

ORIGINAL ARTICLE

Intraoperative radiation therapy for high risk soft tissue sarcoma resection margins

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Abstract

Background and objectives: External beam radiation (EBRT) can reduce local recurrence (LR) of soft tissue sarcomas (STS). The addition of intraoperative radiation therapy (IORT) can deliver high dose radiation boost to anticipated “high risk” margins while sparing adjacent structures.

Methods: A retrospective review (2004-2012) was performed of STS treated with surgical resection and IORT using HDR brachytherapy for anticipated close/positive margins.

Results: Twenty-four patients underwent 25 resections with IORT (1 patient had 2 separate recurrences). Tumors were primary in 72%, deep in 96% and intermediate/high grade in 84%. Tumor locations were extremity (44%), retroperitoneal (40%), truncal (12%) and neck (4%). Common histologies included pleomorphic (32%), liposarcoma (12%) and myxofibrosarcoma (12%). Neoadjuvantly, 3 received chemotherapy and 13 received EBRT (median 50Gy; range 45-54). Median IORT dose was 12Gy (range 10-17.5). Margins were microscopically positive in 20%; none were grossly positive. Adjuvantly, 5 received EBRT (median 46Gy, range 45-50) and 2 received chemotherapy. Median follow-up was 20.1 months (range 2.7-96.4). No recurrences occurred at the IORT sites. Two-year LR free survival was 60.8% and disease specific survival was 84%.

Conclusion: Use of IORT at time of STS resection was effective at preventing LR at the treated site despite “high risk” features.

Key words

Intraoperative radiation, Sarcoma, High risk, Margins, Brachytherapy, Intraoperative radiation therapy

1 Introduction

Soft tissue sarcomas (STS) can occur throughout the body, but most commonly occur in the extremities, trunk, and retroperitoneum. Surgical resection with pathologically negative margins remains the treatment of choice but local recurrences continue to be problematic. This is especially true when tumors lie in close proximity to critical, unresectable structures. Use of external beam radiation therapy (EBRT) either pre-operatively or post-operatively can improve local

control^[1-7]. Patients with tumors that are high grade, locally recurrent or at high risk for positive margins are at increased risk for local recurrence and distant metastases^[3, 6, 8-11].

Advances in radiation therapy allow for more conformal target coverage, yet normal tissue tolerances limit dose^[6, 12-26]. Intraoperative radiation therapy (IORT) techniques permit high dose delivery to areas at risk while sparing adjacent surrounding normal tissues. IORT boost doses to areas at risk for close or positive margins can be used to enhance local control (LC). As such, IORT is an appealing modality to improve local control by allowing delivery of high doses of radiation while minimizing the dose to adjacent normal tissues that would otherwise be located within external beam radiation fields. IORT allows for local delivery of radiation to a focused field and can be delivered in a single session. Only one randomized trial to date exists showing a significantly improved local control rate of 60% using a combination of 20 Gy IORT and 35–40 Gy EBRT compared to 20% with 50–55 Gy postoperative EBRT alone^[16]. Other reported studies showed intraoperative radiation therapy (IORT) for extremity, retroperitoneal and truncal STS provided excellent local control, with limited acute toxicities^[15, 16, 18, 19, 21-26]. With the benefit of additional radiation therapy to focal high-risk areas while sparing surrounding structures, we hypothesized that use of IORT would decrease local recurrence rates and improve local disease control.

2 Methods

2.1 Data collection

Institutional Review Board approval was obtained and a retrospective review of all STS was performed. Our institution's cancer registry database was queried to identify patients for evaluation who had IORT at time of definitive surgery for STS. Patients were included if they underwent surgical resection and IORT treatments at our institution. Patients were excluded if they did not undergo IORT at time of resection or if they had uterine or genitourinary based sarcomas. Chart based review was performed for data collection.

2.2 Treatment

In general, it is our institutional practice to consider preoperative radiation for patients at high risk for local recurrence. This includes tumors that are large, high grade, or in close proximity to critical and/or unresectable structures. All patients with STS are discussed and treated by a multidisciplinary team with expertise in sarcoma. Postoperative EBRT is used when it is unclear if radiation was needed prior to resection positive margins. This includes tumors at different locations but also allows patients with extremity tumors an attempt for limb salvage. IORT was used as a boost to address specific areas at risk for close or different locations. In patients with recurrent extremity tumors, IORT was used with re-resection in attempt for limb salvage.

