Advances in Radiation Oncology (2024) 9, 101619

advances in radiation oncology

www.advancesradonc.org

Scientific Article

Clinical Outcomes of Carbon Ion Radiation Therapy for Malignant Peripheral Nerve Sheath Tumors

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Received 27 February 2024; accepted 26 July 2024

Purpose: To investigate the outcome and toxicity of patients affected by malignant peripheral nerve sheath tumors (MPNSTs) treated with high-dose carbon ion radiation therapy (CIRT).

Methods and Materials: We retrospectively analyzed the outcome of 23 patients with MPNSTs treated between July 2013 and December 2020. Out of these, 13 patients (56.5%) had incompletely resected tumors, 8 patients (34.7%) experienced recurrence after surgery, and 2 patients (8.7%) had unresectable tumors. Before CIRT treatment, 4 patients underwent a second surgery after the first local recurrence (LR), and 1 patient underwent a third surgery for the second local relapse of the disease. Six (26%) patients received neoadjuvant chemotherapy. The most frequent tumor site was the brachial plexus (n = 9; 39.1%). In 5 patients (21.7%), neurofibromatosis type 1 disorder was found, while 4 patients (17, 4%) had radiation-induced MPNSTs. The median CIRT prescribed total dose was 69.8 Gy (relative biological effectiveness; range, 54-76.8) delivered in a median of 16 fractions (range, 15-22). Eleven patients (47.82%) were treated according to a sequential boost protocol with a median prescribed dose to clinical target volume LR of 45 Gy (relative biological effectiveness; range, 41.4-54).

Results: After a median follow-up time of 23 months (range, 3-100 months), the overall survival rates at 1 and 2 years were 82.38% and 61.51%, respectively. The 1-year and 2-year local relapse-free survival rates were 65.07% and 48.80%, respectively, and the 1-year and 2-year progression-free survival rates were 56.37% and 40.99%, respectively. No patients showed acute or late grade 4 toxicity or any treatment-related deaths. Ten patients (43.48%) reported acute toxicities of grade $\geq$ 2, which included dermatitis in 6 patients, mucositis in 2 patients, and peripheral neuropathy in 4 patients. Eight patients (34.78%) reported late toxicities of grade $\geq$ 2, mainly due to loco-regional neuropathy.

Conclusions: High-dose CIRT shows favorable local effects with acceptable toxicities in patients with gross residual and LR after surgery or unresectable malignant peripheral nerve sheath tumors. Advanced treatment modalities such as particle therapy should be considered for MPNSTs.

Sources of support: This work had no specific funding.

The research data relating to patients are confidential based on hospital-relevant policies and regulations of protecting patients' information security and privacy.

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https://doi.org/10.1016/j.adro.2024.101619

Introduction

Malignant peripheral nerve sheath tumors (MPNSTs) are recognized as aggressive malignancies with a poor prognosis, often resulting in high rates of local recurrence (LR) and distant metastasis. MPNSTs constitute 5% to 10% of all soft tissue sarcomas, primarily arising from peripheral nerve sheath components.[1] Approximately half of MPNSTs are associated with neurofibromatosis type 1 (NF1) and often develop from preexisting plexiform neurofibromas. Spontaneous occurrences unrelated to NF1 account for about 40% of cases, while 10% originate in previously irradiated areas.[2,3] The prognosis is generally unfavorable, characterized by a high recurrence rate despite multimodal therapy.[4,5] Surgery with adequate oncologic margins remains the mainstay therapy for nonmetastatic disease. Nevertheless, complete resection with negative margins is often complicated by the necessity to sacrifice the involved peripheral nerves. The LR rate increases in case of positive margins. Even when aggressive surgery obtains negative margins, the outcomes are not satisfactory. After complete microscopic resection, the LR rate stands at 20% to 38%. The risk increases in cases with negative prognostic factors such as larger tumor size, positive surgical margins, residual disease, or when the disease is localized in the head and neck region.[6,7]

Radiation therapy (RT) is largely recommended in the adjuvant setting and can potentially enhance local disease control. On the other hand, curative RT may be recommended for MPNST patients in situations where the tumors are inoperable or when the proposed surgical intervention is extensive, resulting in organ function loss and is thus declined by the patient.[8,9]

