Teaching Case

Response to Central Boost Radiation Therapy in an Unresectable Retroperitoneal Sarcoma: A Case Report

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Introduction

Retroperitoneal sarcomas (RPS) comprise 10% to 15% of soft tissue sarcomas and grow to a median of 15 to 18 cm before causing symptomatic invasion or mass effect on surrounding structures.1 Curative treatment for non-metastatic RPS requires surgical resection, with 65% to 83% undergoing complete resection, while others may be unresectable owing to the tumor invading major vessels or the spinal cord.1-5 In an early series of 278 patients with primary RPS, unresectability was the strongest prognostic factor for disease-specific survival on multivariate analysis (relative risk, 4.7; 95% confidence interval, 2.9-7.5; P < .001), followed by positive margins, high-grade, and size >10 cm.¹ For patients with unresectable RPS, the prognosis is poor and palliative chemotherapy may be offered; the evidence for radiation therapy (RT) in this scenario is limited. One early series with 15 unresectable abdominopelvic sarcoma patients reported a 5-year control rate of 23% with RT. Although no clear dose-response was observed, patients receiving more than 65 Gy appeared to have a higher duration of local control.6 Another more recent series of 112 patients with unresectable sarcomas, including 29 patients with RPS, reported 5-year local control of 45% across all sarcoma sites. Higher local control was observed above 63 Gy, but higher major complications were also seen above 68 Gy, suggesting a narrow therapeutic window.7 Typically, high RT doses are not feasible in the abdomen owing to radiosensitivity of the stomach, small bowel, kidneys, and liver. Thus, other RT strategies have also been reported for unresectable primary RPS, notably particle therapy, brachytherapy, and altered fractionation. Studies regarding particle therapy with protons, carbon ions, and pions have been published, including a larger series of 128 patients with unresectable localized axial sarcoma receiving 64 to 73.6 Gy equivalents of carbon ion RT with 65% 5-year local control.8-10 Computed tomography (CT)—guided I-125 seed brachytherapy has also been reported with 87% short-term local control in 23 patients.¹¹ Hypofractionation is also an attractive strategy, as sarcomas are thought to have a low α/β of 0.4 to 4.¹² Neoadjuvant and adjuvant hypofractionated radiation for extremity and trunk sarcomas has demonstrated acceptable local control and toxicity in several retrospective and

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This article is a teaching case, and all of the data analyzed in this case are contained in the published article.

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nonrandomized prospective studies. Fewer studies have examined outcomes from hypofractionated RT alone. In 1 series of 18 patients with unresectable trunk sarcomas receiving stereotactic body radiation therapy alone of 20 to 48 Gy in 1 to 5 fractions, a 5-year local control rate of 28% was observed. Management of unresectable primary RPS remains challenging. Here, we present a patient treated with RT alone using a novel technique of a central radiation boost, which led to a durable period of symptomatic control.

Case Report

A 75-year-old male presented to his primary care physician with 4 months of progressive weight loss, abdominal pain, and bloating after meals. Physical examination revealed a palpable, firm, central abdominal mass. The initial diagnostic CT scan of the abdomen and pelvis showed a $14 \times 9 \times 13$ cm abdominal mass. The mass appeared to arise from the infrahepatic inferior vena cava, with mass effect on the superior mesenteric vein, circumferential encasement of the superior mesenteric artery (Fig 1A), encasement of the bilateral renal arteries (Fig 1B), and obliteration of the left renal vein. CT chest showed nonspecific subcentimeter pulmonary nodules. CT-guided core needle biopsy showed sheets of stellate to spindle cells in a marked myxoid background, with few mitotic figures and no lipoblasts (Fig 2). Immunohistochemistry was positive for CD34 and negative for S100, smooth muscle actin, desmin, pancytokeratin, and STAT6. MDM2 amplification and FUS RNA Binding Protein-DNA Damage Inducible Transcript 3 fusion oncogene (FUS-DDIT3) translocation were negative by fluorescence in situ hybridization. Based on this analysis, the diagnosis was low-grade myxofibrosarcoma.

Figure 1 Diagnostic axial slice computed tomography (CT) showing retroperitoneal sarcoma before radiation therapy with vascular involvement including (A) superior mesenteric artery (SMA) circumferential encasement and (B) right renal artery encasement. Four months after radiation therapy, tumor decreased in size. However, vascular involvement persisted, including (C) SMA encasement and (D) right renal artery encasement.
multidisciplinary evaluation, the tumor was deemed unresectable as a result of the aforementioned arterial involvement. Given the progressive abdominal symptoms, a course of palliative RT was recommended.

