Advances in Radiation Oncology (2024) 9, 101431

advances in radiation oncology

www.advancesradonc.org

Research Letter

Dose-Escalated Preoperative Proton Therapy for Retroperitoneal Sarcomas: Initial Outcomes of a New Treatment Paradigm

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Received 28 April 2023; accepted 14 December 2023

Purpose: Retroperitoneal sarcomas (RPS) have varied treatment practices with regard to the use of radiation therapy (RT). Preoperative RT ~50 Gy is commonly used, but the Surgery With or Without Radiation Therapy in Untreated Nonmetastatic Retroperitoneal Sarcoma (STRASS-1) randomized trial demonstrated no improvement in abdominal recurrence-free survival with preoperative RT. Dose escalation has been proposed to improve the efficacy of preoperative RT. We analyzed RPS treated with preoperative intensity modulated proton therapy (IMPT) to an escalated dose of 63 Gy at a single institution.

Methods and Materials: Patients who received preoperative RT with IMPT with RPS between January 2015 and October 2021 were reviewed. IMPT 63 Gy in 28 fractions to the clinical target volume high-risk and 50.4 Gy in 28 fractions to clinical target volume low-risk was used. Patient baseline characteristics, RT dose parameters, toxicities, margin status, and recurrence patterns were recorded. Local control was computed by Fine-Gray analysis and overall survival by Kaplan-Meier analysis.

Results: Sixteen patients met the study criteria (n = 16): 12 primary and 4 isolated local recurrences. Median age was 62 years (IQR, 43.5-66 years) and 62.5% were male; 10 were liposarcoma. The median maximum tumor diameter was 19.9 cm (IQR, 12-24 cm). With a median follow-up of 18 months (IQR, 11.5-37 months), the estimated 3-year freedom from local failure rate was 68.2% (95% CI, 41.7%-94.7%); 3-year overall survival (OS) rate was 68.8% (95% CI, 41.9%-95.8%). No Radiation Therapy Oncology Group grade ≥3 acute or late toxicities were noted.

Conclusions: In our RPS cohort, preoperative dose-escalated RT to 63 Gy demonstrated comparable local control without G3 acute toxicities. Given the high local recurrence rates of RPS, this approach warrants further study to validate these results and identify patients most likely to benefit from therapy.

Introduction

Retroperitoneal sarcomas (RPS) are rare tumors, accounting for <1% of cancer cases in 2022.[1] Lesions typically present as large masses, with nearly 50% larger than

Sources of support: This work had no specific funding.

Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

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https://doi.org/10.1016/j.adro.2023.101431

20 cm at diagnosis.[2] As with extremity sarcomas, curative treatment requires en bloc surgical resection with the goal of obtaining appropriate negative margins. For retroperitoneal liposarcomas, ipsilateral retroperitoneal fat resection is also performed.[3] Multidisciplinary care at tertiary centers is associated with improved outcomes,[4] but even with appropriate surgery, reports show that roughly 40% to 75% of patients with RPS recur locally.[2,5]

The optimal management of retroperitoneal sarcomas remains controversial, specifically regarding the use of perioperative radiation therapy (RT). Retrospective analyses support its use to reduce the risk of local recurrence,[6] although in practice there has been considerable variability in RT timing, delivery, and dosage.[3] Previous prospective studies (ACOSOG-Z9031) closed early due to poor patient accrual. However, the Surgery With or Without Radiation Therapy in Untreated Nonmetastatic Retroperitoneal Sarcoma (STRASS-1) trial, which compared preoperative RT (50.4 Gy in 28 fractions) followed by surgery to surgery alone, reported no statistically significant difference in abdominal recurrence-free survival between treatment arms.[5]

With unclear benefits reported for standard preoperative RT for RPS, dose-escalated preoperative RT has been explored. A phase 1 trial from Harvard used preoperative proton therapy to boost the tumor region judged to have the highest risk of close or positive margins to 63 Gy in 28 fractions (radiobiologically equivalent to 66 Gy, the dose given in extremity sarcoma cases with positive margins) while simultaneously treating the standard target region to 50.4 Gy in 28 fractions.[7] Dose escalation to the high-risk region may reduce local recurrences without worsening treatment morbidity, and our center adopted this treatment paradigm for RPS starting in August 2019. The present study reports our real-world outcomes with dose-escalated preoperative proton therapy 63 Gy in 28 fractions for RPS.