All patients were evaluated preoperatively at our institution by the performing surgeons and radiation oncologists. Treatment plans were formulated accordingly for resection, additional radiation with external beam and systemic therapy. The areas of concern for close or positive margins were identified. All patients were treated with IORT at the time of surgical resection. Margins were considered positive if tumor was present at the inked margin.

IORT HDR brachytherapy technique

High dose rate (HDR) brachytherapy using an Iridium192 source was delivered using Freiburg flaps and delivered in a specially designed and shielded operating room. The customized applicators were designed to treat the operative bed and areas of concern as defined intra-operatively by the surgeon and radiation oncologist. Treatment plans were generated on either Plato® Treatment planning system or Oncentra® Treatment planning system utilizing the standard geometry available for the Freiburg applicator. MicroSelectron® high dose rate (HDR) unit (model digital V3, Manufacturer Elekta Inc., Stockholm, Sweden) was used for dose delivery. The number of catheters, active dwell positions along each catheter, prescription depth, and dose prescription were defined. In the majority of the cases, prescription depth was 5 mm from the

surface of the flap (10 mm from the source center and 5 mm in tissue). Catheter dose points along all the active dwell positions at the prescription depth were defined. Dose point optimization was then carried out to ensure a uniform dose to all the dose points. The Freiburg flap and catheters were secured to the operative bed and normal surrounding tissues were shielded. Adjacent uninvolved normal tissues including ureters, nerves, vessels and skin were typically shielded with lead and held in place with retractors. The patient was monitored throughout treatment delivery. The flap and shielding were then removed and the remainder of the operative procedure completed.

Figure 1 shows HDR brachytherapy for a multiply recurrent well-differentiated right retroperitoneal liposarcoma, with areas of myxoid dedifferentiation. Recurrent tumor measured 4.3 cm × 4 cm × 3.3 cm and was located between the right external iliac vessels and bladder. Potentially close/microscopically margins were suspected at the right external iliac vessels. A customized Freiburg Flap was designed to treat the areas of concern overlying the surface of the vessels. Customized lead shielding was utilized to shield the bowel, bladder and ureter (wrapped in sterile impermeable draping and held in place with towels and retractors). These organs were displaced with retractors, shielded with lead shielding with wet lap packs. The skin surface was additionally shielded. A treatment plan was designed to treat 10 Gy to the surface of the Freiburg flap (5 mm from the source) using HDR brachytherapy using an Iridium 192 source.

Figure 1. HDR brachytherapy is used to treat a multiply recurrent well-differentiated right retroperitoneal liposarcoma, with areas of myxoid dedifferentiation. A customized Freiburg Flap was designed to treat the areas of concern overlying the surface of the vessels. Customized lead shielding was utilized to shield the bowel, bladder and ureter (wrapped in sterile impermeable draping and held in place with towels and retractors). These organs were displaced with retractors, shielded with lead shielding with wet lap packs. The skin surface was additionally shielded. A treatment plan was designed to treat 10 Gy to the surface of the Freiburg flap (5 mm from the source) using HDR brachytherapy using an Iridium 192 source.



2.3 Statistical analysis

Statistical analyses were conducted per tumor treatment. Summary statistics for the entire sample were reported as means, medians, and standard deviations for continuous variables; and as frequencies and relative frequencies for categorical variables. The patient and treatment characteristics calculated included: locations, margin status, recurrent disease, and complication status/grade when available and/or appropriate. The Clavien-Dindo Classification was used to score postoperative wound complications ^[27]. Comparisons of patient and treatment characteristics between groups were assessed using the Wilcoxon's and Chi-square or Fisher's exact tests for continuous and categorical variables, respectively.

