Original Article

Particle beam radiation therapy for head and neck rhabdomyosarcoma in adults

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Background: Rhabdomyosarcoma (RMS) is rare in adults, with a significantly worse prognosis than its pediatric counterpart. Radiotherapy (RT) plays a significant role in treating head and neck RMS (HNRMS), but the outcomes of conventional RT are limited by the complex anatomy and unfavorable pathology subtypes of the adult H&N RMS. Here, we aim to report the effectiveness and safety of carbon-ion beam RT (CIRT), either alone or in combination with proton radiotherapy (PRT) in the management of adult HNRMS.

Methods: Fifteen adult patients with HNRMS were enrolled on a prospective registry protocol between 06/2015 and 12/2019. Eight patients presented with parameningeal tumors, and eight had unfavorable pathology subtypes [alveolar =7, not otherwise specified (NOS) =1]. Eleven patients had gross tumors before the start of RT (volume range, 46.1–137.6 cm^3). Two patients failed the earlier RT. All except for one patient received multi-drug chemotherapy. The median absolute dose of particle beam RT was 70.0 Gy [relative biological effectiveness (RBE)].

Results: With a median follow-up of 21 months, local or distant recurrence occurred in three and four patients, respectively, and two added patients had both local and distant failure. One patient died of distant metastasis (DM), and another died of an unrelated condition. The 1- and 2-year overall survival (OS), local relapse-free survival (LRFS), distant metastasis-free survival (DMFS), and progression-free survival (PFS) rates were 87.5% and 70.0%, 92.3% and 67.1%, 72.2% and 54.2%, and 65.0% and 24.4%, respectively, for the entire cohort. Both patients who failed earlier RT and received salvage CIRT developed DM but were alive at last follow-up. No acute toxicity of ≥ grade 3 or late toxicity of ≥ grade 2 was observed.

Conclusions: CIRT, either used alone or in combination with PRT, is not only feasible and safe but also useful in local disease control for HNRMS. DM is the most important cause of treatment failure; thus, more effective systemic treatment is needed to improve the prognosis of HNRMS further.

Keywords: Rhabdomyosarcoma (RMS); adult; head and neck; particle beam radiation therapy (PBRT); carbon-ion radiation therapy (CIRT)

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Introduction

Rhabdomyosarcoma (RMS) is an exceedingly rare malignancy and is mostly a disease of childhood with >80% of cases diagnosed before the age of 15 (1). Adults are uncommonly afflicted with RMS, which comprise 2% of all adult soft-tissue sarcomas (STS) (2). Significant improvement in prognosis has been achieved for pediatric and adolescent patients with RMS, with long-term survival of 70–80%, after multidisciplinary treatments (3,4). However, the outcome of adult RMS patients remains unsatisfactory, with a 5-year overall survival (OS) rate between 20% and 40% (2,5-10).

Approximately 40% of RMS cases originate in the head and neck region (3). Like in other types of soft-tissue sarcoma, radiation therapy (RT) is often considered as the local treatment of choice due to the high morbidity associated with extensive surgery (11,12). Despite the prevailing use of intensity-modulated RT (IMRT), adverse effects induced by radiotherapy remain to be a significant concern for oncologists, especially for lesions in the orbital and parameningeal regions (13). Furthermore, higher RT doses are needed for adult RMS due to their biological behavior and may further diminish the therapeutic ratio.

Because of Bragg peak particle (e.g., proton or carbon ion beam) beam radiation therapy (PBRT), the treatment exhibits high precision. PBRT deposits a relatively low dose when beams travel in a uniform medium but distributes most of the dose at once before it stops at the Bragg peak. Such a feature makes it possible to deliver high doses to the tumor while limiting the dose to the adjacent normal tissues and organs (14). As a result, only mild toxicities of PBRT including grade 1 to 2 reactions were observed in this study. On the other hand, in addition to its physical property the carbon-ion beam features more significant linear energy transfer (LET) and higher relative biological effectiveness (RBE) than the proton beam. It may show a greater probability in improving the control of malignancies, which are relatively resistant to conventional RT (15,16). Based on these advantages, carbon-ion radiation therapy (CIRT) may substantially improve the therapeutic ratio for head and RMS. Nevertheless, there is a paucity of knowledge of the management of head and neck RMS (HNRMS) in adult populations using CIRT. So in this study we focusing on adult RMS using carbon ion technology, specific in head and neck region, giving more instructive and more valuable suggested radiotherapy pattern, as well as aiming to bolster the current literature with clinical results in terms of disease control, patients' survival, as well as treatment-associated adverse effects of a group of adult patients diagnosed with HNRMS prospectively treated with intensity-modulated CIRT at the Shanghai Proton and Heavy Ion Center (SPHIC) over the past five years. We present the following article in accordance with the STROBE reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-20-8238/rc).

