0.14–5.18)
Disease status	0.46	0.42 (0.04–4.06)	–	–
RT parameters	0.48	2.30 (0.23–23.06)	–	–
Surgery status	0.01	7.69 (1.50–39.44)	0.12	4.19 (0.68–25.87)
Primary site	0.69	1.32 (0.34–5.17)	0.23	2.68 (0.54–13.36)
Histology	0.56	1.50 (0.38–5.92)	0.84	0.85 (0.17–4.26)
T classification	–	–	–	–
N classification	0.47	0.52 (0.09–3.07)	0.18	0.25 (0.03–1.89)
Stage	–	–	–	–

PFS, progression-free survival; DMFS, distant metastasis-free survival; RT, radiotherapy; HR, hazard ratio; CI, confidence interval.

Table 5 Type and frequency of adverse events

Toxicity	Grade, n (%)				
	1	2	3	4	5
Acute					
Mucositis	14 (25.5)	4 (7.3)	1 (1.8)	0	0
Dermatitis	29 (52.7)	4 (7.3)	0	0	0
Xerostomia	18 (32.7)	0	0	0	0
Hearing impairment	4 (7.3)	0	0	0	0
Tinnitus	5 (9.1)	0	0	0	0
Dysphagia	1 (1.8)	0	0	0	0
Late					
Xerostomia	9 (16.4)	0	0	0	0
Hearing impairment	4 (7.3)	0	0	0	0
Tinnitus	5 (9.1)	0	0	0	0
Dysphagia	4 (7.3)	0	0	0	0
Hemorrhage	0	0	0	0	1 (1.8)
Lower cranial neuropathy	1 (1.8)	0	0	0	0
Limited mouth opening	2 (3.6)	0	0	0	0

Toxicities were evaluated according to the CTCAE version 4.03.

management of major SGCs appears to be significantly improved compared with photon-based RT.

DM is the most common pattern of failure in the current study. This finding is consistent with previous reports (14,31,33,34). In a study consisting of 255 patients with major SGCs, 57 (22%) patients developed DM after radical or adjuvant photon RT within a median follow-up period of 31 months (34). Hsieh *et al.* also reported that 20 out of 65 patients (30.1%) with submandibular gland carcinoma treated with postoperative photon RT developed DM within a median follow-up period of 42 months. DM was also associated with lymph node status (N-classification) and primary size (T-classification) (29). These results are also consistent with our findings, insofar as DM occurred in seven (13%) out of 55 of our patients. In addition, our univariate analysis indicated that the N/T classification and stage factors were associated with DMFS. Major SGCs are prone to develop DM, especially in patients with ACC, sarcoma, and nodal involvement. Preclinical research has found that carbon ion and proton have the potential to suppress the capability of malignant tumor cells to metastasize (35,36), and has provided evidence that PBRT may be superior to conventional photon RT in decreasing the rate of DM in clinical settings. However, the potential for an antimetastatic effect using particle beam RT in major SGCs has not been confirmed in our study, and should be further investigated.

None of our patients experienced grade 3 or higher acute toxicity except for 1 (2%) who developed grade 3 acute mucositis. Only one patient with recurrent disease died of grade 5 hemorrhage after re-irradiation using CIRT to 54 Gy RBE (18 fractions). Romesser *et al.* compared the acute toxicities of patients with major SGCs after radical surgery, radiation using adjuvant photon, or proton therapy. A total of 41 patients were enrolled in that study, of which 23 patients received photon therapy and the remaining 18 patients received proton beam RT. The incidence of acute side effects in the proton therapy group was remarkably lower than in those who received photon-based RT (grade 2 dysphagia: 5.6% vs. 65.2%, $P < 0.001$; grade 2/3 mucositis: 16.7% vs. 52.2%, $P = 0.019$) (37). In another study, Spratt *et al.* reported that 13 (48%) patients experienced acute grade 3 acute toxicities such as mucositis and dysphagia, and three (11%) patients developed grade 3 late toxicities including dysphagia, mucositis, and hearing loss in unresectable salivary gland tumors after photon RT to radical dose (25). On the contrary, our study showed that only one patient experienced grade 3 acute mucositis, and one additional patient with recurrence with re-irradiation

developed massive hemorrhage. Hayashi *et al.* showed that 14 (20.3%) patients developed grade 3 acute mucositis or dermatitis during CIRT, and 2 (3%) patients developed grade 3 late dysphagia or brain abscess, demonstrating that the incidence and degree of toxicities significantly decreased with proton or carbon ion radiation by virtue of its physical characteristic advantage (31).

Several limitations in the present study need to be addressed. Firstly, our study was a retrospective case series with a relatively small sample size. Given the rarity of major salivary gland neoplasms, most of the published literature on this subject is limited by its retrospective nature and limited number of cases. Secondly, the median follow-up period of the present study (24 months) is relatively short. For certain histology subtypes, especially those with relatively indolent natures, longer follow-up is needed to further assess the long-term outcomes.

Conclusions

Our results indicated that IMPT and/or IMCT provided satisfactory therapeutic effectiveness in patients with malignancies of the major salivary gland and produced a low incidence of acute and late toxicities. The 2-year OS, PFS, LRRFS, and DMFS rates were 91.6%, 78.6%, 94.2%, and 83.9%, respectively. Long-term follow-up is required to confirm the efficacy and safety of PBRT in the treatment of major salivary gland malignancies.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at <https://atm.amegroups.com/article/view/10.21037/atm-20-7988/rc>

Data Sharing Statement: Available at <https://atm.amegroups.com/article/view/10.21037/atm-20-7988/dss>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://atm.amegroups.com/article/view/10.21037/atm-20-7988/coif>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Institution Review Board (IRB) of the Shanghai Proton and Heavy Ion Center, Shanghai, China (No. 201022EXP-01). Individual consent for this retrospective analysis was waived.

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