A renal scan before radiation planning showed balanced kidney function, and the patient underwent CT simulation supine with intravenous and oral contrast. Two planning target volumes (PTVs) were created (Fig 3A). PTV1 was the entire gross tumor volume (GTV) plus a 0.5-cm uniform margin and was prescribed 36 Gy in 1.8 Gy fractions delivered 4 days per week (Fig 3C). PTV2 was the GTV minus a 1-cm uniform margin, then further cropped 1 cm from organs at risk including the bowel, liver, kidney, and aorta, and was prescribed 20 Gy in 4 Gy fractions delivered 1 day per week (Fig 3C). Dose constraints are shown in Table 1. The weekly boost to the center of the tumor was 4 Gy per fraction because 5 Gy × 5 in addition to the 36 Gy in 1.8 fractions exceeded the kidney dose constraint. An intensity modulated radiation therapy plan with 15 MV photons was designed and initiated (Fig 3B). Two weeks into RT, routine weekly cone beam CT demonstrated that the tumor had increased in size beyond PTV1; therefore, the patient was replanned with slight enlargement of PTV1, while keeping the central PTV2 the same size. Just after initiating the new RT plan, the patient was also hospitalized for acutely worsening abdominal pain, nausea, and vomiting. Endoscopy showed severe, extrinsic compression from the tumor on the fourth part of the duodenum, which could not be traversed. The patient underwent endoscopic gastrojejunostomy with stent placement to bypass the blocked duodenum, which ultimately required a 1 week-long break in RT for recovery (Fig 3C). After this break, the patient resumed and completed RT.

About 2 weeks post-RT, the patient underwent restaging with a diagnostic CT chest, abdomen, and pelvis, which showed slight increase in the tumor to 16 × 8 × 14 cm with more central fluid attenuation, with persistent vascular involvement and stable nonspecific pulmonary nodules. Although the patient’s pain and
symptoms of outlet obstruction had improved after stent placement and RT, vascular involvement was unchanged and performance status remained poor, and he was not a candidate for surgery or systemic therapy.

At 4 months post-RT, the patient had improved significantly, with improved energy and appetite, weight increase from a nadir of 52 kg to 55 kg, and resumption of light outdoor activity. CT showed decreased size in the abdominal mass to 12 × 5 cm in the axial dimension, but with persistent vascular involvement including superior mesenteric artery encasement (Fig 1C) and bilateral renal artery encasement (Fig 1D). At 10 months post-RT, he continued to do well with stable 12 × 6 cm abdominal mass, stable pulmonary nodules, functional gastrojejunal stent, and no gastrointestinal or renal issues. Unfortunately, at 16 months post-RT, the patient experienced worsening fatigue with more constant abdominal pain. CT demonstrated that the stent and scattered small pulmonary nodules were unchanged; however, the abdominal mass had enlarged to 19 × 9 cm. Further options including palliative liposomal doxorubicin or focus on patient comfort were discussed, and ultimately the patient decided to pursue hospice care.

Discussion

Surgery is the cornerstone of curative treatment for localized sarcoma. In unresectable localized disease, palliative RT is an option to provide local control, although the evidence for RT alone in primary RPS is limited.7,16 Retrospective series on adjuvant RT for resectable RPS can provide insight into the efficacy of RT for local control, although even here the conclusions differ. For example, in a retrospective study of 382 patients, 121 of whom received a median of 45 Gy peri-operatively, RT was not associated with abdominal recurrence or overall survival.17 However, in another retrospective series of 1007 patients, 322 of whom received a median of 50 Gy peri-operatively, RT did reduce local recurrence (hazard ratio, 0.58; 95% confidence interval, 0.42–0.80; \( P = .001 \)) but not overall survival on multivariate analysis.18 More recently, a phase 3 trial of preoperative RT, Surgery With or Without Radiation Therapy in Treating Patients With Previously Untreated Nonmetastatic Retroperitoneal Soft Tissue Sarcoma (STRASS) (European Organisation for Research and Treatment of Cancer [EORTC] 62092), has completed accrual, and the oral presentation at American Society of Clinical Oncology [ASCO] 2019 reported no improvement in 3-year abdominal recurrence-free survival with preoperative RT of 50.4 Gy compared with surgery alone for all patients.19 A sensitivity analysis did find that preoperative RT appeared to benefit the liposarcoma subgroup, a histologic subtype where local rather than distant failures are more common.18,19

