Comparison of the efficacy and toxicity of postoperative proton versus carbon ion radiotherapy for head and neck cancers

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Background: To compare the efficacy and toxicity of adjuvant proton beam *vs.* carbon-ion beam radiotherapy for head and neck cancers after radical resection and to explore the value of particle beam radiotherapy (PBRT) in postoperative radiotherapy for head and neck cancers.

Methods: Data from 38 head and neck cancer patients who received adjuvant PBRT after complete surgical resection at the Shanghai Proton and Heavy Ion Center (SPHIC) between October 2015 and March 2019 were retrospectively analyzed. In total, 18 patients received adjuvant proton beam therapy (54–60 GyE/27–30 fractions) and 20 received adjuvant carbon-ion radiotherapy (CIRT) (54–60 GyE/18–20 fractions). Survival rates were calculated using Kaplan–Meier analysis. Toxicity was evaluated according to the Common Terminology Criteria for Adverse Effects (version 4.03).

Results: With a median follow-up time of 21 (range, 3–45) months, the 2-year overall survival (OS), progression-free survival (PFS), local-regional recurrence-free survival (LRRFS) and distant metastasis-free survival (DMFS) rates were 93.3%, 87.4%, 94.1%, and 90.7%, respectively, for the entire cohort. The rates after proton beam therapy *vs.* CIRT were 94.1% *vs.* 91.7% (P=0.96), 88.1% *vs.* 86.2% (P=0.96), 94.4% *vs.* 93.3% (P=0.97), and 88.1% *vs.* 92.9% (P=0.57), respectively. Furthermore, 16 of the 18 (88.9%) patients developed acute grade I/II dermatitis (13 grade I; 3 grade II) after proton beam therapy, and only 7 of the 20 (35%) patients developed acute grade I dermatitis after CIRT (P=0.001). The incidence of acute grade I/II mucositis and xerostomia in proton and carbon ion cases were 45% *vs.* 55% (P=0.75) and 56% *vs.* 50% (P=0.87) respectively.

Conclusions: Adjuvant proton beam therapy and CIRT after radical surgical resection for head and neck cancers provided satisfactory therapeutic effectiveness, but no significant difference was observed between the two radiotherapy technologies. However, adjuvant CIRT was associated with a more favorable acute toxicity profile as compared to proton beam therapy with significantly lower frequency and severity of acute dermatitis observed.

Keywords: Proton; carbon ion; postoperative radiotherapy; head and neck cancers

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Introduction

Head and neck cancers (HNC) approximately account for 5% of all new cancer cases. Treatment approaches for head and neck cancers basically include surgery, radiotherapy, and chemotherapy or a combination of these options (1). Postoperative radiation therapy (PORT) is an important component of management for patients with locally advanced head and neck cancers. The use of PORT is usually recommended based on the stage of the disease stage (pT3–T4/N2–3) and other high-risk factors including the status of surgical margin, lymphovascular invasion (LVI), perineural invasion (PNI), extra-nodal extension (ENE), and differentiation of the tumor. These high-risk factors have been confirmed to negatively impact both local control (LC) and survival outcomes (2-5), and the use of PORT significantly improves disease control and survival in high-risk patients (6,7). However, toxicities induced by PORT with photon may significantly affect the quality of life (QoL) of patients who survive their disease and treatment (7-9). Clearly, more tolerable radiotherapy technologies with satisfactory but preferably improved efficacy and the potential of long-term disease control and survival are needed for patients with head and neck malignancies in particular.

Charged particle (such as proton and carbon ions) beams provide favorable physical and biological advantages in comparison with conventional photon-beam radiation (10,11). Particle beam radiotherapy (PBRT) has the potential to deliver higher doses to the tumor while sparing normal tissues/organs near the target volume(s). Clinical results after PBRT as definitive or salvaged treatment for head and neck cancers have been encouraging (12-14). Nevertheless, the value of PBRT in the adjuvant setting after complete radical resection has not been well investigated. Although results of a dosimetric comparison between proton beam therapy *vs.* photon-based intensity-modulated radiation therapy (IMRT) in PORT suggested the potential lower toxicity of proton therapy due to lower mean doses to several midline and contralateral organs at risk (OARs) (15,16), conclusive clinical results are lacking and limited to a single retrospective study for pediatric patients with parotid gland cancers (15).