Methods

Patients and pretreatment workups

The treatment protocol of PBRT for H&N sarcoma, including RMS, was registered with and approved by the institutional review board (IRB) of the Shanghai Proton and Heavy Ion Center (approval No. 171031EXP-03). All patients or their parents/guardian supplied consent before the inclusion of the protocol and our institutional database of H&N sarcoma. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

We analyzed data from all patients presented to the Department of Head and Neck/Central Nervous System Oncology of the SPHIC between May 2015 and December 2019. All patients diagnosed at age 15 or older were included in this analysis. At SPHIC, all patients with head and neck sarcoma, including RMS, were evaluated based on our institutional sarcoma treatment protocol and underwent a complete history and physical examination, full blood counts with differential, serum electrolyte profile, hepatic/renal functional tests, urine analysis, and EKG. Confirmation of pathologic diagnosis was required for all patients and performed at the Fudan University Shanghai Cancer Center using the paraffin bedded specimen provided by the patients. MRI of the head and neck was mandatory for all patients, and CT was used only if MRI was clinically contraindicated. FDG-PET/CT scan (chest CT, ultrasound of the abdomen, and whole-body bone scan were used if PET/CT were unavailable) to rule out distant metastasis (DM). The extent of the primary and neck lesion(s) was determined by imaging studies and surgical reports (if applicable). Patients were staged using the International Rhabdomyosarcoma Study Group (IRSG) staging system and IRS-modified TNM stage (17).

However, due to the limitation of the pathology studies, i.e., lack of the PAX/FOX01 fusion gene status in some patients, Children's Oncology Group (COG) risk grouping, an important prognostic indicator, was not performed in this study. The indications of PBRT for all patients were evaluated and approved at the multidisciplinary tumor clinic

Table 1 Characteristics of the 15 patients and their disease

Patient No.	Age	Gender	Pathology	Tumor site	RT status	T classification	N classification	IRSG clinical group	IRSG modified stage	Tumor volume/ GTV* (mm^3)
1	19	Female	Alveolar	Oral cavity	Naive	2	0	3	1	0.0**
2	24	Female	Alveolar	Parameningeal***	Naive	4	1	3	3	46.05
3	30	Female	Alveolar	Parameningeal	Naive	4	0	3	3	47.15
4	14	Female	NOS	Major salivary gland	Naive	4	0	3	3	133.25
5	30	Female	Embryonal	Parameningeal	Naive	4	1	3	3	22.18
6	27	Male	Sclerosing	Major salivary gland	Naive	2	0	2	3	24.15
7	23	Male	Alveolar	Parameningeal	Naive	1	0	3	2	137.61
8	26	Female	Alveolar	Parameningeal	Naive	4	0	3	3	83.50
9	19	Female	Embryonal	Parapharyngeal	Naive	4	0	3	3	55.28
10	32	Male	Sclerosing	Oral cavity	Re-irradiation	4	0	3	Recurrent 1	67.48
11	28	Female	Alveolar	Parameningeal	Re-irradiation	4	0	3	Recurrent 2	49.24
12	17	Female	Embryonal	Parameningeal	Naive	4	0	3	3	58.18
13	30	Female	Embryonal	Parapharyngeal	Naive	4	0	3	3	50.71
14	14	Male	Embryonal	Orbital	Naive	2	0	2	1	2.36
15	17	Female	Alveolar	Parameningeal	Naive	4	1	3	3	54.70

*, GTV after surgery or induction chemotherapy; **, achieved complete response after chemotherapy; ***, parameningeal sites: areas next to the membranes covering the brain, such as the nasal passages and nearby sinuses, middle ear, and the uppermost part of the throat. RT, radiation therapy; IRSG, International Rhabdomyosarcoma Study Group; GTV, gross tumor volume; NOS, not otherwise specified.

