

Radiotherapy of Soft tissue sarcomas

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Historically, patients with localized soft tissue sarcomas (STS) of the extremities would undergo limb amputation. It was subsequently determined that the addition of radiation therapy (RT) delivered prior to (neoadjuvant) or after (adjuvant) a limb-sparing surgical resection yielded equivalent survival outcomes to amputation in appropriate patients.^{ty}

Soft-Tissue Sarcoma

Wound healing

Radioprotective Agents

1. Introduction

Soft tissue sarcomas (STS) are a relatively rare group of malignancies with multiple histological subtypes ^[1]. The majority of STS originate from the extremities (46% lower, 13% upper) ^{[2][3][4][5][6][7][8][9][10][11][12][13][14][15][16][17][18][19][20][21][22][23][24][25][26][27][28][29][30][31][32][33][34][35][36][37][38][39][40][41][42][43]}, but may arise in any region including the torso/trunk (18%) ^{[21][35][39][44]}, retroperitoneum (13%) ^{[45][46][47][48][49][50]}, or head and neck (9%) ^{[51][52]}. Because STS commonly presents as a painless enlarging mass, diagnosis is often delayed until tumors become large in volume, often abutting critical nerves and vessels ^[53].

STS can be locally infiltrative with microscopic tumor deposits extending up to 4 cm beyond the primary tumor ^{[28][54]}, limiting the ability of surgeons to preserve limbs without risking microscopic residual disease or positive margins. Amputation was therefore the primary treatment modality for STS of the extremities until limb-sparing surgeries combined with radiotherapy (RT) showed similar outcomes ^[55]. Randomized prospective trials and retrospective studies demonstrated similar local control and overall survival rates between limb-sparing surgery combined with RT compared to amputation ^{[43][56]}, as well as the importance of including RT for successful limb-sparing resection ^{[4][57]}. The addition of RT is thought to eliminate microscopic residual tumor cells located around the gross tumor. Any additional RT after resection is based on the patients risk for local recurrence.

Modern limb-sparing surgery aims to achieve similar local tumor control and survival outcomes compared to amputation, while preserving as much long-term limb function as possible. While RT improves survival and local control outcomes, it also increases the risks of acute sequelae including acute wound complications and radiation dermatitis ^{[30][36][51][58][59]}, as well as late toxicities of fibrosis, necrosis, edema, pathologic fractures, and long term decrease in limb function ^{[11][30][36][51][52][58][59]}.

RT in STS can be delivered pre-operatively (neoadjuvant), intraoperatively (IORT), or post-operatively (adjuvant) via external beam RT (EBRT) or with brachytherapy (BT) using radioactive isotopes. While the choice of neoadjuvant vs. adjuvant radiotherapy is always considered on an individualized patient basis, most studies have demonstrated equivalent disease control, but significant differences in toxicity profiles between these two approaches. In general, neoadjuvant RT is associated with more acute wound complications [51][58] while adjuvant RT is associated with higher rates of late toxicities and decreased limb function [52][58]. Current guidelines slightly favor neoadjuvant RT because of reduced radiation dose and reduced radiation volumes thereby reducing the cumulative exposure of normal tissues to RT.

2. Radiotherapy in Soft Tissue Sarcoma (STS)

The discovery of similar local control and overall survival outcomes between amputation and limb-sparing surgery combined with RT have led to this approach becoming the standard of care for STS of the extremity [60]. Since the initial introduction of RT, there have been tremendous advancements in image guidance, radiation delivery techniques/modalities, and clinical regimens for combining radiation with surgery and/or chemotherapy. We will examine radiotherapy in STS by radiation modality, clinical regimen (neoadjuvant vs. adjuvant), and anatomic disease site with associated toxicity outcomes.

2.1. Radiotherapy Modalities

While 3D Conformal Radiation Therapy (3D-CRT) is the more traditional method of planning External Beam Radiation Therapy (EBRT) treatments, for many tumors Intensity Modulated Radiation Therapy (IMRT) provides the best dose conformity to the target area while reducing toxicity to normal structures [30][36][45][48]. Brachytherapy (BT) utilizes radioactive isotopes to deliver RT from within the target volume, while Intraoperative radiotherapy (IORT) refers to the delivery of dose at the time of surgery (which can be achieved via either brachytherapy or linear accelerators).

2.1.1. External Beam Radiation Therapy (EBRT)

Target coverage and protection of normal tissues appear to be superior for IMRT compared with 3D-CRT in STS of the extremity [17][60] and the retroperitoneum [45][48]. Retrospective studies have demonstrated that patients treated with IMRT have lower rates of local recurrence compared with 3D-CRT (7.6% IMRT vs. 15.1% 3D-CRT; $p = 0.02$) [19][36][61] or BT (8% IMRT vs. 19% BT; $p = 0.04$) [24]. Though there has never been a prospective trial randomizing patients to IMRT vs. either 3D-CRT or BT, IMRT has been associated with lower rates of wound complications compared with historical 3D-CRT results (30.5 vs. 43%, respectively) [11][30], but higher rates compared with BT (19% IMRT vs. 11% BT) [24] though neither of these results were statistically significant. IMRT has some evidence of lower rates of femoral fracture [62].