The physical characteristics of carbon-ion beams are similar to those of proton beams; however, as carbon ion beams have high linear energy transfer (LET) radiation, their relative biological effectiveness (RBE) is higher than that of proton and photon beams, indicating a potential biologic advantage in cancer treatment as compared to proton therapy (11). And the treatment planning comparison of CIRT and photon-based IMRT for nonresectable head and neck cancers showed CIRT has the potential to improve the target dose conformity and OAR sparing (17). Unfortunately, the use of adjuvant CIRT and PBRT in the PORT setting has never exclusively been addressed in head and neck cancers.

The Shanghai Proton and Heavy Ion Center (SPHIC) started clinical application research of intensity-modulated PBRT using pencil beam scanning (PBS) technology in May of 2015. The purpose of this study is to explore the value of post-operative PBRT for head and neck cancer patients who achieved radical resection, and to compare the efficacy and acute and late toxicity profiles of adjuvant proton beam therapy versus CIRT. We present the following article in accordance with the STROBE reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-20-5078/rc).

Methods

Patients and Pretreatment evaluation

Between October 2015 and March 2019, 38 consecutive head and neck cancer patients who previously achieved radical resection received adjuvant PBRT at SPHIC. All newly diagnosed cases were confirmed by pathology and received radical resection (no residual tumor). In total, 18 patients received adjuvant proton beam therapy, and 20 patients received adjuvant CIRT. Patient evaluation included a complete history and physical (H&P) examination, complete blood count (CBC), serum electrolyte panel, renal and hepatic function tests, enhanced magnetic resonance imaging (MRI) of the head and neck region; enhanced computed (CT) was permitted if MRI was contraindicated. Positron emission tomography (PET)/CT (preferred) or chest CT, abdominal ultrasonography, and bone scan were used to rule out distant metastasis. In the institutional multidisciplinary tumor clinic of SPHIC, all patients were consulted on their indication for PBRT prior to registration and inclusion to the institutional tumor registry. Patients diagnosed before January 1, 2018 were staged according to the seventh edition of the American Joint Committee on Cancer (AJCC) staging system, and those diagnosed after January 1, 2018 were staged according to the updated eight edition. All procedures performed in this study were 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. 200313EXP-01). The requirement for informed consent was waived because of the retrospective nature of the research.

Particle beam radiation therapy

All patients were immobilized in supine position with individualized thermoplastic masks. Plain CT for simulation from the vertex to the inferior margin of clavicular heads were performed at 1.5-mm slice thickness. MRI-CT fusion was performed for all patients prior to target delineation for better visualization of OARs. For subclinical tumor extension to deliver the prescribed dose, we defined a clinical tumor volume (CTV) for patients who achieved radical resection (R0) as the pretreatment tumor bed plus high-risk areas, which were based on tumor (T) and (node) N classification and laterality of the diseases. The planning target volume (PTV) was created based on the CTV and 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% of the beam.

The prescribed dose used for patients who received intensity-modulated proton beam therapy was 54–60 Gy (RBE) at 2.0 Gy (RBE)/daily fraction, and the regimen used for patients who received intensity-modulated CIRT was 54–60 Gy (RBE) at 3.0 Gy (RBE)/daily fraction. The dose constraints of the OARs were based on TD5/5 as described by Emami *et al.* with the exception of 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 previous experience from the National Institute of Quantum and Radiation Science (NIQRS) of Japan (18,19).

PBRT was planned using the Siemens Syngo® planning system (version VC11-13) with PBS technology. The beam arrangement varied depending on target volume geometry. Individual factors such as beam angles and/or patient positioning reproducibility were considered for optimal dosimetry. All patients were planned using multi-field optimization (MFO) without robust planning to maximize conformality and to reduce dose to nearby OARs. Setup accuracy was confirmed with daily orthogonal X-ray using bony landmarks as a reference. Verification CT scans were typically performed on a weekly basis after the second week of the PBRT to assess any changes in anatomy. Recalculation was utilized if clinically needed.