(MDT) before registration, planning, and inclusion of the institutional registry.

Follow-up

All patients were followed up according to our institutional protocol after the completion of PBRT. The first follow-up was scheduled at four weeks post-treatment. Patients were then examined every 3–4 months during the first two years, every six months until the fifth year, then annually.

The Common Terminology Criteria for Adverse Events (CTC.AE) (version 4.03) was used to grade both acute and late adverse effects. Acute adverse effects include toxicities that occurred from the start to 3 months after the completion of PBRT. Late effects were those observed at any time after three months post PBRT.

Statistics

Time to locoregional or distant failure, death, and progression (including any locoregional/distant failure and/or death) were estimated from the start date of PBRT until the documented event. The time of OS was estimated from the date of diagnosis for the current disease. Survival data was analyzed using the Kaplan-Meier method. Statistical calculation was performed with SPSS (version 19.0).

Results

Cohort and treatment characteristics

Between 6/2015 and 12/2019, 15 consecutive and non-selected patients with histologically confirmed RMS of the head and neck region received PBRT with PBS technology at the SPHIC. The age of patients was 14 or above. Two patients presented with neck adenopathy. None of the patients had DM at presentation. Two patients failed an earlier course of photon-based radiotherapy and received salvage carbon-ion beam re-irradiation. The characteristics of the patients, their conditions, and treatment techniques are detailed in *Tables 1*,*2*.

Table 2 Treatment details of the 15 patients with rhabdomyosarcoma and their outcomes

Patient No.	Surgery	Neoadjuvant chemo	Cycle	Response	PRT dose (GyE)	PRT Fx	CIRT dose (GyE)	CIRT Fx	Local-regional failure (month)	Distant failure (month)	Death (month)	Status	Follow-up (month)
1	R2	Yes	10	CR	0	0	60.0	20	–	–	–	NED	23.00
2	R2	Yes	6	PR	56	28	15.0	5	16.27	–	–	AWD	41.53
3	Biopsy	Yes	7	PR	56	28	17.5	5	–	–	–	NED	8.00
4	Biopsy	Yes	9	PR	56	28	15.0	5	9.27	–	–	AWD	15.67
5	Biopsy	Yes	5	PR	56	28	15.0	5	–	9.23	30.40	DOM	30.40
6	R1	No	0	NA	0	0	70.0	20	–	–	–	NED	34.80
7	R2	Yes	4	PR	0	0	63.0	18	–	–	20.93	DOO	20.93
8	R2	Yes	6	PR	56	28	15.0	5	–	6.43	–	AWD	7.47
9	R2	Yes	4	SD	0	0	63.0	18	–	16.23	–	AWD	29.23
10	R2	Yes	4	PD	0	0	63.0	21	30.79	9.07	–	AWD	39.17
11	R2	Yes	5	SD	0	0	54.0	18	–	3.27	–	AWD	18.90
12	Biopsy	Yes	4	PR	56	28	17.5	5	16.63	16.63	–	AWD	16.90
13	Biopsy	Yes	8	PR	0	0	70.0	20	–	–	–	NED	11.33
14	R1	Yes	6	PR	0	0	63.0	18	16.70	–	–	AWD	17.84
15	R2	Yes	6	CR	0	0	63.0	21	–	–	–	NED	34.63

PRT, proton radiation therapy; CIRT, carbon-ion radiation therapy; R1, incomplete resection; R2, residual resection; CR, complete remission; PR, partial response; NA, not applicable; SD, stable disease; PD, progressive disease; NED, no evidence of disease; AWD; alive with disease; DOO, die of other reason; DOM, die of distant metastasis.

Surgery and chemotherapy

All 15 patients underwent surgery, but only two achieved R1 resection. The remaining 13 patients received biopsy or R2 resection.

Fourteen patients received chemotherapy before PBRT. The regimen(s) used were at the discretion of their referring medical oncologists. Among the patients with neoadjuvant chemotherapy, one RT-Naive case with alveolar RMS of parameninges achieved a complete response, nine achieved a partial response, one had stable disease, and another developed progression. No patients of this cohort received concurrent chemotherapy during PBRT (*Table 2*).