Given the limited sensitivity of MPNSTs to radiation, achieving improved local control (LC) after RT requires the use of high radiation doses.[10,11] In conventional photon beam RT, delivering such high doses would result in a significant risk of morbidity due to the challenge of effectively sparing adjacent healthy tissues within the irradiated area. On the other hand, carbon ion RT (CIRT) offers different physical and biological characteristics compared with conventional RT. Physical characteristics include a low dose delivered into the particle beam input channel, followed by a deposition dose, with a sharp fall of dose immediately after the target. Furthermore, carbon ions offer significant radiobiological advantages by causing damage to nucleic acids that are subsequently difficult to repair with cellular repair mechanisms. This results in a higher relative biological effectiveness (RBE), which can lead to improved clinical results.[12,13] Moreover, CIRT has proved to be effective on hypoxic tumors, considering that the oxygen enhancement ratio decreases with increasing particle linear energy transfer.[14]

Due to the rare incidence of the disease, there are only a few series in the literature reporting on MPNST outcomes with particle therapy.[15-17] The present study aimed to report the results in terms of efficacy and safety in patients affected by MPNSTs treated with CIRT in pre- and postoperative settings and unresectable tumors.

Methods and Materials

Patient population

This was a retrospective mono-institutional study that included consecutive MPNST patients treated with CIRT between July 2013 and December 2020. The inclusion criteria were as follows: (1) age > 18 years; (2) histologic diagnosis of MPNST; (3) previous RT in the same localizations was allowed; (4) nonradical tumor resection, postsurgical local relapse, unresectable disease, or patient's refusal of surgery; and (5) minimum follow-up of 3 months.

All enrolled patients gave their written informed consent for treatment and the use of their anonymized data for research and educational purposes. The present study obtained approval from our Institute Referral Ethical Committee (CNAO-OSS-51-2022). All patients were collected in a retrospective/prospective institutional clinical registry study (NCT05203250).

The coprimary endpoints of this study were overall survival (OS), local relapse-free survival (LRFS) in accordance with the Response Evaluation Criteria in Solid Tumors 1.1,[18] and progression-free survival (PFS). The secondary endpoint was represented by acute and late toxicity scored according to the Common Terminology Criteria for Adverse Events (CTCAE) v5 grading system[19] during the treatment and follow-up period. In particular, we evaluated the risk of achieving high-grade toxicity (defined as grade ≥ 2 according to CTCAE v5) both in the acute and late phases. We considered acute toxicity within the first 6 months following the end of treatment, whereas late toxicity was assessed after the 6-month follow-up period posttreatment.

CIRT procedures

During the simulation phase, the patients were positioned in a supine or prone position, depending on the site of disease, and immobilized with a personalized thermoplastic mask to optimize setup reproducibility and minimize inter- and intrafraction uncertainties. Computed tomography (CT) scans for treatment plan optimization without contrast agent were acquired with 2 mm slice thickness in the treatment position. After the acquisition of CT scans, all patients were imaged with a 3 Tesla

magnetic resonance imaging (MRI, Siemens Healthineers) with contrast medium in the same CT scan setup conditions. Subsequently, CT and MRI images were rigidly registered for target definition. We defined the following on CT and MRI images: (1) the gross tumor volume (GTV) that included all visible gross disease in MRI, and (2) the clinical target volume (CTV) that was the GTV expansion of 3 to 10 mm, taking into account the anatomic location and subclinical extension, including typical pathways of spread disease. In case of a double level of doses, we divided the CTV into (1) high-risk CTV (CTV-HR), including the GTV with 3 to 10 mm margins, and (2) low-risk CTV (CTV-LR) that was CTV-HR with 10 to 20 mm margins. Volumes were adjusted to account for anatomy, tumor spread way, surgical pathway, and natural barriers or to spare immediately adjacent radiosensitive organs at risk (OARs). The choice between using a single or 2 dose levels for tumor treatment was based on various factors such as tumor size, its location near critical areas (eg, intracanal involvement), the extent of disease before surgery, the surgical approach, NF1-related conditions, and radiation-induced effects. Given the heterogeneity of the patients, each treatment was personalized after a team discussion. Typically, 1 dose volume was used for large tumors close to critical structures (Fig. 1). Two dose volumes were mainly considered after surgery when the preoperative volume was excessively large, or the surgical procedure was limited by critical organs or carried a risk of dissemination (Fig. 2). No concomitant chemotherapy was administered during CIRT. Up to October 2019, the treatment plans were optimized with the Syngo RT Treatment Planning System (Siemens AG Healthcare). Afterward, the treatment plans were optimized with the RayStation Treatment Planning System (software version 8.1, RaySearch Laboratories), and the RBE of the particle beam was incorporated into the planning software according to the local effect model 1. Intensity modulated particle therapy was employed for optimization. In the treatment room, the patient setup was verified and corrected based on a bone-optimized rigid registration of 2 orthogonal in-room x-ray acquisitions and the related planning of CT digitally reconstructed radiographs. In patients with pelvic disease, a daily cone beam CT scan was performed for organ filling control. Reevaluation CT scans were planned weekly for robust optimization and evaluation strategy. Regular clinical examinations were also performed once a week, or more often when needed, for the assessment and management of acute toxicity.