Follow-up

All patients were suggested to adhere to our institutional standardized follow-up protocol after the completion of their adjuvant PBRT. The first follow-up was arranged within 4–6 weeks after the completion of radiation, in 3-month intervals in the first 2 years, every 6 months in the following 3 years, and then annually thereafter. MRI of the head and neck area were performed at each follow-up. PET/CT and other studies such as chest CT and abdominal ultrasonography were performed based on clinical evidence of disease progression. Acute toxicities (occurring during or within 3 months after the initiation of PBRT) and late toxicities (occurring >3 months after initiation of PBRT) were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Event (CTC. AE version 4.03).

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 surgery until the documented date of failure/progression. Survival rates were calculated using the Kaplan-Meier method. All analyses were performed in SPSS statistics version 23.0 software package (Chicago, IL, USA).

Results

Patient characteristics

38 consecutive head and neck cancer patients who received postoperative PBRT at SPHIC between October 2015 and March 2019 were analyzed. Primary sites of the malignancies included the oral cavity (16 cases), salivary glands (14 cases), paranasal sinus (4 cases), lacrimal gland (3 cases), and cervical adenopathy from unknown primary site (1 case). Histologic types included squamous cell carcinoma (SCC, 17 cases), adenoid cystic carcinoma (ACC, 7 cases), adenocarcinoma (5 cases), mucoepidermoid carcinoma (4 cases), lymphoepithelial carcinoma (4 cases), and acinar cell carcinoma (1 case). Among them, 18 patients received adjuvant proton beam therapy, and 20 patients received adjuvant CIRT. From all the cases, 14 patients with stage I–II received adjuvant radiotherapy because of adverse pathological factors (high grade). The characteristics of the patients and their adjuvant radiotherapy are summarized in

Table 1. No statistically significant difference between the 2 groups existed.

Disease control and survival

With a median follow-up time of 21 (range, 3–45) months, 2 patients who developed lung and bone metastasis died after CIRT and proton therapy respectively. In addition, 1 patient developed both local and distant recurrence after proton therapy, and another had local recurrence only after CIRT. The 2-year overall survival (OS), progression-free survival (PFS), local-regional recurrence-free survival (LRRFS), and distant metastasis-free survival (DMFS) rates were 93.3%, 87.4%, 94.1%, and 90.7%, respectively, for the entire cohort; meanwhile the rates after adjuvant proton beam therapy *vs.* CIRT were 94.1% *vs.* 91.7% (P=0.96), 88.1% *vs.* 86.2% (P=0.96), 94.4% *vs.* 93.3% (P=0.97), and 88.1% *vs.* 92.9% (P=0.57), respectively (*Table 2* and *Figure 1*).

Adverse events

All patients completed PBRT without unplanned interruption. In the proton therapy group, 16 patients (88.9%) developed acute grade I/II dermatitis (13 grade I and 3 grade II), 8 patients (45%) developed grade I/II mucositis (5 grade I and 3 grade II), and 10 patients (56%) developed grade I xerostomia. In the CIRT group, only 7 patients (35%) developed acute grade I dermatitis, 11 patients (55%) developed I/II mucositis (9 grade I and 2 grade II), and 10 patients (50%) developed grade I xerostomia (9 grade I and 1 grade II). There was a statistically significant difference in terms of acute dermatitis between the proton therapy and CIRT groups (P=0.001), but no significant difference in terms of acute mucositis (P=0.75) and xerostomia (P=0.87) was observed. The acute toxicity profiles are detailed in *Table 3*. No difference between the proton therapy and CIRT groups was observed for grade I or II late adverse events. No patients had grade III or higher treatment-induced acute or late adverse effects.

Discussion

We investigated the clinical efficacy and acute toxicity of 38 head and neck cancer patients who received adjuvant radiotherapy using proton or carbon ion beam after radical resection. In total, 18 and 20 patients received adjuvant proton beam therapy or CIRT, respectively. At the time of this analysis, 4 patients developed recurrence/metastasis and 2 died on account of progression. With a median follow-up time of 21 (range, 3–45) months, the 2-year OS, PFS, LRRFS, and DMFS after adjuvant PBRT for the entire cohort were 93.3%, 87.4%, 94.1%, and 90.7%, respectively. No difference between proton beam therapy and CIRT was observed in any of the survival outcomes. However, patients who received post-operative CIRT experienced significantly less acute dermatitis, although no difference in mucositis and xerostomia was observed.