The time-to-event outcomes were summarized for the overall sample and by group using the standard Kaplan-Meier methods. Outcomes evaluated included: local recurrence (time from surgery until local recurrence, death or last follow-up; LR), local recurrence free survival (time from surgery until local recurrence, death, or last follow-up; LRFS), disease specific survival (time from surgery until death with/from disease, death from other cause or last follow-up; DSS), disease

free survival (time from surgery until local/distant recurrence, death, or last follow-up; DFS), and distant disease free survival (time from surgery until distant recurrence, death, or last follow-up; DDFS). Comparisons of time-to-event outcomes between groups were assessed using the log-rank test.

All analyses were conducted in SAS v9.3 (Cary, NC) at a significance level of 0.05.

3 Results

3.1 Patient characteristics and prior treatment details

Twenty-four patients and 25 tumors were treated with IORT at time of resection (1 patient for 2 separate recurrences). Median age at time of treatment was 61 years (range 19-81, SD=15.8). Patient, tumor and prior treatment characteristics can be seen in Tables 1 and 2. All extremity tumors were deep and 1 (33%) truncal tumor was superficial. Most common subtypes included: 32% pleomorphic, 12% liposarcoma, and 12% myxofibrosarcoma. Prior treatment courses for the 7 patients with recurrent disease included prior definitive resections, 5 of which were performed at outside institutions. One patient received preoperative radiation, 1 received preoperative chemotherapy. One patient was treated with resection and IORT after recurring after resection and adjuvant radiation. The recurrence for this patient was local but not at the site of prior IORT. Prior adjuvant treatments included 3 tumors with radiation, 1 with chemotherapy, and 1 with chemotherapy and radiation.

Table 1. Overall Patient, Tumor and Treatment Characteristics

Variables	Character	N	%
Gender	Female	14	66
Tumor Status	Primary	17	72
	Recurrent	7	28
Location	Retroperitoneal	10	40
	Upper Extremity	3	27
	Lower Extremity	8	73
	Proximal Extremity	6	55
	Distal Extremity	5	45
	Trunk	3	12
Depth	Neck	1	4
	Superficial	1	4
Grade	Deep	24	96
	Low	4	16
Median Size (cm)	Intermediate	4	16
	High	17	68
History of RT	Extremity	6.5	
	Retroperitoneal	9.5	
	Trunk/Neck	9	
Prior Resection	Any	3	12
	Any	7	28
Adjuvant Tx After Prior Resection	Outside Institution	5	20
	Any	5	20
Neoadj Tx	Chemo	2	40
	RT	2	40
	Both	1	20
Neoadj Tx	EBRT Only (Median 50Gy)	13	52
	Chemo Only	1	4
	ChemoRT	1	4

Note. RT= radiation therapy, Tx= treatment, chemo= chemotherapy, Neoadj= neoadjuvant, EBRT= external beam radiation therapy, ChemoRT= chemoradiation

Table 2. Tumor Characteristics and Treatment Specifics

Tumor	Location	Age at Diagnosis (years)	Recurrent Tumor	Histology	Grade	Previous Surgery	Prior RT	Preop RT	Dose (Gy)
1	Anterior R lower leg	61	Yes	Myxofibrosarcoma	Interm	Yes	No	No	0
2	Anterior R lower leg, over tibia	61	Yes	Myxofibrosarcoma	Interm	Yes	Yes	No	0
3	Anterior L thigh	35	No	Pleomorphic leiomyosarcoma	High	No	No	Yes	50
4	Anteromedial R lower leg	78	No	Pleomorphic sarcoma	High	No	No	Yes	50
5	Medial gastrocnemius	61	No	Myxofibrosarcoma	Low	No	No	Yes	50
6	Anterolateral R leg	59	No	Myxoid liposarcoma	Interm	No	No	Yes	50
7	R pelvic sidewall	65	Yes	Epithelioid hemangioendothelioma	High	Yes	No	Yes	45
8	Anterior R thigh	65	No	Leiomyosarcoma	High	No	No	No	0
9	Proximal L thigh	80	No	Pleomorphic sarcoma	High	No	No	Yes	54
10	R paraspinal	48	Yes	Myxoid pleomorphic/leiomyosarcoma	High	Yes	No	No	0
11	Left retroperitoneal	60	No	Myxofibrosarcoma	Low	No	No	Yes	45
12	Left retroperitoneal	58	Yes	Myxoid NOS	High	Yes	No	Yes	53
13	L psoas	19	No	Alveolar soft part	High	No	No	Yes	50
14	L paraspinal thoracic	61	No	Monophasic synovial cell	High	No	No	No	0
15	R lateral breast	56	No	Pleomorphic spindle cell	High	No	Yes	No	0
16	L retroperitoneum	56	No	Pleomorphic leiomyosarcoma	High	No	No	No	0
17	L retroperitoneum	24	Yes	Periph nerve sheath	High	No	No	No	0
18	R retroperitoneum	57	No	Leiomyosarcoma	Interm	No	No	No	0
19	L upper posterior arm	50	No	Hemangiopericytoma	High	No	No	Yes	50
20	L axilla	60	No	Pleomorphic sarcoma	High	No	No	Yes	50
21	L retroperitoneum	23	No	Liposarcoma	Low	No	No	Yes	50
22	L posterior shoulder	49	Yes	Pleomorphic sarcoma	High	Yes	Yes	No	0
23	L retroperitoneum	73	No	Malignant fibrous histiocytoma	High	No	No	Yes	54
24	R cervical paraspinal region	77	No	Peripheral nerve sheath	High	No	No	No	0
25	L retroperitoneum	78	No	Hemangiopericytoma/clear cell	Low	No	No	No	0