Follow-up

After the end of treatment, each patient was followed up every 3 months for the first year and every 6 months in the subsequent years with clinical examination in order to assess toxicity, as well as with a regional MRI according to the CIRT target to evaluate tumor response. CT scans of the thorax and abdomen were performed at least every 6 months or more often based on any clinical need or evidence of metastasis.

Statistical analysis

Patients and treatment characteristics were collected, with categorical variables described by counts and percentages, while median and IQR values summarized quantitative variables. The 2-sided type I error was set at 5%. Statistical analyses were carried out using R version 4.0.1 (R Foundation for Statistical Computing).

The coprimary endpoints of this study were OS, LRFS, and PFS.

The median survival time and survival curves were estimated using the Kaplan-Meier product-limit method

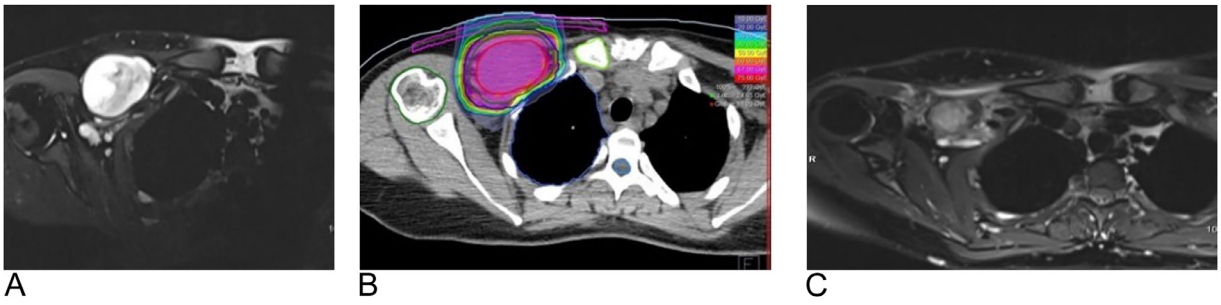

Figure 1 Representative plan with 1 dose level. MPNST treated with postoperative carbon ions RT. A 21-year-old female with low-grade MPNST NF1-associated, and of brachial plexus. The patient underwent postoperative CIRT for recurrence after surgery, with a total dose of 70.4 Gy (RBE) in 16 fractions. (A) Tumor volume pretreatment and (B) CIRT. (C) MRI after 16 months showed a partial response. Follow-up after 8 years still showed partial response in stable disease. The low-grade and complete high-dose coverage were associated with long-term local control.

Abbreviations: CIRT = carbon ion radiation therapy; MNPST = malignant peripheral nerve sheath tumor; MRI = magnetic resonance imaging; NF-1 = neurofibromatosis type 1; RBE = relative biological effectiveness; RT = radiation therapy.