To the best of our knowledge, this is the first study on the use of PBRT in the PORT setting for patients achieving R0 resection. Our study demonstrated that adjuvant PBRT after surgical resection for head and neck cancers provided satisfactory therapeutic effectiveness by comparison to previously published reports on photon adjuvant radiation (20,21). However, histologies included in our study were diverse, while studies on PORT using conventional photon-based treatment usually focus on a single type of malignancy (e.g., SCC) or site of the disease (e.g., oral cavity cancer). Although direct comparison of our results with those after photon-based radiation cannot be made, the observation that no patient experienced grade III acute and late toxicities indicated that PBRT is potentially safer and more favorable for patients' quality of life than photon-based radiation therapy for patients who may achieve long-term survival and disease control.

This study is also the first to compare the clinical efficacy and safety of proton versus carbon ion adjuvant radiotherapy for head and neck cancer patients after radical resection. However, a comparison between proton versus carbon ion treatment in mixed cases for definitive or salvaged purposes has been published previously. In a retrospective study by Demizu *et al.*, 62 patients with head and neck mucosal melanoma received proton therapy or CIRT. For the 33 patients treated with proton therapy, 1-/2-year OS, PFS and LC rates were 91%/58%, 64%/30%. and 92%/83%, respectively. For the 29 patients treated with CIRT, the 1-/2-year OS, PFS, and LC rates were 96%/62%, 63%/41%, and 95%/59%, respectively (22). The study compared the patient characteristics (e.g., total dose) of the 2 groups (P<0.05), and was considered to be sufficient to compare the efficacy and side effects of the 2 beam types. Interestingly, the statistical results showed that proton therapy achieved a LC rate (P=0.569) and toxicities (P=1.000) comparable to that of carbon ions. The authors

Table 1 Characteristics of patients and their adjuvant PBRT

Characteristics	Proton therapy (n=18)	Carbon-ion therapy (n=20)	P value
Age (years), mean ± SD	44.4±11.1	51.1±15.4	0.14
Gender			
Male	10 (55.6%)	8 (40%)	0.52
Female	8 (44.4%)	12 (60%)	
Diagnosis of disease			
Oral cavity	7 (38.9%)	9 (45%)	0.85
Salivary gland	8 (44.4%)	6 (30%)	
Paranasal sinus	2 (11.1%)	2 (10%)	
Lacrimal gland	1 (5.6%)	2 (10%)	
Cervical metastatic carcinoma of unknown primary site	0	1 (5%)	
Histology			
Squamous cell carcinoma	6 (33.3%)	11 (55%)	0.12
Adenoid cystic carcinoma	4 (22.2%)	3 (15%)	
Mucoepidermoid carcinoma	1 (5.6%)	3 (15%)	
Adenocarcinoma	3 (16.7%)	2 (10%)	
Lymphoepithelial carcinoma	4 (22.2%)	0	
Acinar cell carcinoma	0	1 (5%)	
Tumor (T) classification			
T1–2	12 (66.7%)	12 (60%)	1.00
T3–4	6 (33.3%)	7 (35%)	
TX	0	1 (5%)	
Nodal (N) classification			
N0-1	14 (77.8%)	17 (85%)	0.69
N2	4 (22.2%)	3 (15%)	
Stage			
Stage I–II	6 (33.3%)	8 (40%)	0.86
Stage III–IV	12 (66.7%)	11 (55%)	
NA		1 (5%)	
Treatment of ipsilateral neck			
Yes	14 (78%)	15 (75%)	0.90
No	4 (22%)	5 (25%)	

PBRT, particle beam radiotherapy; SD, standard deviation.

acknowledged that the carbon ion beam should be more effective in the treatment of melanomas that were thought to be radiation-resistant by reason of its higher RBE. However, the previous findings suggested that the sensitivity of melanoma to radiation ranges widely and overlaps considerably with that of common epithelial

Table 2 Two-year survival rates after proton and carbon ion beam radiotherapy

Survival rate	Proton therapy	Carbon-ion therapy	P value
2-year OS	94.1%	91.7%	0.96
2-year PFS	88.1%	86.2%	0.96
2-year LRRFS	94.4%	93.3%	0.97
2-year DMFS	88.1%	92.9%	0.57