Note. R= Right, L= Left, RT= Radiation, Gy= Gray

3.2 Treatment details

Sixty-four percent of tumors were treated with neoadjuvant treatment, 48% (n=12) with radiation and 8% chemotherapy (n=2) with 1 patient undergoing both. Median preoperative radiation dose was 50Gy (range 45-54). Preoperative chemotherapy included Mesna, Adriamycin, and Ifosfamide (MAI) in 2 patients and Gemcitabine and Docetaxel in one patient.

Sites of IORT treatment varied based on location of the tumor and adjacent at risk normal tissues and included 17 bone, 4 joint, 6 soft tissue, 2 neurovascular, 1 nerve and 1 pancreas. IORT treatment details, complications and recurrences can be seen in Table 3. One tumor was treated at 2 separate sites (iliofemoral vessels and hip joint). Median IORT dose was 12Gy (range 10-17.5), most often prescribed to a depth of 5 mm from the surface of the flap (range 0-7.5).

Table 3. IORT Treatment Details, Complications and Outcomes by Tumor

Tumor	Area of concern	Dose (Gy)	Prescribed tx. Depth (cm)	# Cath. Placed	# Cath. Used	Catheter Length (cm)	Defect Size	Adjacent Structures Shielded	Compl.	Compl. Grade	Compl. treatments	R1 Margin	Recurrence
1	Tibia	10	Surface	5	5	7	7×5	Skin, soft tissue	Blistering skin necrosis	1	Local wound care	No	Local
2	Tibia	10	Surface	7	6	7×5; 8×3	6×7	Skin, soft tissue	Drainage	1	Packing	No	N
3	Femur	10	Surface	1	1	7	NA	Skin, soft tissue	0	0	NA	No	Distant
4	Tibia	10	Surface	3	3	11	3×11	Skin, soft tissue	Wound dehiscence	3b	Debridement in OR	No	N
5	Fascia; Neuro-vascular	10	Surface	4	4	4 cm + 14 cm gap + 4 cm	4	Nerve	Dehiscence cellulitis	1	NA	Yes	N
6	Tibia	10	Surface	5	5	8, 10×3, 9	11×5		Necrosis, wound dehiscence, cellulitis	3b	OR for flap	No	N
7	Sacral Promontory	10	0.5	4	4	4 cm	4×4	Vascular graft, intra-abdominal organs, skin	0	0	NA	No	Distant
8	Femur	12.5	0.5	10	10	20 cm	20×10		0	0	NA	No	Distant
9	Ileofemoral Vessels; Hip Joint	10	0.5	5	5	6	5×7		Cellulitis	2	Readmitted for abx	No	Distant
10	Bony Spine	17.5	0.5	6	6	12	NA		0	0	NA	No	N
11	Pancreas	10	0.3	4	4	12 cm	NA		Cellulitis	1	Wound care	Yes	N
12	Bony Spine	15	0.5	8	8	18	8×18	Ligament of Treitz, aorta, iliac artery, etc	Cellulitis, Abscess, fistula	3b	Abx, OR for washout and colostomy	No	N
13	Bony Spine	12.5	0.5	3	3	10	9×3	Bowel, pancreas, spleen and skin	0	0	0	No	Distant
14	Bony Spine	15	0.5	8	8	6.5 cm×4, 12 cm×4	8×12 and 8×7	Dura, spinal cord, esophagus, aorta, pericardium, heart, soft tissue, skin	Chyle leak, cardiopulmonary instability	4b	OR Debridement /mesh removal, ligation thoracic duct	No	N
15	R Chest Wall, Axillary Vein	6.25	0.75	6	6	7 cm	6×7	NA	Erythema, joint pain	2	Abx, joint injections	No	Distant
16	L Pelvic Floor	12.5	0.5	10	10	16 cm	10×16	L kidney, ureter, distal femoral nerve, small bowel, and skin	Wound infection	2	Abx, wound care	No	Distant
17	Vertebral Foramina	7.5	0.5	6	6	16 cm	6×16	L kidney	Bilateral lower extremity weakness, incontinence	1	NA	Yes	N
18	Vertebral Body	12.5	0.5	7	7	9 cm	7×9	R kidney, duodenum, inferior vena cava, R iliac vessels, ureter, subcutaneous tissue	R leg weakness	1	NA	No	Distant