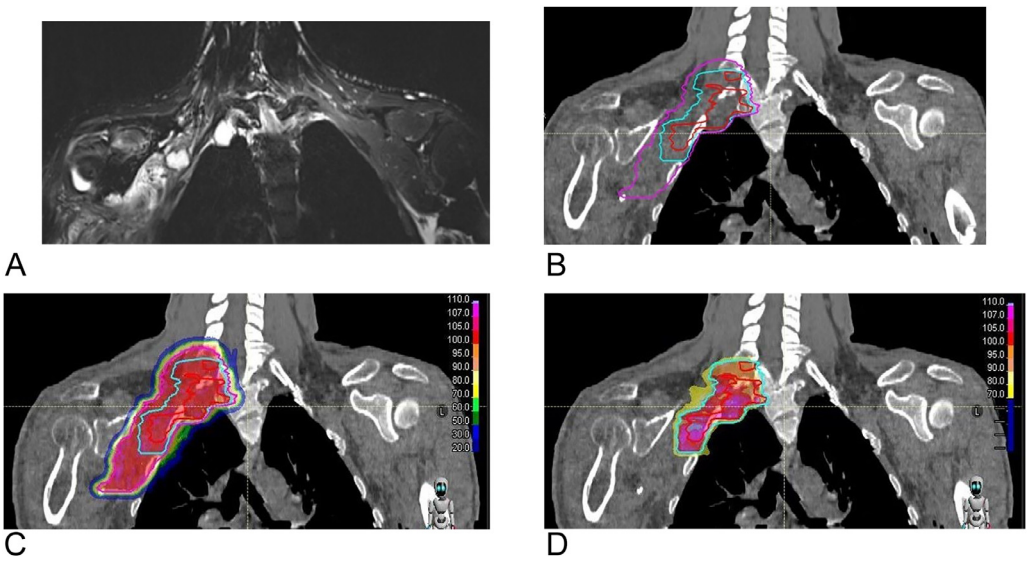

Figure 2 Representative plan with 2 dose levels. MPNST treated with postoperative CIRT. A 34-year-old male with high-grade MPNST, NF1-associated, and of brachial plexus with soft tissue component protruding on the right lung apex and perineural spread along the nerves. The patient underwent postoperative CIRT of 76.8 Gy (RBE) in 16 fractions for macroscopic residual disease, showing a fast increase after surgery. (A) MRI pretreatment showing residual mass. (B) Volume description: GTV is shown as the red line, CTV-HR light blue, and CTV-LR in pink. (C) CTV-LR isodose 100% red color wash. (D) CTV-HR isodose 95% orange color wash. Note that the smaller area of low-dose spillage is 20%.

Abbreviations: CIRT = carbon ion radiation therapy; CTV-HR = clinical target volume-high risk; CTV-LR = clinical target volume-low risk; GTV = gross tumor volume; MPNST = malignant peripheral nerve sheath tumor; MRI = magnetic resonance imaging; NF1 = neurofibromatosis type 1; RBE = relative biological effectiveness.

for the appropriate event. The OS, LRFS, and PFS time were defined as the time from the end of CIRT to death from any cause or last follow-up time; the time from the end of CIRT to tumor regrowth in the CTV or absence of further tumor regrowth after the best response of the treated lesion or time of last follow-up; and the time from the end of CIRT to loco-regional or any distant disease progression or last follow-up time, respectively. A 95% CI was provided. Moreover, the log-rank test was used to explore the impact on the survival outcomes of the following clinical and treatment factors: maximum lesion diameter, age, sex, MPNST histologic grading (MPNST grade 1 and 2 vs MPNST and Triton grade 3), tumor presentation (primary vs recurrent), tumor site (trunk vs brachial plexus vs head and neck), radiation-induced tumor (yes vs no), and NF1 syndrome (yes vs no). Quantitative variables were stratified based on the distribution median value. Due to the reduced sample size, only univariable analysis was performed, while multivariable analysis was not deemed reasonable.

The secondary endpoint was represented by acute and late toxicity scored according to the CTCAE v5 grading system[19] during the treatment and follow-up period. In particular, we evaluated the risk of achieving a high grade (defined as grade $\geq$ 2 according to CTCAE v5) both in the acute and late phases. The proportion of patients with grade $\geq$ 2 acute and late toxicities was presented with a 95% binomial CI.

Results

Patients and treatment characteristics

Twenty-three patients met the inclusion criteria and were included in the analysis. Table 1 summarizes the main patient, disease, and treatment characteristics. Overall, we treated 13 (56.5%) incompletely resected tumors, 8 (34.7%) recurrences after surgery, and 2 (8.7%) unresectable MPNSTs. Before CIRT treatment, 4 patients underwent a second surgery after the first LR and 1 patient underwent a third surgery for the second LR. Six (26%) patients received neoadjuvant chemotherapy. The most frequent tumor site was the brachial plexus (n = 9; 39.1%). In 5 patients (21.7%), NF1 disorder was found, while 4 patients (17, 4%) had radiation-induced MPNSTs. The median CIRT prescribed total dose was 69.8 Gy (RBE; range, 54-76.8) delivered in a median of 16 fractions (range, 15-22). Eleven patients (47.82%) were treated according to a sequential boost protocol with a median prescribed dose to CTV-LR of 45 Gy (RBE; range, 41.4-54).

Clinical outcomes

After a median follow-up time of 23 months (range, 3-100 months), the OS, LRFS, and PFS median time were

Table 1 Patient, disease, and treatment characteristics

Characteristics	N or median (IQR)	% or range
Sex		
Female	10	43.5
Male	13	56.5
Age (y)	51 (31.5)	22-85
Site		
Trunk	6	26.1
Brachial plexus	9	39.1
H&N	8	34.8
Presentation at CIRT		
Primary	15	65.2
Recurrence	8	34.8
Chemotherapy		
Yes	6	26.1
No	17	73.9
Surgery		
0	2	8.7
1	17	73.9
2	4	17.4
Radio-induced tumor		
Yes	4	17.4
No	19	82.6
Syndrome NF1		
Yes	5	21.7
No	18	78.3
Grading		
G1	3	16.7
G2	4	22.2
G3/Triton G3	9/2	50/11.1
Maximum diameter (mm)	55 (33.7)	22-150
Fractions	16 (0)	15-22
Dose/fraction, Gy (RBE)	4.6 (0.4)	3-4.8
Total dose, Gy (RBE)	73.6 (6.4)	54-76.8
Boost		
Yes	11	47.8
No	12	52.2

Abbreviations: CIRT = carbon ion radiation therapy; H&N = head and neck; MPNST = malignant peripheral nerve sheath tumors; NF1 = neurofibromatosis type 1; RBE = relative biological effectiveness.