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

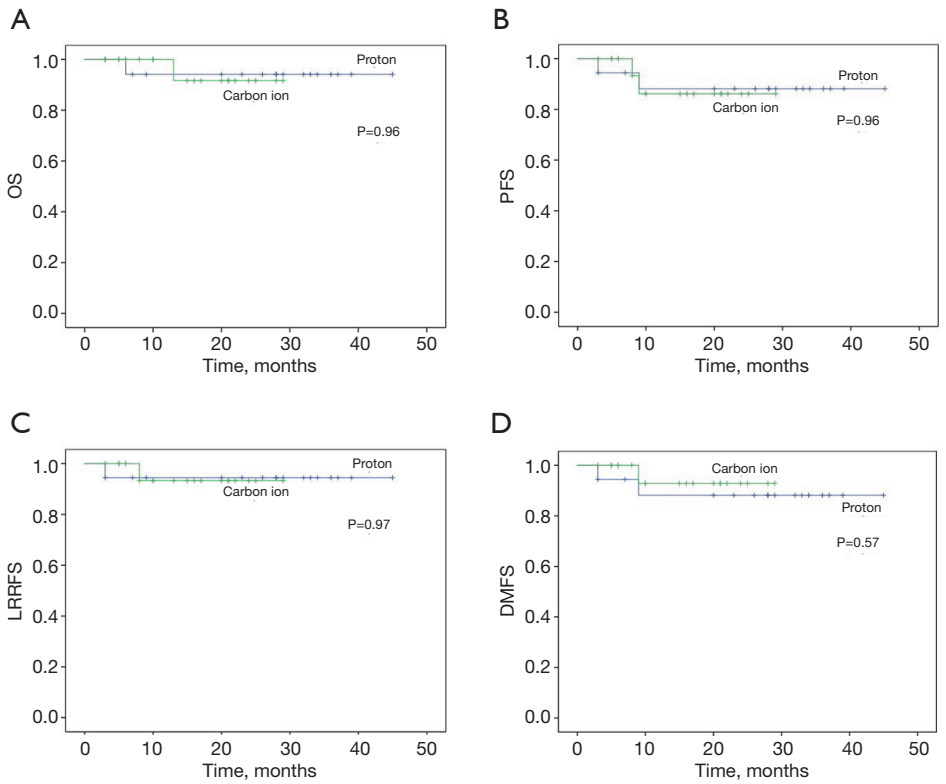

Figure 1 Overall survival (OS), progression-free survival (PFS), local-regional recurrence-free survival (LRRFS), and distant metastasis-free survival (DMFS) curves of the proton beam therapy group (blue) *vs.* carbon-ion beam radiotherapy (green). No statistically significant difference was observed between the 2 groups.

cancers (23), thus showing similar therapeutic effect to protons or carbon ions in the study.

Mattke *et al.* compared the clinical results of skull base chondrosarcomas patients irradiated with protons or carbon ions. A total of 101 patients were enrolled in this study, of whom 79 received carbon ions and 22 received proton treatment. The median dose of carbon ion and proton cases was 60 and 70 GyE, respectively. For proton cases, the 4-year LC and OS rates were both 100%, and the rates for carbon ion treated patients were 90.5% and 92.9%, respectively (24). A statistically significant difference in terms of therapeutic effect and toxicities between the carbon ion and proton beams could not be detected (P>0.05) on account of the patient numbers and the median follow-up time (30.7 months for proton and 43.7 months for carbon ion) that were not equal between proton and carbon-ion cases. The results of both above-mentioned studies suggest that the efficacy of CIRT might be similar to that of proton therapy in the setting of definitive treatment. This echoes our results in which the therapeutic effects of proton or

Table 3 Acute adverse effects after proton and carbon ion beam radiotherapy

Acute toxicity	Grade	Proton therapy, n=18 [%]	Carbon-ion therapy, n=20 [%]	P value
Dermatitis	0	2 [11]	13 [65]	0.001
	I	13 [72]	7 [35]	
	II	3 [17]	0	
Mucositis	0	10 [55]	9 [45]	0.75
	I	5 [28]	9 [45]	
	II	3 [17]	2 [10]	
Xerostomia	0	8 [44]	10 [50]	0.87
	I	10 [56]	9 [45]	
	II	0	1 [5]	

Acute toxicities were evaluated according to the CTCAE version 4.03.

carbon ion beams in adjuvant radiotherapy were roughly similar as there was no evident tumor in the target volume after radical surgery, although carbon ion beams have a higher RBE as compared to proton beams (25).