Particle beam radiation therapy

Techniques of PBRT were detailed previously (18,19). Briefly, after the immobilization of patients using low-temperature thermoplastic masks, computed tomography (CT) image slices at 1.5 mm thickness were acquired for PBRT planning. The fusion of the planning CT with MRI taken in a treatment position with an immobilization mask was required for all patients before the delineation of gross tumor volume (GTV) and clinical target volume (CTV).

The GTV was defined based on physical examination and imaging studies. Surgical beds of patients who underwent resection were also included in GTV. The CTV was defined as the GTV plus a margin of 1–2 cm and an area of risk for subclinical diseases. The planning target volume (PTV) was defined as CTV plus a margin of 3.5% of the beam range +2 mm for setup error and range uncertainty. Elective nodal irradiations (ENI) were provided to patients with regional lymph node metastasis and patients with an elevated risk of lymphatic metastasis. Weekly verification CT scans were typically performed after the second week of PBRT to assess any changes in anatomy during treatment.

Nine patients received CIRT alone, and six received PRT plus carbon ion boost. For the 13 RT-Naive patients, the total dose to the GTV ranged from 60–73.5 (median =70) Gy (RBE) at conventional fractionations [3/3.5 Gy (RBE) of carbon ion per daily fraction, 2 Gy (RBE) of proton per daily fraction]. For the two re-irradiated patients, a dose recovery of 70% from the earlier courses were applied for

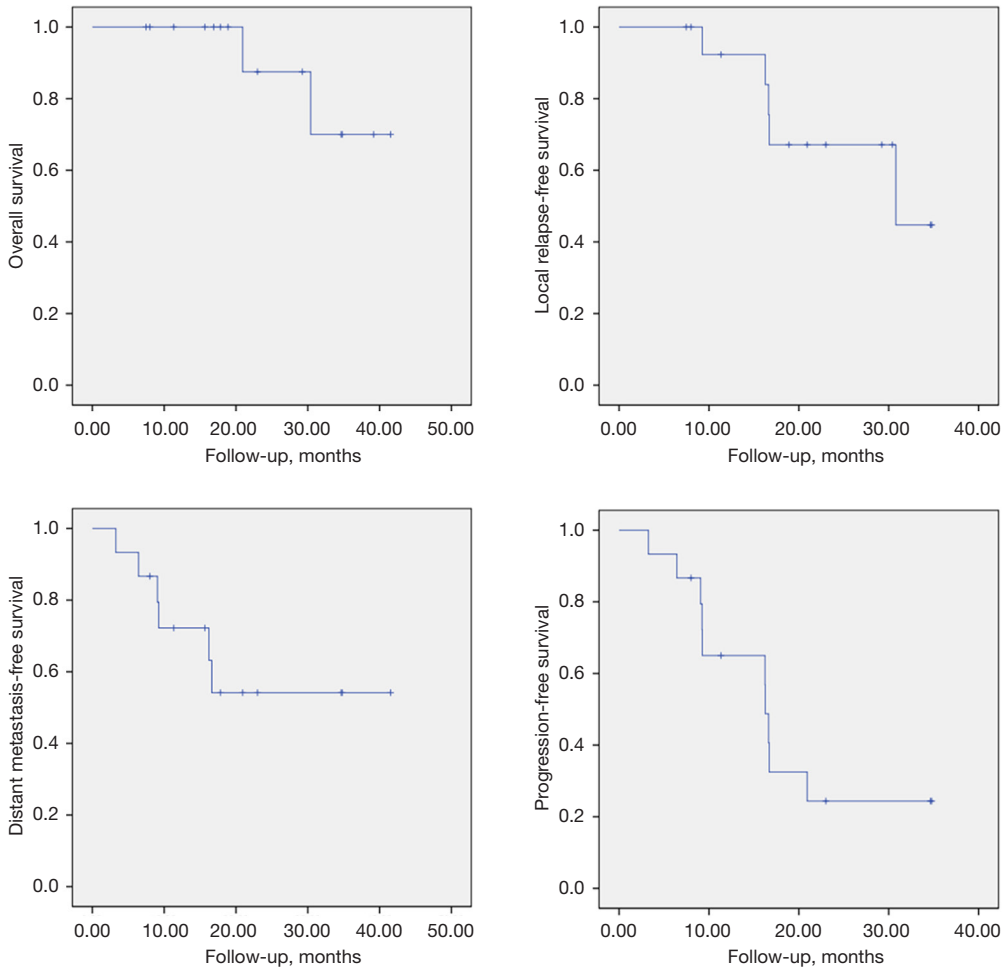

Figure 1 Overall survival, local relapse-free survival, distant metastasis-free survival, and progression-free survival curves for all patients.

calculating OAR dose constraints. Salvage CIRT of 54 Gy (RBE)/18 fractions and 63 Gy (RBE)/21 fractions were provided (*Table 2*).

