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Preoperative Intensity Modulated Radiation Therapy for Retroperitoneal Sarcoma

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The use of intensity modulated radiation therapy (IMRT) has allowed for the administration of high doses to retroperitoneal sarcomas (RSTS) while limiting toxicity to adjacent organs. The purpose of our study is to assess the outcome and toxicities of patients with RSTS treated with neo-adjuvant external beam radiation (EBRT) therapy using IMRT. This is a retrospective study of 21 patients treated with preoperative IMRT for primary or recurrent RSTS between 2005 and 2011. Overall survival (OS) and local recurrence free survival (LRFS) were computed using the Kaplan-Meier method (log-rank test). Acute and chronic toxicities were assessed using the CTCAE v. 3 criteria. The actuarial 2 and 3-year OS was 66% for both and the 5-year OS was 51%. As for LRFS it was 57% at 2 and 3-year and 51% for the 5-year LRFS. Factors predictive for local control were microscopically negative margins ($p = 0.022$), a median tumor diameter <15 cm ($p = 0.007$) and pathology of liposarcoma ($p = 0.021$). Furthermore, patients treated for recurrent disease fared worse ($p = 0.04$) in local control than patients treated for primary disease. As for OS, patients treated for Grade 1 histology had a better outcome ($p = 0.05$). EBRT was generally well tolerated. Acute gastrointestinal (GI) Grade 1 or 2 toxicities occurred in 33% of patients and one patient had unexplained post-radiation Grade 2 fever that resolved after tumor resection. As for chronic toxicities 24% of our patients presented Grade 1 GI toxicity and one patient presented Grade 3 small bowel stenosis not clearly due to radiation toxicity. Despite the location and volume of the tumors treated, preoperative IMRT was very well tolerated in our patients with retroperitoneal sarcoma. Unfortunately local recurrences remain common and dose escalation is to be considered.

Key words: Retroperitoneal sarcoma; Preoperative radiotherapy; Intensity modulated radiation therapy.

Introduction

Retroperitoneal soft tissue sarcomas are rare and represent 10-15% of adult soft tissue sarcomas (STS) (1). The primary treatment modality is surgical extirpation (2, 3). However, surgery is often not curative as a single modality. Because of the size and location of RSTS, negative margins are difficult to obtain and loco-regional recurrences will be the primary cause of death. Five-year survival rates are 50-60% following initial tumor resection (4). Data from retrospective

Abbreviations: ACOSOG: American College of Surgeons Oncology Group; EBRT: External Beam Radiation; GTV: Gross Tumor Volume; IMRT: Intensity Modulated Radiation Therapy; IORT: Intra-operative Radiation Therapy; IOERT: Intraoperative Electron-beam therapy; LC: Local control; LCR: Local Control Rates; LRFS: Local Recurrence Free Survival; OS: Overall Survival; STS: Retroperitoneal Sarcomas; STS: Soft Tissue Sarcoma; GI: Gastrointestinal.

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and limited prospective studies have shown, as it is the case for sarcomas of the extremities, that radiation therapy can improve local control (5). However, because of tumor location and size, radiation treatments are more toxic and collateral irradiation of the gastrointestinal tract limits tolerability. It is hoped that more modern treatment techniques can improve the tolerability and efficacy of external beam radiation therapy (6).

Means of addressing the therapeutic ratio have included intraoperative radiation therapy (IORT) or proton therapy. Unlike these specialized modalities, intensity modulated photon radiation therapy is widely available. In our department, it has been routinely used since 2004. In the present study we report our use of IMRT for preoperative treatment of retroperitoneal sarcomas.

Method and Material

Study Population

The data was collected retrospectively by reviewing the medical records of 26 consecutive patients with primary or recurrent non-metastatic retroperitoneal sarcomas treated with curative intent at our institution between August 2005 and October 2011. The study received institutional review board approval. Patients were included if they had confirmed retroperitoneal sarcomas, were at least 18 years of age and were intended for gross total resection. Five patients were excluded because they received postoperative radiation. The patients had grade 1 to 3 sarcomas according to the FNCLCC grading system.