The incidence and severity of toxicities caused by PBRT in our study were tolerable. None of the patients had grade III or higher acute or late adverse effects in our study. Grant *et al.* retrospectively analyzed 24 pediatric patients with parotid gland carcinoma after radical surgery, including 11 who received adjuvant photon-based radiotherapy and 13 who received adjuvant proton beam radiotherapy. The incidence and severity of acute toxicity were significantly lower in patients who received adjuvant proton beam therapy than in those who received photon treatment (grade II/III mucositis: 46% *vs.* 91%, P<0.05; grade II/III dysphagia: 0 *vs.* 27%, P=0.08) (15). The findings in our patients after adjuvant proton beam therapy were consistent with those of other studies in which patients received proton therapy. However, when compared with patients who completed adjuvant CIRT, more patients experienced grade I/II acute dermatitis after proton therapy (88.9% *vs.* 35%, P=0.001), suggesting that carbon ion therapy may be superior to proton therapy in terms of normal tissue sparing. In view of this, we compared the biological effective dose of skin adjacent to CTV between the 2 groups from the treatment planning and found that biological effective doses were roughly similar between the 2 groups of patients. It is well-known that carbon ion beams have a higher LET as compared with proton beams. However, the RBE for carbon ion beams are mixed with low LET at the entrance plateau and high LET at the "Bragg peak" area (10). Hence, the RBE of a carbon beam could be selectively enhanced in the target volume while maintained at a low value in the entrance channel (26). On the contrary, the RBE of proton beam is approximately 1.1 based on both *in vitro* and *in vivo* experiments, and the RBE variations of proton beams were found to be relatively minor as compared to carbon ion beams (27,28). Therefore, despite the similar biological equralent doses (BEDs) observed at the skin regions, the potentially RBE of CIRT at the entrance of the body (i.e., skin) might be overestimated by the treatment planning system based on the local effect model (LEM) (29), which might have resulted in a much lower physical dose as compared to that from proton therapy. Obviously, this hypothesis needs to be verified in a separate study. Except for the difference in the severity of dermatitis observed, we found no significant difference in either acute mucositis or xerostomia, which is consistent with the observation in previous reports by Demizu *et al.* and Mattke *et al.* (22,24). However, it is important to note that different biophysical models were used for carbon ion treatment centers in Japan (based on the modified microdosimetric kinetic model, MKM) versus those in China and Germany (based on LEM), although similar BEDs in CIRT planning were used and similar findings in clinical manifestations were observed.

Several limitations of this study should also be discussed. First, a direct comparison between 2 different treatment modalities is best evaluated by a randomized clinical trial. The retrospective nature of this study with relatively small sample size certainly introduces selection bias. However, there has been no published literature on the differences

between CIRT and proton therapy under the setting of PORT for head and neck cancer. Our results were valuable for generating hypotheses for future investigations, and a randomized trial is planned to compare proton therapy with CIRT in head and neck cancer patients after radical resection at the SPHIC. Secondly, the median follow-up time of 21 months in our study is relatively short for understanding the long-term disease control and adverse effects. Considering the majority of the recurrences in head and neck cancer patients occur in the first 2 years after definitive treatment (30), the 2-year survival and disease control rates were relatively reliable for comparing the 2 PBRT modalities. Also, although the follow-up was relatively short, the fact that no patient experienced grade III late effects indicates that both proton therapy and CIRT might be safer than photon-based radiotherapy.

Conclusions

Adjuvant proton or carbon-ion beam radiation therapy for head and neck cancers after radical surgical resection provided satisfactory therapeutic effectiveness. No significant difference in terms of disease control and patients' survival was observed between the 2 radiotherapy technologies. However, adjuvant CIRT was associated with a more favorable acute toxicity profile as compared to proton beam therapy, and significantly less frequent and severe acute dermatitis was observed after CIRT.

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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-20-5078/rc

Data Sharing Statement: Available at https://atm.amegroups.com/article/view/10.21037/atm-20-5078/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-20-5078/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. All procedures performed in this study were 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. 200313EXP-01). The requirement for informed consent was waived because of the retrospective nature of the research.

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