33.2 months (95% CI, 21.4-NA), 17.03 months (95% CI, 9.87-NA), and 14.40 months (95% CI, 6.03-NA), respectively. The 1-year and 2-year OS were 82.38% (95% CI, 68.09%-99.67%) and 61.51% (95% CI, 43.49%-86.99%), respectively; the 1-year and 2-year LRFS rates were 65.07% (95% CI, 47.05%-89.99%) and 48.80% (95% CI, 30.80%-77.33%), respectively; and the 1-year and 2-year PFS rates were 56.37% (95% CI, 38.41%-82.73%) and 40.99% (95% CI, 24.19%-69.47%), respectively. Lower histologic grade reported significantly better OS ($P = .043$; Fig. 3); similarly, the same impact was reported for lower maximum lesion diameter (≤55 mm; $P = .083$) and recurrent tumor ($P = .1$), while the other evaluated variables ($P > .1$) did not influence the OS based on the univariable analysis. Lower maximum lesion diameter ($P = .036$; Fig. 4) reported a statistically significantly better LRFS rate, as well as the absence of NF1 syndrome ($P = .062$), which seemed to influence LRFS positively, while all the other factors ($P > .1$) did not affect the LRFS. No clinical nor treatment factors reported a statistically significant impact on the PFS, although a lower maximum diameter ($P = .096$) and lower histologic grade ($P = .056$) seemed to have a high chance of achieving a better PFS.

Toxicity

Treatment was well tolerated, and no interruptions were needed. No patients experienced any cases of acute or late grade 4 toxicity or any treatment-related deaths. Ten patients (43.48%; 95% CI, 23.22%-63.74%) reported acute toxicities of grade ≥ 2, which included dermatitis in 6 patients, mucositis in 2 patients, and peripheral neuropathy in 4 patients. Eight patients (34.78%; 95% CI, 15.32%-54.25%) reported late toxicities of grade ≥ 2, mainly due to loco-regional postactinic neuropathy. In particular, we recorded peripheral nerve-related late toxicity, including grade 2 peripheral neuropathy (n = 2), grade 3 peripheral neuropathy (n = 3), optic nerve neuropathy grade 2 (n = 1) and grade 3 (n = 1), and grade 2 vestibulocochlear nerve neuropathy (n = 1).

Discussion

We provided an overview of our 7-year experience of CIRT for incompletely resected, recurrent, or unresectable MPNSTs, focusing on the efficacy and safety profile. To our knowledge, this is the largest long-term cohort of MPNST patients treated with CIRT. CIRT has proved to be advantageous over photon beam RT in several settings of radioresistant tumors, including soft tissue sarcomas.[20-25] The MPNSTs, due to their intrinsic neurotrophism leading to a high recurrence rate (range 20%-38%) after radical surgery,[26,27] appeared to be an ideal disease to test the biological efficacy of CIRT. Despite their rarity, several retrospective series from high-volume sarcoma centers have shown that adjuvant photon RT can effectively control MPNSTs, especially after incomplete tumor resection. Notably, the Mayo Clinic reported improved