The radiation targets of GTV ranged from 0–137.61 (median =50.71) cm^3 and were delineated according to residual tumor size, surgical status, and chemotherapy response.

Disease control and survival

With a median Follow-up of 21 (range, 7.5–41.5) months, five patients experienced local progression, and six patients developed distant metastases. Two patients had succumbed to DM (one case) or unrelated reasons (one case) (*Table 2*). The 12- and 24-month OS, local relapse-free survival (LRFS), and DMFS rates were 87.5% and 70.0%, 92.3% and 67.1%, and 72.2% and 54.2% for the entire cohort, respectively (*Figure 1*).

Toxicity

No acute adverse effects of grade ≥3 adverse effects were observed. Six (40%) and five (33%) patients experienced grade 1 or 2 mucositis, and six (40%) and two (13%) patients experienced grade 1 or 2 radiation dermatitis, respectively (*Table 3*). No late toxicity of ≥ grade 2 was observed. Grade 1 xerostomia, parageusia, and facial edema persisted beyond or occurred three months after the completion of PBRT were observed in one case.

Discussion

Here we report the first series of adult HNRMS patients treated with PBRT, CIRT as part of multimodality therapy.

Table 3 Type and frequency of acute toxicities

Toxicity	Grade									
	1		2		3		4		5	
	No.	%	No.	%	No.	%	No.	%	No.	%
Mucous membrane	6	40	5	33	0	0	0	0	0	0
Skin	6	40	2	13	0	0	0	0	0	0

With a median follow-up of close to two years, the disease-associated outcomes in terms of local control (LC) (92.3% at 1 year and 67.1% at 2 years) and OS (87.5% at 1 year and 70.0% at 2 years) appear to be more favorable when compared to other modern series using definitive radiotherapy. Prior reports based on photon-based IMRT generally described LC and OS rates between 36–65% (5-year) and 18–44% (5-year) in similar cohorts of patients (2,6). PBRT also supplied its local efficacy without inducing severe adverse effects. No patients in our series suffered from radiation-induced acute toxicity of ≥ grade 3. And only grade 1 late toxicity was observed. Unfortunately, 2 patients died during the follow-up: Case 5 developed axillary lymph node and breast metastasis after receiving proton and heavy ion radiotherapy, and died of uncontrolled metastasis after cycles of chemotherapy; Case 7 returned to our hospital for follow-up examination 18 months after proton and heavy ion radiotherapy, the images showed no sign of tumor recurrence or metastasis at that moment, but the family later reported the patient died of newly diagnosed neurological disease. Thus, DM is the only disease-related cause of death in our cohort.

HNRMS accounts for 1/3 of all RMS cases, but its occurrence is exceedingly rare in adult patients. It is a uniquely challenging condition to oncologists given the necessary anatomy background and is typically grouped into three categories, including parameningeal (~44%), orbital (~28%), and other H&N areas (~28%), based on anatomical and prognostic considerations. For pediatric cases, the general use of multimodal therapy has significantly reduced the propensity of distant failure. However, local recurrence is the main form of treatment failure in HNRMS, the OS rates after a multidisciplinary treatment approach 80% at 5 years (20-23). However, the prognosis of adult RMS patients, regardless of the origin of their disease, is substantially worse than its pediatric counterpart. DM is the primary mode of treatment failure in adult patients, where the reported long-term OS rates of patients with DM are usually <5% (2,5,24).