Radiation Therapy

Treatment planning was typically based on a contrast-enhanced three-dimensional axial CT image set with 3×3 mm slices. Patients were immobilized with custom lower extremity vacuum cushions. Treatment plans were optimized using Eclipse (Varian medical systems, Palo Alto, CA) or Hi-Art Tomotherapy (Accuray, Sunnyvale, CA) treatment-planning systems. Six patients were treated with helical tomotherapy, 15 with sliding-window fixed-field IMRT. The gross tumor volume (GTV) was contoured as all gross visible tumor and MRI images were often fused to the planning CT images. The clinical target volume was equivalent to the GTV. Planning target volume margins of 1-2 cm were used around the GTV however they were reduced to 5 mm at the interface with small bowel. Daily cone beam CT scans were done for the 6 patients treated with Tomotherapy, the other 15 patients had portal images done at least once a week.

A dose of 50-55 Gy in daily fractions of 180-225 cGy was prescribed to the PTV. The dose was prescribed to an isodose; the 95% isodose had to cover 99% of the PTV. Normal tissue constraints followed our practice for gastrointestinal malignancies. Dose constraints for the small bowel were less than 200 cc receiving no more than 30 Gy, less than 150-200 cc receiving no more than 35 Gy, 70-100 cc receiving less than 40 Gy, less than 20-50 cc receiving no more the 45 Gy and 0 cc receiving no more than 50 Gy. The small bowel was contoured as the entire abdominal cavity excluding: the liver, kidneys, spleen, periaortic region and the PTV + 3 mm. Dose constraints for the spinal cord was that the maximum dose had to be below 45 Gy; for the liver, less than 60% of the volume had to receive a dose above 30 Gy. All patients had a renal scan before beginning radiation treatment in order to assess their baseline function. It was ensure that a least one kidney received less than 15 Gy.

Surgery and Chemotherapy

When possible an "en bloc resection" was the surgery of choice. Along with bulk tumor resection, involved adjacent organ resection was often required. Nephrectomy was needed in 3 patients, gastrointestinal (GI) resection in 9 patients and vertebral body excision in 3 patients. Resection of the psoas muscle was done in 3 patients, 1 patient needed a femoral nerve resection and 4 patients required venous or arterial resection with bypass reconstruction. Histological grade was determined by the pathology report. The tumor diameter was the maximal pre-treatment diameter on pre-radiation imaging.

Five patients received chemotherapy before radiation treatments. Four patients received Adriamycin with or without Ifosfamide and one patient received chemotherapy in another center.

Follow-up

Patient follow-up was done by the surgeon and the radiation oncologist alternatingly. Usually, clinical exams were done every 3 months and a CT scan was performed yearly or upon development of symptoms. Local recurrence free survival was defined as an absence of recurrence at the surgical bed or in the radiation field.

Statistical Analysis

Acute and chronic toxicities were assessed according to the CTCAE v. 3 criteria. All treated patients were included and analyzed as intended to treat. Overall survival and LRFS was computed using the Kaplan-Meier life table method with log-rank testing. All results were considered significant with a p-value ≤ 0.05. Survival was calculated from the date of end of radiotherapy. Analysis was done using IBM-SPSS version 16 (IMB, Chicago, IL).

Results

Patients

Median follow-up for all patients was 22 months (range: 0-84 months). Of patients alive, 4 have a follow-up of <1 year. The patient characteristics are shown in Table I. In our cohort 38% we treated for primary disease and 62% for a locally recurrent tumor. More than half of patients (62%) had liposarcoma (38.5% well differentiated and 61.5% poorly differentiated) and four had leiomyosarcoma. Histologies were obtained prior to any radiation or chemotherapy treatment either by way of a biopsy or from a previous surgery for patients treated for local recurrences.

Table I
Patient characteristics.