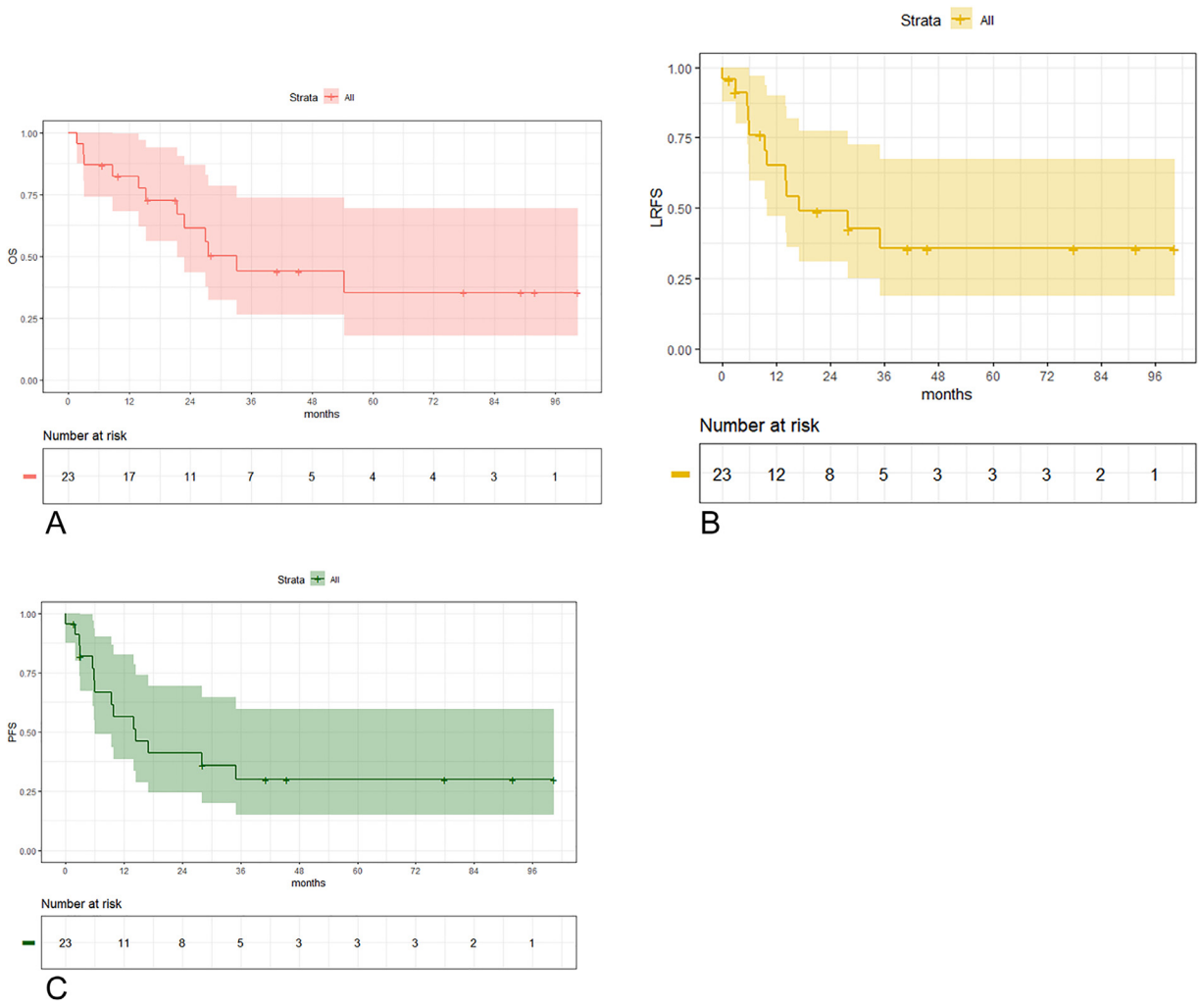

Figure 3 Kaplan-Meier plots of (A) overall survival (OS), (B) local relapse-free survival (LRFS), and (C) progression-free survival (PFS).

5-year LC rates when RT was combined with surgery (65% vs 34%). They also found better results with doses in excess of 50 Gy.[10] In the following update of this study, the authors found that in 175 patients retrospectively reviewed, the LR rate decreased from 42% to 22%. Advancements in RT and surgical techniques probably influenced the improvement of the results over time.[28] The University of Texas MD Anderson Cancer Center study showed a high 5-year LC and OS rate of 84% and 66%, respectively. In this study, the patients not suitable for macroscopic resection were excluded from the analysis. They found that positive surgical margins led to worse LR outcomes (28% vs 5% for negative margins).[29] A large study on 280 patients from Massachusetts General Hospital confirmed that postoperative RT reduced LR for patients with positive margins or partial resections and that combining surgery with RT improved OS compared with surgery alone. It is notable that the best results come from the analysis of patients undergoing curative surgical treatment, while larger tumor size and partial resection are commonly identified as significant predictors for poor LC and OS.[30-32] Our cohort included patients with residual tumors, postsurgical recurrences, or tumors that were inoperable. Taking into account the unfavorable prognostic factors of our patients, we demonstrated a favorable local effect of CIRT with a 1-year and 2-year LRFS of 65.07% (95% CI, 47.05%-89.99%) and 48.80% (95% CI, 30.80%-77.33%), respectively. Interestingly, the LRFS seemed to be related to the lower maximum lesion diameter (P = .036) and the anamnesis of NF1 (P = .062). The current study updated our previous pilot experience on the first 13 patients treated with high doses of CIRT for MPNSTs.[15] Compared with the first analysis, the 2-year LC appeared slightly worse in the current study than the previous one (48.8% vs 63%). There might be several reasons to explain this difference. Firstly, the current series differs in terms of the median delivered dose, which was lower compared with the previous data (69.8 Gy [RBE] vs 73.6 Gy [RBE]). Further factors influencing the results are the extended overall follow-up period in the current work