The poor prognosis of adult RMS is associated with, at least in part, the more unfavorable pathology subtypes when compared to the pediatric counterpart (25). Historically, three more common histology subtypes have been reported in adult RMS. In addition to the favorable embryonal histology, which is more common in children, the alveolar subtype is far more common in adolescents and adults and carries a worse prognosis, which often arises in the extremities (26,27). The so-called pleomorphic subtype, rare in children and mainly arise in deep soft tissues of adult patients, should be a pleomorphic sarcoma with myogenic RMS differentiation. This specific entity is more similar to the non-RMS soft-tissue sarcomas of adults than other RMS (28). Based on the updated classification, no patients in the current cohort were classified with the historical pleomorphic subtype. 50% of the cohort were of alveolar subtype and the remaining were embryonal.

Adult RMS is more sensitive to radiation therapy than other subtypes of adult soft-tissue sarcomas but more radio-resistant than pediatric RMS, where doses around 50 Gy result in insufficient LC. However, due to the rarity of the disease, only a few studies have reported the treatment outcome of conformal RT for HNRMS in children (20-23), and each study was limited in its sample size. There have been no studies that have been published on radiotherapy, including PBRT for adult HNRMS. The optimal dose and field arrangements of radiotherapy for adult RMS have not been standardized. Higher doses of RT may improve disease control, especially for patients with gross residual disease (29).

Nevertheless, RT doses are usually limited by the critical OARs next to the tumor for patients with head and neck malignancies. As such, definitive RT for adults with HNRMS, especially the parameningeal subtype, is particularly challenging. The unique physical property of particle beams enables precise localization of RT doses to the tumor targets while spearing the critical OARs from high collateral doses. We have reported the effectiveness of CIRT, alone or following proton therapy, for both newly diagnosed and recurrent bone and soft-tissue sarcomas of head and neck previously (18,19). Our results echoed those from Japan (30,31). Data from both countries revealed favorable local disease control with limited severe toxicities. However, the literature on the use of PBRT for adult HNRMS is lacking. Before our series, only one study reported the patterns of failure following proton therapy for 46 children with HNRMS (32).

RMS is one of the few STS with a known propensity for lymph node spread, especially for the alveolar subtype (33). Lymph node metastasis is relatively uncommon in pediatric HNRMS; however, the reported frequencies range between 30~45% overall in adult RMS patients (5,6). Only 3 of our 15 patients presented with neck lymphadenopathy. This frequency is somewhat similar to the occurrence of regional nodal metastasis of pediatric RMS patients (3,34-36). Although nodal status at presentation is an essential prognosticator in pediatric RMS (34-36), it is not significant in adults (5,6).

Furthermore, ENI has not been shown to improve adults (6). In our series, the use of ENI was not universal and was determined by the origin and extent of the disease. None of our patients have experienced neck failure so far. Nevertheless, it is essential to note that standard recommendation of ENI for adult HNRMS patients is lacking, and many centers recommend ENI to a dose of ~50 Gy for all patients with RMS of unfavorable (e.g., alveolar) pathology.

The most common pattern of failure after definitive therapy in adults with RMS is DM, especially to the lungs (2,5,6). In our series, six patients had a distant failure, either alone (n=4) or with local recurrence (n=2). However, the target organs of DM included distant lymph nodes, breast, brain, muscle (of the arm), and bone. Only one patient had synchronous pulmonary and pericardial metastases. The underlying reason for such a diverse pattern of DM in our cohort is unknown. Also, due to the limited number of patients, we were not able to associate the volume of the tumor or other disease characteristics with the probability of DM.

Despite the prospective nature of our treatment protocol and data collection process, the major limitations of our study include the small number of patients and events as well as a relatively short follow-up time. The fact that only one patient died of DM when six also had DM was also due to the relatively short follow-up time. These limitations prevent the use of uni- and multivariate analysis that could address the relative importance of numerous factors associated with prognoses. With the accumulation of more cases into our database, further follow-up and analysis will provide further insights into the use of PBRT for this rare condition. Nevertheless, this is the first study on PBRT, CIRT, for adult HNRMS. The fact that only three patients developed local failure alone and no patient experienced severe acute, or late toxicity suggests the feasibility, efficacy, and safety of CIRT for this malignancy.