Variables	
Age, median (range)	53 (35-83)
Dose, median (range)	50.0 Gy (25.2-56.25)
Female	63.6%
Disease	
Primary	38%
Recurrent	62%
Histology	
Liposarcoma	62%
Leiomyosarcoma	10%
Other sarcoma	28%
FNCLCC grade	
1	35%
2	15%
3	50%
Diameter at time of EBRT	
<10 cm	35%
10-15 cm	15%
>15 cm	50%
Margins	
R0	44%
R1	22%
R2	17%
Unknown	17%

R0: Microscopically negative margins
R1: Microscopically positive margins
R2: Macroscopically positive margins

Poorly differentiated sarcomas were seen in 50% of patients. The median tumor diameter was 15.0 cm. Median planned dose was 50 Gy (range: 45-56.25 Gy) with 4 patients receiving a dose of less than 50 Gy. Two patients had to stop radiation treatments because of disease progression and two were prescribed 40 and 45 Gy.

Radiation and Surgery

Median delivered dose was 50 Gy (25.2-56.25 Gy). 62% received ≥50 Gy.

Of the 21 patients treated, 19 underwent the planned surgical exploration and in 18 patients the tumor was resected. Of the two patients that were not explored, one patient became inoperable due to local and distant progression, the second was re-evaluated and showed local disease too extensive for surgery. The two patients who had to interrupt radiation treatments because of local disease progression were still able to undergo surgical resection.

Survival and Toxicity

At last follow-up, seven patients (33%) had died. One patient's death was due to postoperative complications and, the remaining 6 patients died from disease recurrence. Disease recurrence was seen in 52% of patients, 7 had local recurrence only, 1 had metastatic recurrence and 2 had local and distant recurrence. Median time to local recurrence was 17 months (7.5-30). The actuarial OS at 2-3 and 5-year was 66%, 66% and 51% respectively. The actuarial local recurrence-free survival at 2-3 and 5-year was 57%, 57% and 41% (Figure 1). Factors predictive for local control were having a liposarcoma (0/8 recurrences) ($p = 0.021$), R0 resection ($p = 0.018$) and a median tumor diameter <15 cm ($p = 0.007$). Furthermore, patients treated for recurrent disease had poorer local control than patients treated for primary disease ($p = 0.04$). No men (0/7) died so far ($p = 0.050$). Other factors predictive for a better OS were low histologic grade ($p = 0.05$): none of the patient with a Grade 1 sarcoma have died so far (Table II).

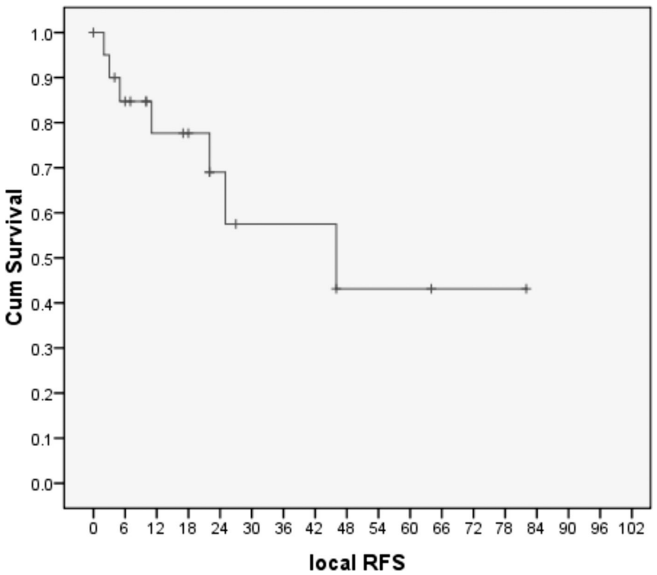

Figure 1: Local recurrence free curve ($n = 21$).

EBRT was generally well tolerated (Table III). Acute Grade 1-2 GI toxicity was seen in 52% of patients. Grade 1 vomiting occurred in 24% of our cohort and Grade 1 fatigue in 48%. Only 3 patients experienced any Grade 2 GI toxicity.

Table II
Kaplan-Meier analysis for overall survival (OS) and local recurrence free survival (LRFS).