(Table 3 continued on page 31)

Table 3. (Continued.)

Tumor	Area of concern	Dose (Gy)	Prescribed tx. Depth (cm)	# Cath. Placed	# Cath. Used	Catheter Length (cm)	Defect Size	Adjacent Structures Shielded	Compl.	Compl. Grade	Compl. treatments	R1 Margin	Recurrence
19	Shoulder Joint Capsule	12.5	0.5	5	5	5 cm	5×5	Skin, humerus, adjacent nerves	Erythema	2	Abx	No	Distant
20	Glenohumeral Joint	15	0.5	7	7	4.5 cm	7×6	NA	Lymph-edema	1	NA	No	N
21	L Bony Spine, Retroperitoneum	10	0.5	5	5	4.5 cm	NA	NA	Ascites	3a	Paracentesis	Yes	N
22	Joint Capsule	12	0.5	6	6	5 cm	6×5	NA	0	0	NA	No	Local
23	Quadratus Lumborum/ L Hemidiaphragm Base	12	0.5	10	10	13	10×13	L retroperitoneum	0	0	NA	Yes	Distant
24	C2 Vertebra l Body	15	Surface	4	4	6cm *1, 8cm * 3	4×8	Trachea, esophagus	Fascial cellulitis	2	Readmission	No	N
25	Psoas, Ribs	12.5	Surface	11	11	21 [max]	NA	Small bowel, kidney		4a	Prolonged intubation	No	N

Post-resection tumor sites were closed primarily in 60%. Complex closures included 1 mesh for abdominal wall reconstruction, 6 advancement/rotational flaps, 2 advancement/rotational flaps in combination with a split-thickness skin graft, and 1 reconstruction with a prosthetic device (spine). Median estimated blood loss was 300ml (5-2000). When stratifying by location, we observed significant associations with estimated blood loss. Extremity sarcomas had a median of 30ml (5-300) versus retroperitoneal sarcomas with a median of 500ml (300-1700) of blood loss ($p<0.001$).

Margins were microscopically positive in 20% (n=5). No resections had macroscopically positive margins. Sites of margin positivity correlated with areas pre-operatively suspected to be at risk and included: pancreas, paraspinal/vertebral foramina, bony spine, left hemidiaphragm and fascial/neurovascular bundle of the lower extremity. Five patients had tumor within 2 mm of the inked margin. When stratifying for margin status, significant associations were observed with tumor grade, with low-grade tumors having higher positive margin status ($p=0.032$). Median intraoperative radiation dosing for negative resections margins was 12.5Gy versus 10Gy in patients with positive margins. When stratifying for positive margin status, no increases were found for either local or distant recurrences ($p= 1.00$ and 0.62 respectively). Lower extremities tumors received a median of 10.3Gy versus 13.1Gy for upper extremities ($p=0.013$). When stratifying for location with extremity versus retroperitoneal tumors, no significant differences were found for local or distant recurrences ($p=0.48$ versus 0.67 respectively) in this patient cohort.