Conclusions

Adult HNRMS is a highly malignant disease with a poor prognosis. Our study reveals that high-dose PBRT yields favorable results in terms of local disease control and treatment-associated toxicity compared to historical data based on photon radiotherapy. None of the patients suffered from local failure and severe acute or late adverse effects in our study. This cohort supplies the first modern experience supporting the favorable role of PBRT in the management of adult HNRMS. Nevertheless, distant recurrence is the single major cause of treatment failure, and thus the development of an effective systemic treatment strategy is urgently needed.

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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-20-8238/rc

Data Sharing Statement: Available at https://atm.amegroups.com/article/view/10.21037/atm-20-8238/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-20-8238/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). The treatment protocol of PBRT for H&N sarcoma, including RMS, was approved by the institutional review board (IRB) of the Shanghai Proton and Heavy Ion Center (approval No. 171031EXP-03). All patients or their parents/guardian supplied consent before

the inclusion of the protocol and our institutional database of H&N sarcoma.

References

1. Ognjanovic S, Linabery AM, Charbonneau B, et al. Trends in childhood rhabdomyosarcoma incidence and survival in the United States, 1975-2005. Cancer 2009;115:4218-26.
2. Hawkins WG, Hoos A, Antonescu CR, et al. Clinicopathologic analysis of patients with adult rhabdomyosarcoma. Cancer 2001;91:794-803.
3. Crist WM, Anderson JR, Meza JL, et al. Intergroup rhabdomyosarcoma study-IV: results for patients with nonmetastatic disease. J Clin Oncol 2001;19:3091-102.
4. Crist W, Gehan EA, Ragab AH, et al. The Third Intergroup Rhabdomyosarcoma Study. J Clin Oncol 1995;13:610-30.
5. Esnaola NF, Rubin BP, Baldini EH, et al. Response to chemotherapy and predictors of survival in adult rhabdomyosarcoma. Ann Surg 2001;234:215-23.
6. Little DJ, Ballo MT, Zagars GK, et al. Adult rhabdomyosarcoma: outcome following multimodality treatment. Cancer 2002;95:377-88.
7. Van Gaal JC, Van Der Graaf WT, Rikhof B, et al. The impact of age on outcome of embryonal and alveolar rhabdomyosarcoma patients. A multicenter study. Anticancer Res 2012;32:4485-97.
8. Dumont SN, Araujo DM, Munsell MF, et al. Management and outcome of 239 adolescent and adult rhabdomyosarcoma patients. Cancer Med 2013;2:553-63.
9. Gerber NK, Wexler LH, Singer S, et al. Adult rhabdomyosarcoma survival improved with treatment on multimodality protocols. Int J Radiat Oncol Biol Phys 2013;86:58-63.
10. Fischer TD, Gaitonde SG, Bandera BC, et al. Pediatric-protocol of multimodal therapy is associated with improved survival in AYAs and adults with rhabdomyosarcoma. Surgery 2018;163:324-9.
11. Greto D, Livi L, Saieva C, et al. Neoadjuvant treatment of soft tissue sarcoma. Radiol Med 2014;119:195-200.
12. Nussbaum DP, Rushing CN, Lane WO, et al. Preoperative or postoperative radiotherapy versus surgery alone for retroperitoneal sarcoma: a case-control, propensity score-matched analysis of a nationwide clinical oncology database. Lancet Oncol 2016;17:966-75.
13. Lockney NA, Friedman DN, Wexler LH, et al. Late Toxicities of Intensity-Modulated Radiation Therapy for Head and Neck Rhabdomyosarcoma. Pediatr Blood Cancer 2016;63:1608-14.
14. Kempe J, Gudowska I, Brahme A. Depth absorbed dose and LET distributions of therapeutic 1H, 4He, 7Li, and 12C beams. Med Phys 2007;34:183-92.
15. Kagawa K, Murakami M, Hishikawa Y, et al. Preclinical biological assessment of proton and carbon ion beams at Hyogo Ion Beam Medical Center. Int J Radiat Oncol Biol Phys 2002;54:928-38.
16. Romano F, Cirrone GA, Cuttone G, et al. A Monte Carlo study for the calculation of the average linear energy transfer (LET) distributions for a clinical proton beam line and a radiobiological carbon ion beam line. Phys Med Biol 2014;59:2863-82.
17. Early detection, diagnosis, and staging. Available online: https://www.cancer.org/cancer/rhabdomyosarcoma/detection-diagnosis-staging/staging.html
18. Yang J, Gao J, Qiu X, et al. Intensity-Modulated Proton and Carbon-Ion Radiation Therapy in the Management of Head and Neck Sarcomas. Cancer Med 2019;8:4574-86.
19. Yang J, Gao J, Wu X, et al. Salvage Carbon Ion Radiation Therapy for Locally Recurrent or Radiation-Induced Second Primary Sarcoma of the Head and Neck. J Cancer 2018;9:2215-23.
20. Wolden SL, Wexler LH, Kraus DH, et al. Intensity-modulated radiotherapy for head-and-neck rhabdomyosarcoma. Int J Radiat Oncol Biol Phys 2005;61:1432-8.
21. Yang JC, Wexler LH, Meyers PA, et al. Parameningeal rhabdomyosarcoma: outcomes and opportunities. Int J Radiat Oncol Biol Phys 2013;85:e61-6.
22. Curtis AE, Okcu MF, Chintagumpala M, et al. Local control after intensity-modulated radiotherapy for head-and-neck rhabdomyosarcoma. Int J Radiat Oncol Biol Phys 2009;73:173-7.
23. Combs SE, Behnisch W, Kulozik AE, et al. Intensity Modulated Radiotherapy (IMRT) and Fractionated Stereotactic Radiotherapy (FSRT) for children with head-and-neck-rhabdomyosarcoma. BMC Cancer 2007;7:177.