Factors	LRFS	OS
Male vs. Female	0.390	0.050
Liposarcoma vs. other histology	0.021	0.410
Grade 1 vs. 2-3	0.910	0.050
Grade 1 vs. 2 vs. 3	0.560	0.051
R0 vs. R1-2	0.018	0.260
Radiol. diameter (≤15 cm vs. >15 cm)	0.007	0.731
Age (<53 vs. ≤53)	0.940	0.730
Tx recurrent disease*	0.040	0.648

*Treatment for primary sarcoma fared better.
R0: Microscopically negative margins
R1: Microscopically positive margins
R2: Macroscopically positive margins

Table III
Acute toxicity according to the CTCAE v. 3 criteria.

Toxicity	Grade 1 (%)	Grade 2 (%)
Fatigue	48 ($n = 9$)	–
Nausea	52 ($n = 11$)	10 ($n = 2$)
Vomiting	24 ($n = 5$)	–
Diarrhea	29 ($n = 6$)	5 ($n = 1$)
Abdominal pain	43 ($n = 10$)	–
Dermatitis	5 ($n = 1$)	–
Dysphagia	5 ($n = 1$)	–
Fever	–	5 ($n = 1$)

One patient presented with recurrent unexplained post-radiation Grade 2 fever which only abated following tumor resection. Three patients lost >5% of their body weight during radiotherapy.

As for late toxicity, one patient treated for recurrent disease presented Grade 3 duodenal stenosis 4 months after radiation treatments. Due to the retrospective nature of this study we are not able to evaluate the dosimetry to evaluate whether this complication could be radiation-induced.

Three patients had Grade 1 chronic abdominal pain and two had Grade 1 chronic diarrhea. Bilateral lower extremity oedema was seen in one patient who had had bilateral distal iliac vein resection.

Discussion

The role of radiation therapy in RSTS, whether it is preoperative, postoperative, intraoperative or a combination of modalities has been the object of dispute (7). Although some reports have shown improvements in local control (LC) with higher radiation doses (>55 Gy) (8), LC and OS often remain disappointing. Stoeckle *et al.* found in their review, that radiation was the single most important independent prognostic factor for local control (9). In a contradictory finding, Pirayesh *et al.* found no benefit in adding either chemotherapy or radiation to surgical resection (5).

Despite aggressive treatments, prognosis remains poor with 5y-OS typically between 35 and 50% (Table IV) (10). Our results with an actuarial 5y OS of 51% are in accordance with current literature. Prognostic factors such as marginal status, histological subtype and Grade have previously been reported (9). In accordance with our own findings, Feng *et al.* reported that patients with negative resection margins had local control rate of 64% vs. 39% for patients with positive margins (11). Avances *et al.* stated that recurrence rate is strongly associated with positive surgical margins (12). Furthermore, in a study by Bonvalot *et al.* low grade tumors resected with negative margins fared better with a significant decrease in intra-abdominal recurrences (13). Thus, more aggressive local treatments appear to be key in improving outcomes. Gronchi *et al.* demonstrated this in their comparison between conservative surgical resections with a more liberal en bloc resection of adjacent organs. They found a statistically significant decrease in local recurrences with a more aggressive surgery (14).

Locally recurrent disease often has a worse outcome than primary RSTS. In our study, 61% of our cohort were referred for recurrent disease and fared significantly worse in local

Table IV
Literature review of treatment and outcomes.

Authors	Number of patients	Preoperative RT IMRT (Gy)	Postoperative RT IMRT (Gy)	5 y LC (%)
Pezner, 2011 (27)	33	–	27-65Gy ± Boost IMRT or IORT	–
Paumier, 2011 (4)	14		45-54	–
Bossi, 2007 (21)	18 (6 IMRT)	50	–	–
Tzeng, 2006 (26)	16	45 (boost ad 57.5)	–	80% (2 y)
Present study	21	50	–	41% (5 y)

control than patients treated for primary disease. In their study, Jones *et al.* found a significant improvement in 2-year disease free survival for the subgroup of patients treated for primary disease compared to recurrent disease (93% and 80% respectively) (15). Given the large number of patients in our study treated for recurrent disease, we believe that the actuarial local recurrence-free survival at 2-3 and 5-year of 57%, 57% and 41% are good and are comparable to previous studies (16).