Methods and Materials

Data acquisition

After institutional review board approval, we conducted a retrospective review of consecutive cases diagnosed with RPS between January 2015 and October 2021 at a single tertiary care institution. Of the 40 RPS patients, 17 received preoperative intensity modulated proton therapy (IMPT) as part of curative intent treatment. One patient had acute kidney injury after 3 fractions and was excluded due to transitioning to palliative intent treatment. For the 16 patients who completed neoadjuvant therapy, treatment details, and outcomes were analyzed. Patient characteristics including age, sex, performance status, prior surgical and radiation history, and tumor-related characteristics including size, histology, location, grade, stage, involvement of adjacent viscera, and hydronephrosis were recorded. Treatment parameters, such as target and organs at risk dose, and patient outcomes, including Radiation Therapy Oncology Group (RTOG) acute and late toxicities,[8] microscopic margin status, and percentage necrosis, as well as recurrence and survival results, were collected.

Radiation technique

The preoperative intensity modulated proton therapy plans delivered 63 Gy in 28 fractions to the high-risk clinical target volume (CTV high-risk) jointly determined by the radiation oncologist and surgical oncologist and treated 50.4 Gy in 28 fractions to the standard risk CTV (CTV low-risk).[7] Gross tumor volume consisted of the visible tumor on computed tomography or magnetic resonance images. CTV delineation followed a previous report.[9] A representative case is shown in Figure 1. Treatment plans created with RayStation (RaySearch Laboratories) using robust Monte Carlo CTV-based optimization commonly used 2 posterior obliqued fields. In addition to standard abdominal organs at risk constraints, the ureter 0.03 cc dose was maintained at <57.5 Gy.

Patient follow-up

After RT completion, en bloc resection was performed with contiguous structure removal with the goal to attain microscopic negative margins. Pathology reported histologic subtype, tumor size, percentage necrosis, and margin status. Patients were followed to evaluate for local and distant recurrences and overall survival.

Statistical analysis

Local failure was defined as reappearance (post R0/R1 resection) or increase in size (post R2 resection) at the primary site. Time to surgery was computed from the date of RT completion to the date of surgery. Time to local failure was computed from the date of radiation initiation to the date of local failure. Overall survival (OS) was computed from the date of radiation initiation to the date of death or last follow-up. Local failure was estimated using the Fine-Gray method, with death as a competing risk factor. OS was assessed using Kaplan-Meier survival analysis. Statistical analysis was performed using SAS, version 9.4 (SAS Institute).

Results

A consort diagram is included in Figure 2. Of the 16 patients who met the study criteria, 12 had primary RPS