24. Ferrari A, Dileo P, Casanova M, et al. Rhabdomyosarcoma in adults. A retrospective analysis of 171 patients treated at a single institution. Cancer 2003;98:571-80.
25. Egas-Bejar D, Huh WW. Rhabdomyosarcoma in adolescent and young adult patients: current perspectives. Adolesc Health Med Ther 2014;5:115-25.
26. Rosenberg A. Bones, joints, and soft tissue tumors. In: Cotran RS, Kumar V, Collins T. editors. Robbins' pathologic basis of disease, 6th ed. Philadelphia: WB Saunders, 1999:1215-68.
27. Brennan M, Casper E, Harrison L. Soft tissue sarcoma. In: DeVita V. editor. Cancer: principles and practice of oncology, 5th ed. Philadelphia: Lippincott-Raven, 1997:1738-88.
28. Fletcher CDM, Bridge JA, Hogendoorn PCW, et al. WHO classification of tumors of soft tissue and bone. 4th ed. Lyon: IARC Press, 2013.
29. Michalski JM, Meza J, Breneman JC, et al. Influence of radiation therapy parameters on outcome in children treated with radiation therapy for localized parameningeal rhabdomyosarcoma in Intergroup Rhabdomyosarcoma Study Group trials II through IV. Int J Radiat Oncol Biol Phys 2004;59:1027-38.
30. Jingu K, Tsujii H, Mizoe JE, et al. Carbon ion radiation therapy improves the prognosis of unresectable adult bone and soft-tissue sarcoma of the head and neck. Int J Radiat Oncol Biol Phys 2012;82:2125-31.
31. Imai R, Kamada T, Tsuji H, et al. Cervical spine osteosarcoma treated with carbon-ion radiotherapy. Lancet Oncol 2006;7:1034-5.
32. Ludmir EB, Grosshans DR, McAleer MF, et al. Patterns of failure following proton beam therapy for head and neck rhabdomyosarcoma. Radiother Oncol 2019;134:143-50.
33. Mazeron JJ, Suit HD. Lymph nodes as sites of metastases from sarcomas of soft tissue. Cancer 1987;60:1800-8.
34. Lawrence W Jr, Anderson JR, Gehan EA, et al. Pretreatment TNM staging of childhood rhabdomyosarcoma: a report of the Intergroup Rhabdomyosarcoma Study Group. Children's Cancer Study Group. Pediatric Oncology Group. Cancer 1997;80:1165-70.
35. Lawrence W Jr, Hays DM, Heyn R, et al. Lymphatic metastases with childhood rhabdomyosarcoma. A report from the Intergroup Rhabdomyosarcoma Study. Cancer 1987;60:910-5.
36. Mandell L, Ghavimi F, LaQuaglia M, et al. Prognostic significance of regional lymph node involvement in childhood extremity rhabdomyosarcoma. Med Pediatr Oncol 1990;18:466-71.

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