3.3 Treatment results

Any postoperative morbidity occurred in 72%, but complications potentially attributable to IORT at the time of resection were infection (n=8), delayed wound healing (n=3), neuropathy (n=2), and GI fistula (n=1). High-grade complications occurred in 33.3%, for which 4 patients required reoperation and 5 required readmission. Perioperative mortality was 0%.

3.4 Adjuvant treatment

Five tumor sites received postoperative radiation at a median dose of 46Gy (45-50). Three tumors were treated postoperative with chemotherapy, one of which had radiation as well (Gemcitabine/Docetaxel in 2; unknown type in 1).

3.5 Follow up and survival

At a median follow-up of 20.1 months (range 2.7-96.4), 2-year LR free survival was 60.8%, distant metastasis free survival was 38.4% and disease specific survival was 84.0%.

Two year LRFS was 60.8%, distant metastasis free survival was 50.1%, and disease specific survival was 84.0% (see Table 4 and Figure 2 and 3). Overall median survival was 42.2 months and 70.5% at 2 years. Median DFS was 13.7 months and 28.9% at 2 years. No recurrences occurred at the site of IORT. Two tumors recurred within the prior resection fields as well as prior EBRT. One patient had a history of EBRT prior to resection and the other was treated with resection and IORT followed by EBRT but recurred locally (not at site of IORT). When stratified by local recurrence and complication status, no statistically significant associations were found.

Table 4. Two-year survivals for all patients treated with IORT at the time of resection

2 Year Survival	%
Local Recurrence Free	60.8
Distant Metastasis Free	38.4
Disease Free	28.9
Disease Specific	84.0
Overall	70.5

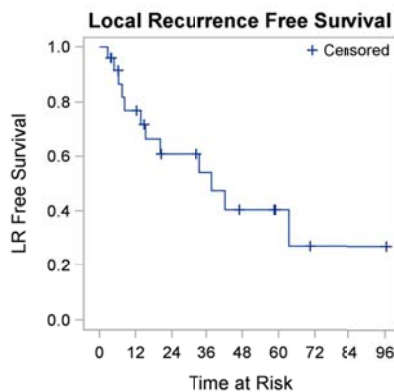


Figure 2. Local Recurrence Free for all Patients Treated with IORT in Months. LR= local recurrence.

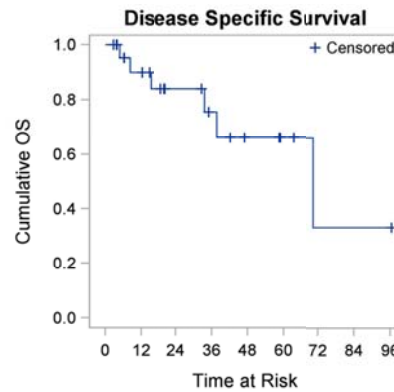


Figure 3. Disease Specific Survival for all Patients Treated with IORT in Months. OS= overall survival.

4 Discussion

In this study we showed that IORT is a safe addition to resection and peri-operative external beam radiation in patients at high risk for local recurrence. There were no recurrences at the site of IORT and our outcomes are comparable to prior literature. For retroperitoneal sarcomas (RPS), Stucky et al. showed a 5-year local recurrence rate of 22% in tumors treated with neoadjuvant RT followed by surgery and IORT, while Sindelar et al. showed an 8-year rate of 40% with surgery, IORT and adjuvant RT [15, 16]. While no retroperitoneal tumors recurred locoregionally in our study, longer follow-up would potentially capture recurrences given the median time to local recurrence in prior literature was approximately 21 months [16]. At a more comparable median follow-up of 20 months, Dzewirski et al. showed a LRFS of 51% for retroperitoneal sarcomas, although median time to recurrence was not described [19]. At 24 months, our LRFS was 61% for all tumors (55% for extremity and 70% for retroperitoneal). For extremity sarcomas, locoregional control ranged from 78% to 100%, comparable to our 81% (2 patients recurred locally) [18, 21, 22, 24-26]. When compared to data including only resection and EBRT, local control rates range from 66%-100% but have shown to be lower in tumors with positive margins, which includes 20% of our patients [2, 3, 9, 10, 28].