Boosting part of the tumor has also been investigated in preoperative RT for resectable RPS. A recent phase 1 trial used intensity modulated proton therapy with a boost to areas at high risk of positive margins, typically the posteromedial and vascular margins.20 The 11 patients in the study received 50.4 Gy relative biological effectiveness in 28 fractions to the entire tumor with a simultaneous integrated boost to 60.2-63 Gy relative biological effectiveness, and no dose-limiting acute toxicities were reported.20 Boosting the central tumor has not been reported in unresectable RPS, but has been studied for other unresectable abdominal malignancies. In a recent retrospective dose-response study of intrahepatic cholangiocarcinoma, tumors close to sensitive gastrointestinal structures received about 45 Gy in 25 fractions to the entire tumor.21 A simultaneous integrated boost of 75 to 100 Gy in 25 fractions was delivered to the central GTV, which was created by cropping the outer 1 cm of the GTV and cropping 5 mm away from gastrointestinal structures.

In this patient, to minimize bowel and renal toxicity from a palliative treatment, a modest PTV1 dose of 36 Gy in 1.8 Gy fractions was delivered to the entire tumor 4 days per week. In hopes of providing more durable local control and considering the lower \( \alpha/\beta \) ratio of sarcomas, an additional 20 Gy in 4 Gy fractions was given to PTV2, the center of the tumor only, 1 day per week. Assuming an \( \alpha/\beta \) of 4 for sarcoma, the equivalent dose in 2 Gy fractions to the center of the tumor from the PTV1

| Table 1 Dose constraints were met with a PTV2 boost prescription of 20 Gy in 5 fractions (bold), with higher doses exceeding kidney constraints |
| Dose constraint | Bowel D2cc <51 Gy | Left kidney D33% <10 Gy | Right kidney D67% <16 Gy | Liver V30 Gy <20% | Spinal cord max <45 Gy |
|-----------------|------------------|---------------------|-----------------|-----------------|-----------------|
| Boost prescription | 3 Gy × 5 | 39 | 9 | 13 | 11 | 30 |
| 4 Gy × 5 | 42 | 9 | 14 | 12 | 32 |
| 5 Gy × 5 | 44 | 10 | 15 | 13 | 34 |
| 6 Gy × 5 | 47 | 10 | 16 | 14 | 36 |
| 7 Gy × 5 | 49 | 11 | 17 | 20 | 38 |

Abbreviations: PTV = planning target volume; D2cc = minimum dose to the most irradiated 2 cm³ of tissue; D33% and D67% = minimum dose to the most irradiated 33% and 67% of tissue, respectively; V30 Gy = volume of tissue receiving 30 Gy or more.
PTV2 prescriptions was 34.8 + 26.67 or 61.47 Gy total. We also tried different PTV2 prescriptions ranging from 3 to 7 Gy/fraction, and kidney dose constraints were exceeded above 4 Gy/fraction and would have required replanning (Table 1). It is difficult to say whether increased central boost dose would have improved outcomes for this patient. Even our boost dose of 4 Gy/fraction resulted in central swelling of the tumor during RT, worsening duodenal obstruction, which required an unplanned treatment break, replanning, and a gastrojejunal stent. Overall, the technique of boosting the central tumor did provide up to 16 months of local control, and clinical improvement and could be considered for other unresectable RPSs.

The low-grade nature of this tumor and the histologic subtype may have also contributed to the marked response just a few months after completing RT. Indeed, we initially suspected that this tumor could have a particularly radiosensitive histology such as myxoid liposarcoma. However, a primary myxoid liposarcoma arising from the retroperitoneum would be exceedingly rare, and ultimately fluorescence in situ hybridization for FUS-DDIT3, resulting from the characteristic t(12;16)(q13;p11) translocation of myxoid liposarcoma, was negative.

Conclusions

In this case of an unresectable low-grade myxofibrosarcoma, palliative RT alone with a central, hypofractionated boost provided a period of durable local control while minimizing dose to adjacent bowel and kidney. Further investigation into techniques for RT alone may be helpful for patients with unresectable primary RPS.

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