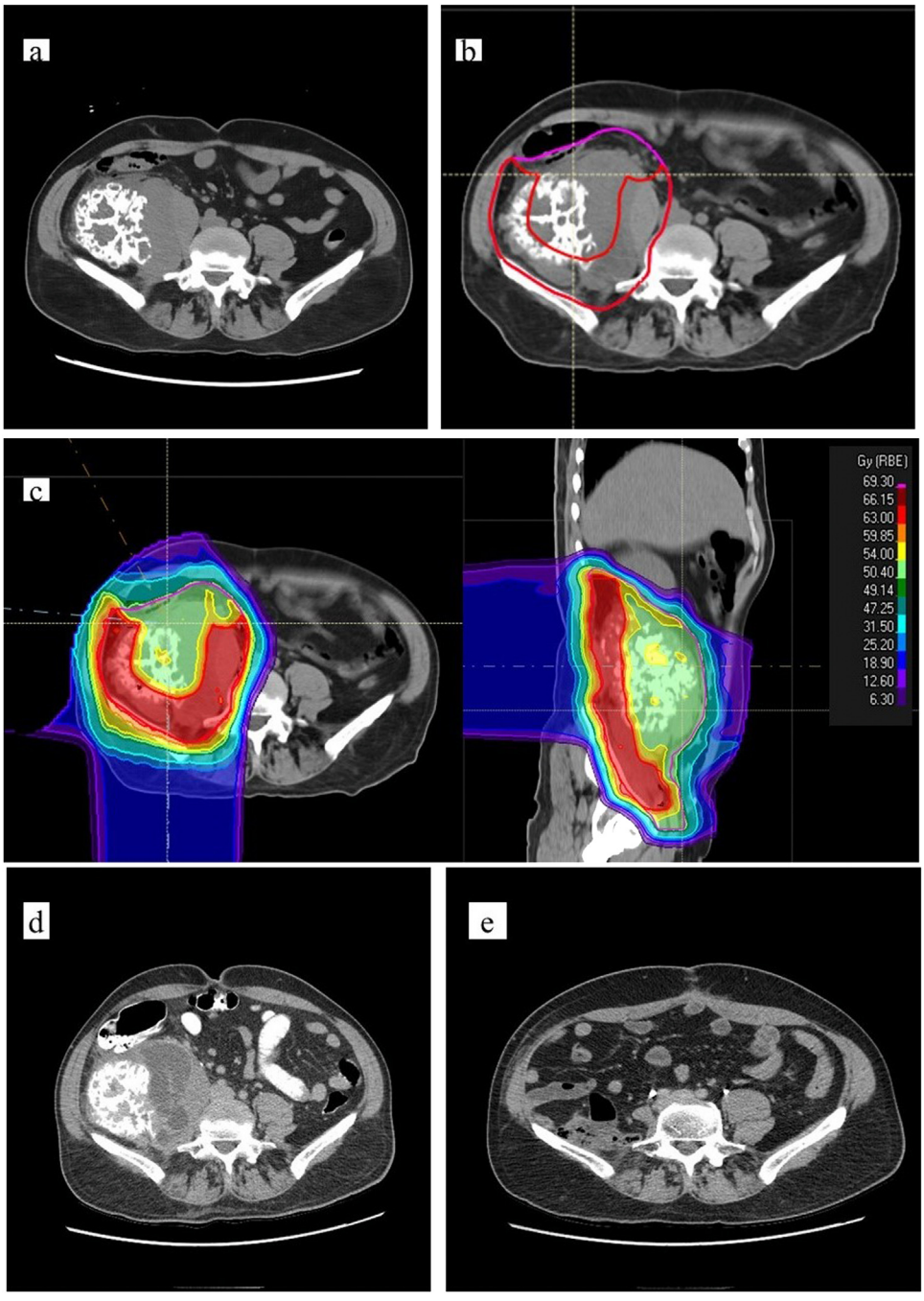

Figure 1 Representative treatment plan. (a) Diagnostic computed tomography (CT) scan with 20 cm retroperitoneal liposarcoma. (b) Simulation CT scan with clinical target volume low risk (pink) and clinical target volume high risk (red). (c) Treatment plan (d) and posttreatment diagnostic CT scan showing tumor necrosis with stable lesion size. (e) Postsurgery surveillance CT scan.

and 4 had isolated local recurrences after previous surgery alone. Patient baseline characteristics are depicted in Table 1. Radiation treatment parameters are listed in Table 2. No patient received neoadjuvant or adjuvant chemotherapy.

Regarding tumor-specific outcomes, one patient was found to have distant metastases after RT completion and did not proceed to surgery. The median time to surgery was 8 weeks (IQR, 6 to 10 weeks). Of the 15 patients who underwent surgery, margin status comprised 1 with gross positive margin, 9 with microscopic positive margins, and 5 with microscopic negative margins. Percentage necrosis ranged from 0% to 95%. During en bloc resection, a median of 2 adjacent viscera were removed (range, 0-6), with the colon being the most common (6 patients) excised organ. Nephrectomy was performed in 5 patients,