Surgical resection with negative margins and radiation therapy in appropriate patients remains the standard of care for local control but distant disease control continues to be a problem. These primary treatment modalities of surgical resection and radiation, EBRT and/ IORT when appropriate, are local therapies. At 2 years, our OS was 75% and DSS was 84%. While we were unable to determine predictors for increased local or distant recurrences, our patients were high risk for any recurrence since 84% of tumors were intermediate to high grade and all were high risk for positive margins.

These multiple high-risk features in our cohort placed them not only at high risk for local recurrence but also distant metastases. Of patients that developed recurrences, 83% were distant metastases. Prior literature show an OS rate of 55%-60% for RPS and a DFS rate of 43%-84% and OS rate of 52%-78% for extremity tumors [15, 17, 21, 22, 24, 29]. We found a lower DFS of 28.9%. While 3 (12%) patients were treated with neoadjuvant chemotherapy and 3 (12%) were treated with adjuvant therapy, no difference in distant metastasis occurrences were seen. Some literature does suggest perioperative systemic chemotherapy may improve disease control and even survival but further studies using all treatment modalities are needed to address distant disease control in high-risk patients [29-34].

The NCCN Guidelines Version 2.2014 recommends IORT boost doses of 10-12.5 Gy for microscopic disease and 15 Gy for gross residual disease for tumors of the extremities, head/neck, and retroperitoneum in general [12, 35]. There are different techniques via which IORT can be delivered, including HDR brachytherapy as used at our institution. We gave a median overall dose of 12 Gy intraoperatively. The choice of dose and depth for dose prescription was based on target site for treatment, risk for depth of invasion, concern of margin status, and normal adjacent tissues in the treatment field. Examples of dose variability for these reasons include an area adjacent to the bony spine treated to 17.5 Gy (prescribed to a depth from the flap of 5 mm), an area at risk near the axillary vein with concern for deep involvement treated to 6.25 Gy (prescribed to a treatment depth of 7.5 mm) and 7.5 Gy (depth of treatment 5 mm) at the vertebral foramina.

Our study had an overall 68% complication rate with a 16% rate of requiring reoperation, and no perioperative mortality. There may be multiple confounding factors contributing to this complication rate. Dziejwinski et al. reported a 21.5% reoperation rate after resection with IORT for RPS with adjuvant EBRT and there was one postoperative death [19]. Rachbauer et al., resulted no morbidity after intraoperative brachytherapy, but their 28% morbidity occurred after adjuvant EBRT where 21% required reoperation [22]. Ll acer et al., in a review of tumors involving the neurovascular bundle, reported a 28% acute morbidity where 12.7% of patients required reoperation and 44% suffered a late morbidity [23]. An increased risk of neuropathy (up to 60%) has also been shown for RPS with IORT [16]. In our study, 4 (16%) required reoperation and neuropathy occurred in 2 (8%) patients, both with RPS. Our overall wound complication rate was 32% and infections were our most common complication. Preoperative radiation has been shown to adversely affect wound healing [7, 36]. Fourteen patients (56%) had neoadjuvant radiation and 3 (12%) more, all presenting with locally recurrent tumors, had a history of prior radiation at the site of resection, likely attributing to an increased wound complication rate.

While future studies are necessary to address distant disease control and survival, IORT can be used to deliver a radiation boost during resection to areas at high risk for recurrence when critical structures preclude wide resection margins. Currently accruing is the German Clinical Phase I/II trial on neoadjuvant IMRT and IORT for retroperitoneal sarcomas [20]. Until further data is available, IORT at the time of resection can be an additional treatment modality in specialized STS centers to improve local tumor control without significantly increased complications.

5 Conclusion

IORT at the time of STS resection was effective in preventing LR at the treated site, despite multiple high risk features for recurrence. Further studies to improve outcomes including local control and DSS are needed.

Competing interests

We have nothing to disclose.

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