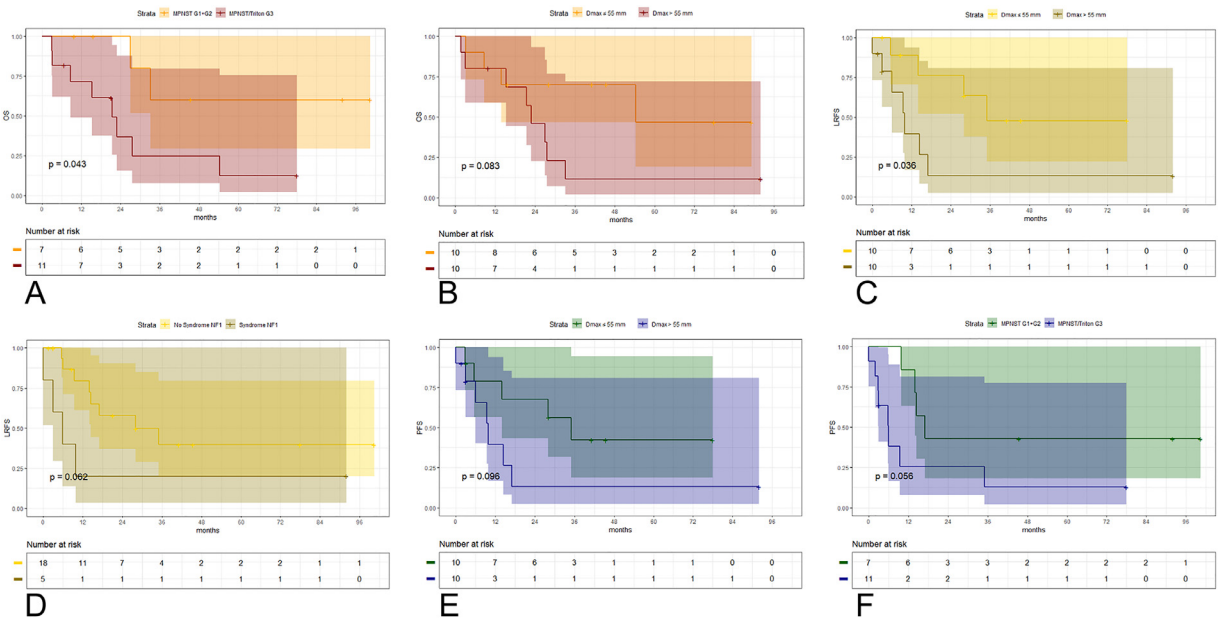

Figure 4 Kaplan-Meier plots with the univariate survival analysis for significant prognostic factors. Overall survival analyses are reported for (A) MPNST G1/G2 versus MPNST G3/triton G3 and (B) Dmax ≤ 55 versus Dmax > 55. Local relapse-free survival analyses are reported for (C) Dmax ≤ 55 versus Dmax > 55 and (D) Syndrome NF1 No versus syndrome NF1 Yes. Progression-free survival analyses are reported for (E) Dmax ≤ 55 versus Dmax > 55 and (F) MPNST G1/G2 versus MPNST G3/Triton G3.
Abbreviations: Dmax = maximum diameter; MPNST = malignant peripheral nerve sheath tumors; NF1 = neurofibromatosis type; OS = overall survival.

as well as the critical anatomic region requiring lower doses close to the high radiosensitive OARs (such as the bowel and spinal cord), which might reasonably justify the different outcomes. However, this encouraging data in terms of LRFS were in line with the international experience where CIRT has proved to be an effective loco-regional option for MPNSTs. In a Japanese study on 128 patients with inoperable soft tissue sarcomas treated with high-dose CIRT, 15 patients had MPNSTs. According to the histology, they reported a 5-year LC rate of 52% for patients with MPNSTs. Despite the better dose distribution of CIRT, which allows for higher irradiation doses to the tumor, 20% of in-field recurrences occurred in MPNST patients. This suggests a potential for increasing the dose in selected tumors, such as MPNSTs, to improve outcomes.[22] Further data on CIRT come from the German approach. Jensen et al[16] treated 11 patients with mixed beam RT, including photon beam intensity modulated RT up to 50 Gy in 25 fractions, and a CIRT boost up to 24 Gy (RBE) over 8 fractions. This fractionation also appeared promising, showing 2-year LC and OS of 65% and 75%, respectively. In the current study, the 2-year OS was slightly worse compared with the mixed beam approach (61.51% vs 75%). It should be stressed that the number of patients included in our cohort was higher, and our follow-up was longer, suggesting that a long-term analysis is crucial for these aggressive tumors.