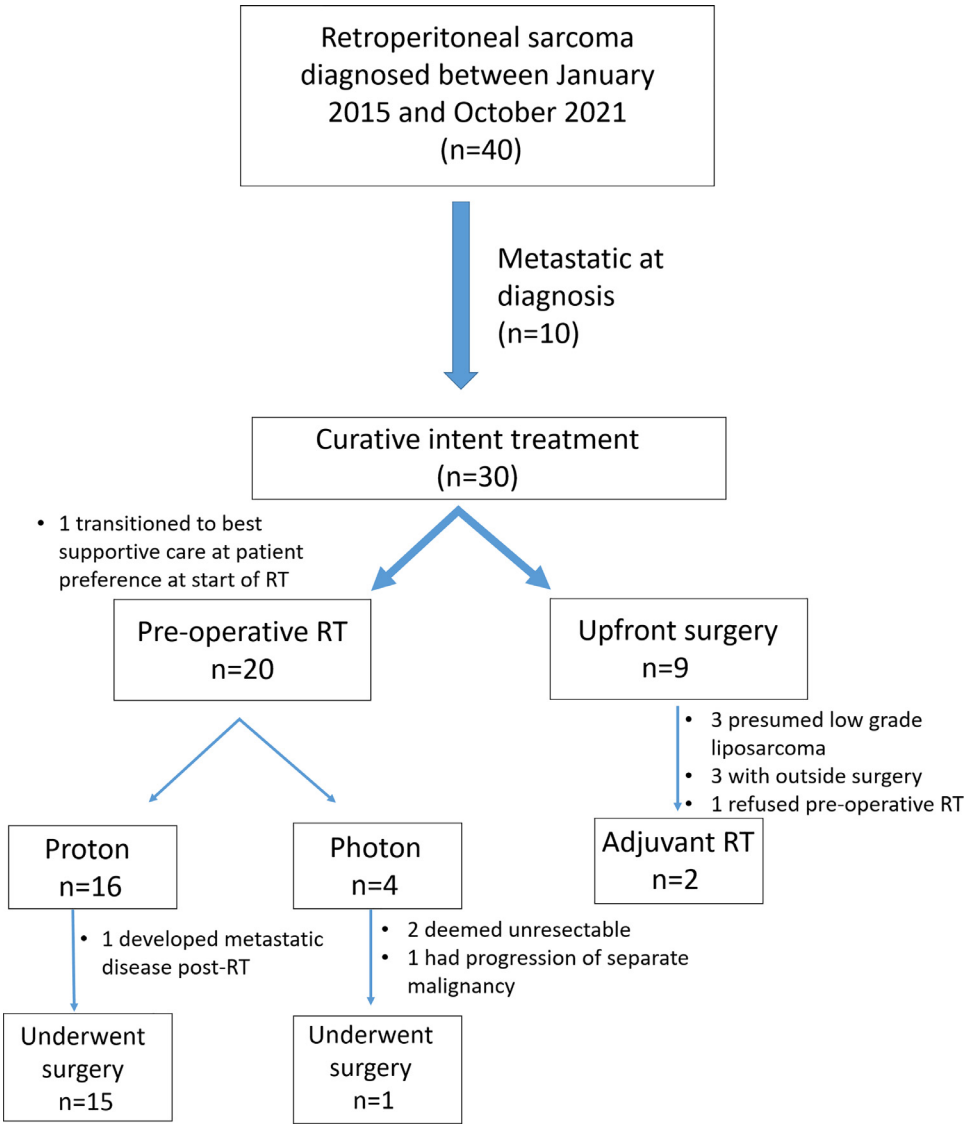

Figure 2 Consort diagram.

and other adjacent viscera that required resection were ileum, pancreas, spleen, liver, and ovary. There was no mortality within 30 days postsurgery, and reoperation was required in 1 patient.

The median follow-up was 18 months (IQR, 11.5-37 months). Local failure occurred in 3 patients, of which 2 patients experienced distant failure as well; one myxofibrosarcoma patient with local only failure developed recurrent disease at the superior aspect of the CTV low-risk, one leiomyosarcoma patient developed recurrent disease >5 cm outside the CTV low-risk with concurrent lung and liver metastases, and one liposarcoma patient recurred at the ileocolonic anastomosis in CTV low-risk with a lung metastasis. One patient had distant failure without local recurrence. At the last follow-up, 4 of 16 patients had died. The estimated 3-year freedom from local failure rate was 68.2% (95% CI, 41.7%-94.7%); 3-year OS rate was 68.8% (95% CI, 41.9%-95.8%; Fig. 3). Radiation-related toxicities are represented in Table 3. Overall, treatment had a favorable toxicity profile with no RTOG grade 3 or more acute or late toxicities noted. Mean local failure free survival for liposarcoma and nonliposarcoma subgroups were 36.5 months (95% CI, 27.2-45.7 months) and 25.8 months (95% CI, 13.7-37.8 months), respectively (P = .43). Cox univariate analysis was done taking into account the variables of age, stage, grade, histology (liposarcoma vs others), primary or recurrence, and maximum gross tumor volume size, but no effect was statistically significant.

Of the 4 patients who underwent neoadjuvant photon radiation, 1 patient received 55 Gy/25 fractions followed by surgery with an outside surgeon (35 cm tumor); the patient was readmitted within 90 days of surgery and was subsequently discharged with home hospice. A second patient received dose-escalated 63 Gy/28 fractions; however, this patient never went for definitive surgery due to

Table 1 Patient baseline characteristics

Characteristic		n (%)
Sex	Male	10 (62.5)
	Female	6 (37.5)
Histology	Liposarcoma	10 (62.5)
	Leiomyosarcoma	3 (18.8)
	Others	3 (18.7)
Primary disease		12 (75)
Isolated recurrence		4 (25)
Primary stage	IB	2 (16.7)
	III A	1 (8.3)
	III B	9 (75)
Adjacent structure involvement	Yes	10 (62.5)
	No	6 (37.5)
Median age (y)		62 (IQR, 43.5-66)
Median maximum tumor diameter (cm)		19.9 (IQR, 12.3-24.1)