Positive margins increase the risk of local recurrence and have prompted the use of adjuvant treatments such as intraoperative radiotherapy or brachytherapy. Gieschen *et al.* reported local control rates (LCR) of 83% in patients treated with IORT (17). However, they reported important morbidity in the form of neuropathy, GI obstruction or fistula. However, in a study by Krempien *et al.*, patients treated with intraoperative electron-beam therapy (IOERT) and adjuvant EBRT with an R0 resection had a 5 and 10 year LC of 100% with 21% grade 2 or higher late toxicity (18). Other modalities for dose escalation have been used such as proton therapy in combination with IMRT or IOERT with 3-year RFS for primary and recurrent disease of 90% and 30% respectively (19).

Preoperative radiation has many theoretical advantages; radiosensitive organs are displaced away from treatment fields by the tumor, decreased risk of microscopic seeding during surgical manipulations, increased tumor vascularisation and therefore oxygenation thus increasing radiosensitivity (15). Despite the above mentioned advantages, the role and timing of radiation in the treatment of RSTS is still debated (20). Moreover, the extent of radiation fields is also subject for debate. In a retrospective study by Bossi *et al.*, the group questioned the necessity of treating the entire tumor and reported their experience in treating only the posterior abdominal wall with preoperative IMRT (21).

There are unfortunately no randomized controlled studies that compare surgery with or without pre or postoperative radiation and our knowledge is based mostly on retrospective studies. In 2004, the American college of surgeons oncology group (ACOSOG) opened a phase III randomised trial (ACOSOG Z9031) comparing surgery alone vs. preoperative radiation followed by surgical resection. Unfortunately the study was closed prematurely due to poor accrual (22). A randomized phase III study, EORTC 62092-22092 comparing surgery with or without neo-adjuvant radiotherapy is open and enrolling patients (23). Furthermore, a German, single center phase I/II study, is underway for preoperative dose escalation of 50-60 Gy (24) and Roeder *et al.* are currently conducting a phase I/II prospective trial for preoperative IMRT to 50-56 Gy followed by IORT to 10-12 Gy to the tumor bed (25). This underlines the continuing interest in preoperative EBRT and dose escalation. As an alternative to standard dose escalation, simultaneous integrated boost (SIB) may provide a means of optimizing the therapeutic ratio of IMRT. Preoperative IMRT of 45 Gy (1.8 Gy/fx) to the tumor PTV with a SIB 57.5 (2.3 Gy/fx) to high-risk margin in 25 fx was well tolerated in a series of 16 patients treated by Tzeng *et al.* (26).

IMRT has been in general use for several years now to increase the dose delivered to the tumor while limiting adjacent organ toxicity. These advantages are key in RSTS treatment. In what is the largest published series, we believe that our results are very encouraging with only 2 patients experiencing acute Grade 2 GI toxicity. The only patient with significant late toxicity, in the form of duodenal stenosis had had previous surgery, which may have contributed to the stenosis through the formation of adhesions. Paumier *et al.* reported acceptable acute and chronic toxicities in 14 patients treated with IMRT and receiving 50.4 Gy postoperatively, with only one patient reporting chronic Grade 3 abdominal pain (4). An interesting discussion is whether a boost should be given to the posterior surgical wall (21) or other parts where positive surgical margins are predicted (26).

In conclusion, RSTS are rare with a paucity of literature to guide optimal treatment. As local recurrences are the primary cause of mortality, a more aggressive local treatment strategy is warranted. The data presented in this study shows that preoperative treatment with 50 Gy of IMRT results in little toxicity. It thus opens the door to dose escalation as a means of improving outcome.

Conflict of Interest Statement

There are no conflicts of interest in this paper.

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