Consistently with the other settings in which CIRT was tested, the safety profile was high. The toxicity rate after particle beam RT for MPNSTs appeared to be acceptable according to the literature data. Jensen et al[16] found grade ≥ 2 toxicities in 15% of patients treated with CIRT using a mixed beam approach. Bachmann et al[17] treated 36 patients with proton beam RT, finding 11% of late grade ≥ 2 toxicities, with no cases of radiation-induced cancers. In line with these previous experiences, the toxicity rate was mild also in our series with no grade ≥ 4. However, when assessing the risk of toxicity related to RT for the MPNSTs, it is necessary not to underestimate the association with NF1, which is related to a high risk of radiosensitivity and the development of radiation-induced tumors.[33-37] Indeed, also in our cohort, 21.7% of patients had a diagnosis of NF1, and 17.4% were treated for a radiation-induced MPNSTs. The ballistic hallmarks of particle therapy have shown a reduced risk of toxicity even in these difficult scenarios.[38] In our experience, we observed acceptable toxicity in high-risk patients, suggesting that CIRT may be a safe approach in this setting. Notably, among patients with NF1, no patient showed acute toxicity > grade 1, and 1 patient had late grade 3 neuropathy. Among the cases of radiation-induced MPNSTs, grade 2 acute toxicity was recorded in 2 patients, and grade 3 late toxicity was observed in an additional 2 patients, also associated with regional neuropathy. This suggests the safety of CIRT also in patients at high risk of toxicity. Regardless, when planning RT for MPNSTs, the presence of NF1 is an important prognostic factor. Careful consideration is needed to minimize healthy tissue exposure due to secondary cancer and toxicity risks. Complete resection (R0) may not require RT, but it is advised for high-grade tumors over 5 cm or after incomplete resection (R1 or

R2).[39,40] On the other hand, the role of chemotherapy remains uncertain. Commonly, chemotherapy is recommended for unresectable, locally advanced, or metastatic tumors. Despite the various chemotherapeutic regimens that have been adopted over the years, the effectiveness remains low.[30] In recent years, there has been increasing interest in targeted therapies for cases unresponsive to first-line treatments. Currently, some studies have yielded preliminary data on the efficacy of targeted therapies, but future research is still required to understand their potential.[39,41]

This study undeniably has limitations. First, this is a mono-institutional experience involving a small number of cases and a short follow-up period. Indeed, the patients included exhibited heterogeneous characteristics, including tumor sites and previous treatments before CIRT, preventing specific statistical analysis. Second, the retrospective nature of the study is noteworthy, considering that it limits the strength of the statistical analyses conducted. Nevertheless, it is worth noting that all the above-reported literature studies have also relied on retrospective designs. However, despite these evident biases, the present report holds significant value for radiation and medical oncologists as well as surgeons. This is attributed to the treatment technique employed, the rarity of the MPNST diagnosis, and the promising results obtained. Unfortunately, due to the incidence of the disease that accounted for 5% to 10% of all malignant soft tissue tumors and its heterogeneity in terms of localizations, randomized prospective studies are difficult. From this perspective, strong collaboration among rare cancer networks, including highly skilled surgeons and oncologists and radiation oncologist experts in particle beam RT, might take a step forward in the comprehension of this rare disease and its management. In this context, multicentric clinical registries are warranted.

Conclusions

High-dose CIRT shows favorable local effects with acceptable toxicities in patients with gross residual and LR after surgery or unresectable MPNSTs. Due to their radioresistance, the typical onset sites that are in close proximity to OARs, and the high risk of radiation-induced tumors in patients with NF1, advanced RT modalities such as particle therapy should be considered for MPNSTs.

Disclosures

Maria Rosaria Fiore, Agnieszka Chalaszczyk, Amelia Barcellini, Viviana Vitolo, Giulia Fontana, Stefania Russo, Marco Rotondi, Silvia Molinelli, Alfredo Mirandola, Alessia Bazani, and Ester Orlandi declare no conflict of interest.

Acknowledgments

Giulia Fontana performed the statistical analysis.

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