Table 2 Dosimetric parameters

Parameter	Median (IQR)
GTV (cc)	1564.3 (405.3-2502.5)
CTV high risk (cc)	479.68 (86-598.9)
CTV low risk (cc)	2720.15 (990.26-3882.24)
GTV D_{max}	66.19 (64.55-66.64)
Ipsilateral kidney mean dose (Gy)	25.08 (5.95-49.24)
Contralateral kidney mean dose (Gy)	0.01 (0-0.46)
D_{1cc} bowel	51.69 (51.17-52.35)
D_{5cc} bowel	51.42 (50.06-51.86)
D_{1cc} ipsilateral ureter	52.19 (25.99-54.35)
D_{1cc} contralateral ureter	27.69 (2.56-52.9)

Abbreviations: CTV = clinical target volume; GTV = gross target volume.

diagnosis of an aggressive lymphoma. An additional 2 patients received 50.4 Gy/28 fractions; 1 had synchronous metastatic disease and never went for surgery; 1 had been treated to a mesenteric recurrence and subsequently was not felt to be a good surgical candidate.

Of the 9 patients who underwent initial surgery, 2 received adjuvant radiation; 1 had outside surgery for a low-grade liposarcoma with positive margins; the other had undergone reresection for recurrent disease in a perinephric region amenable to adjuvant radiation therapy. Both patients are disease free 5 years after adjuvant RT. Of the 7 patients who received surgery alone, 3 had presumed low-grade liposarcoma; the 2 with confirmed low-grade tumors disease free after 4 years, and one patient with high-grade disease on final pathology developed local recurrence 3.5 years after surgery. An additional 3 patients had outside surgery, of which 2 developed recurrence within 6 months and of which 1 remains disease free 2.5 years later. Lastly, 1 patient refused neoadjuvant radiation and was lost to follow-up 4 months after surgery.

Discussion

To our knowledge, this is the first study to report tumor control outcomes of dose-escalated preoperative RT. The STRASS-1 trial cast doubt on the benefit of standard dose preoperative RT for all patients. However, dose escalation may allow for improved outcomes. Our patient cohort, which included representative tumor histologies with mean tumor sizes that exceeded the STRASS-1 trial mean tumor sizes (20 vs 16 cm), demonstrated

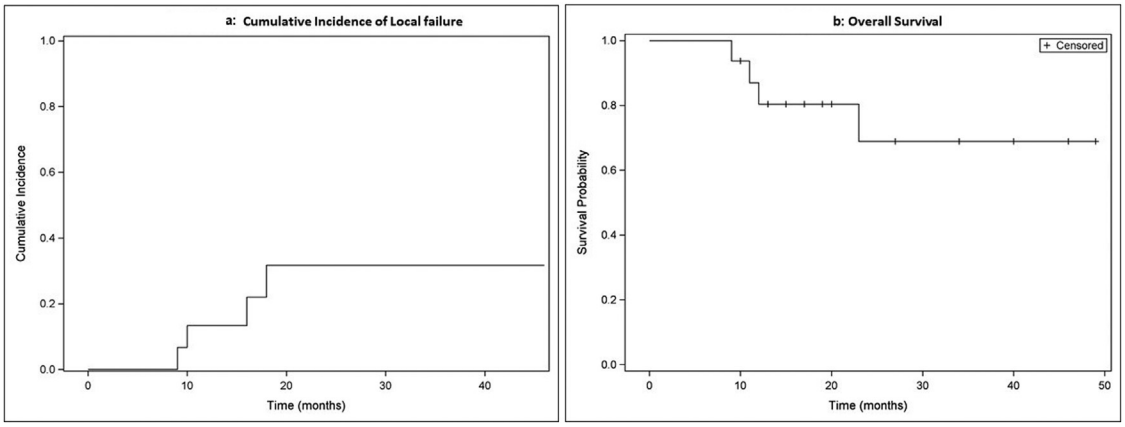

Figure 3 Disease control outcomes. (a) Local failure and (b) overall survival.

Table 3 Acute RTOG toxicities

Toxicity	n (%)	n (%)
	Grade 2	Grade 3+
Radiation dermatitis	1 (6%)	0
Abdominal pain	1 (6%)	0
Fatigue	2 (12%)	0
Nausea or vomiting	2 (12%)	0
Genito-urinary symptoms	2 (12%)	0

Abbreviation: RTOG = Radiation Therapy Oncology Group.

comparable local control outcomes of around 70%. No patient developed local failure in the CTV high-risk.

A Memorial Sloan-Kettering Cancer Center publication that examined primary RPS risk factors demonstrated that histologic type or subtype predicted disease-specific death, local recurrence, and distant recurrence.[10] In our study, histologies of the 4 patients who died comprised undifferentiated epitheloid sarcoma, leiomyosarcoma, myxofibrosarcoma, and liposarcoma. We performed a subgroup analysis of patients with liposarcoma, but no statistically significant difference in outcomes was seen, probably due to small patient numbers. Across other studies, additional factors that affected outcomes included age, tumor size, histologic grade, R0 resection, and number of organs resected.[11-13] Additional subgroup analyses based on these factors similarly did not reveal statistically significant changes in patient outcomes.

Analogous to DeLaney et al, our study demonstrated that dose escalation to 63 Gy using proton therapy was safe, with no observed grade 3+ toxicity.[7] Acute toxicities were mild, and no patient required treatment breaks. This stands in contrast to other studies that used dose escalation. In one trial, patients who received preoperative chemoradiation to 50.4 Gy followed by surgery with 15 Gy intraoperative electron RT experienced 18% grade 3 or 4 nausea.[14] In another trial that compared patients who received or did not receive postoperative brachytherapy after preoperative RT followed by surgery, the brachytherapy group reported similar disease control but had grade 3+ acute toxicities in 39.1% and late toxicity associated with death in 4.3% of patients.[15,16]

Limiting the dose-escalated region to the area deemed to be at the highest risk of recurrence combined with the use of proton therapy appears to be a safe treatment option. Confining the high-dose region to the tumor rind abutting the retroperitoneal wall, vessels, and musculature allowed the treatment plan to respect bowel constraints relative to other treatment paradigms that escalated dose adjacent to bowel. Furthermore, proton therapy with posterior beams and reduced anterior exit dose enabled the reduction of the bowel volume receiving low-dose radiation (i.e V15 Gy), which in other diseases comprises an important treatment parameter.[17]

Late toxicity risks of retroperitoneal RT include nephropathy and ureteral stenosis. Proton therapy allowed for a negligible dose to the contralateral kidney. Because radical surgery often involves kidney resection, sparing the contralateral kidney can help retain long-term renal function. Ureteral stricture was reported in the initial Harvard dose escalation publication, with recommendation to subsequently constrain the ureter dose. In our patients, maintaining the 0.03 cc ureter dose to 57.5 Gy led to some undercoverage of the high-risk CTV, but we observed no post-RT ureteral complications.

Once our center adopted the Harvard paradigm, all nonmetastatic RPS patients with de novo or recurrent resectable disease were recommended dose-escalated preoperative proton therapy. Of the 4 patients who received neoadjuvant photon therapy, 2 had suspicion for metastatic disease and did not receive does-escalated RT. Selection of photon therapy enabled respiratory motion gating for 1 dose-escalated patient whose tumor had >1 cm intrafraction motion; a second patient treated with moderate dose-escalation reflected the treating physician's preference before adoption of the Harvard paradigm. Patients underwent upfront surgery only for suspected

low-grade liposarcomas with expected negative margin resection or if they refused preoperative RT.

The high rates of local recurrence in RPS with surgery alone shows the need for better perioperative therapy to improve local control rates. Standard dose preoperative RT used in the STRASS-1 study reduced local failures but may not be sufficient treatment to change outcomes. Dose escalation with proton therapy could offer a safe solution. Our initial results warrant further investigation. To overcome the limitations inherent in a single institution retrospective study, longer term follow-up and larger patient numbers are needed. Patients with high-risk histologies could also consider further treatment escalation with systemic therapy. The phase 2 study from Harvard that uses the treatment paradigm used here is ongoing, and favorable tumor control and safety results could validate these results and make the case for standardized use of dose-escalated preoperative RT.

Conclusion

Preoperative dose-escalated proton therapy to 63 Gy for RPS was safe and demonstrated acceptable local control. Additional investigation is warranted to validate these results and identify patients most likely to benefit from preoperative treatment.

Disclosures

Matthew D. Hall reports honorarium from Accuray, Inc; Proton Collaborative Group Executive Committee Institutional Representative and Voting Member; grant funding from Live Like Bella Pediatric Cancer Research Initiative, Florida Department of Health Grant 8LA04.

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