2.1.2. Brachytherapy (BT)

Brachytherapy can be used for Intraoperative Radiotherapy (IORT; discussed next section) [46][63][64] or to deliver adjuvant radiation for low-risk/re-irradiation cases as a monotherapy [5][57], or as a boost in combination with EBRT for high-risk cases, or in cases in which the target volume cannot easily be covered by BT alone [5][65]. Brachytherapy can also shorten total treatment time for patients (e.g., 4–5 days for 45 Gy via LDR brachytherapy vs. 5–6 weeks for IMRT) [66][67].

In one of the few prospective trials with randomization with respect to radiation, adjuvant BT monotherapy improved 5-year local control for patients with high-grade STS of the extremities or superficial trunk as compared with no BT (89% BT vs. 66% no BT) [57]. However, at least one analysis of a prospective trial (not randomized with respect to radiation modalities), demonstrated an inferior 5-year local control for BT monotherapy as compared with IMRT (81% BT vs. 92% IMRT, $p = 0.04$), with a non-significant difference in 5-year overall survival (73% BT vs. 62% IMRT, $p = 0.1$) [24]. Other retrospective studies have shown mixed results when comparing EBRT vs. BT vs. EBRT + BT boost [5][6][68].

One retrospective study of adjuvant LDR BT monotherapy had lower rates of wound complications compared with historical EBRT results with 5-year actuarial rates of wound complications requiring reoperation, bone fracture, and grade ≥ 3 nerve damage of 12, 3, and 5%, respectively [6] with similar findings in studies of HDR-BT [69]. One study evaluating HDR-BT monotherapy vs. EBRT vs. EBRT + HDR-BT boost noted higher incidents of seroma/hematoma and deep infection in BT cohorts, whereas EBRT cohorts had greater incidents of chronic edema, fibrosis, and radiation dermatitis [70].

When BT is used as a boost to EBRT, one non-randomized study demonstrated National Cancer Institute (NCI) grade 2–4 wound healing complications of 40 and 18% for LDR and HDR brachytherapy, respectively (though this was not significant at $p = 0.14$). In this study, complications with LDR were correlated with suboptimal implant geometry, while for HDR they were correlated with dose per fraction, total dose, and total biological equivalent dose [65]. Other studies of HDR-BT combined with EBRT have confirmed similar rates of acute and late toxicity [71], with the volume of tissue receiving $>150\%$ of the prescription dose being a possible predictor of toxicity, especially in the lower extremities [72].

2.1.3. Intraoperative Radiotherapy (IORT)

Intraoperative RT (IORT) delivered via brachytherapy [24,46,64] or via an electron beam using specialized linear accelerators [15][34][41][73][74] is almost always combined with EBRT as a means of boosting especially high-risk volumes in the extremity [15][16][33][34][41][73] or retroperitoneum [74][75][76][77][78]. IORT allows for moving at-risk tissues away from the radiation field or blocking off organs at risk using lead shields. IORT requires smaller treatment volumes and a lower total dose (~10–20 Gy) but in a higher dose per fraction.

IORT in combination with EBRT provides excellent local control in STS of the extremities [15][16][33][34][41][56][73][79] and the retroperitoneum [46][74][75][76][77][78] with high rates of good functional outcomes and limb preservation. As IORT is almost always paired with some form of EBRT it is difficult to assess which toxicities can be attributed to IORT as opposed to EBRT. Moderate to severe acute toxicities (mostly radiation dermatitis) have ranged from 1–

24% [15][34][41] with acute wound complications, including the need for revision surgery, ranging from 5–36% [34][78][80][81]. One study noted that the rate of wound complications varied significantly based on whether IORT was paired with neoadjuvant vs. adjuvant EBRT (36 vs. 15%, respectively) [80]. Late toxicities including fractures, neuropathy, and fibrosis, ranged from 10–20% on long term follow up [15][34][41][78][81] with one study noting that a rate of 12% for all grades of neuropathy, which increased to 25% in patients who had a major nerve passing through the high dose IORT field [81].

2.2. Clinical Regimen-Neoadjuvant, Adjuvant, and Combined Modality Radiotherapy

2.2.1. Neoadjuvant Radiotherapy

A typical regimen of neoadjuvant RT in STS consists of 50 Gy delivered in 1.8–2.0 Gy once-daily fractions over 5–6 weeks [82], providing a lower cumulative dose and smaller treatment fields, which are achieved by better target delineation and image guidance [37]. Other aims of neoadjuvant RT include sterilization of microscopic disease on the edge of the tumor and induction of a pseudocapsule around the primary tumor to aid in obtaining negative margins during resection [83][84][85]. Pseudocapsule generation may also allow for preservation of critical structures, improved post-operative functional status, and decreased risk of seeding during resection.

Despite several advantages of neoadjuvant RT, a higher risk of postoperative wound complications remains a substantial challenge. Several studies have reported higher rates of wound complications in neoadjuvant radiotherapy [51][58][86][87], but lower rates of chronic side effects including edema, fibrosis, fracture, and joint stiffness compared with adjuvant RT [11][52][58][88] (Table 1). One study comparing neoadjuvant (50 Gy/25 fractions) to adjuvant RT (66 Gy/33 fractions) demonstrated higher incidence of major wound complications (35 vs. 17% respectively) [58]. The time from completion of neoadjuvant RT to surgery may also influence the rate of acute wound complications with one study suggesting 3-6 weeks as optimal [38] while longer delays may lead to late radiation fibrosis and increased surgical complications [82].

Table 1. Comparison of neoadjuvant vs. adjuvant acute and late wound complication in soft tissue sarcoma.

Reference	Disease Site	RT Course (# Patients)	Acute/Late Toxicity	Measure	Neoadjuvant (%)	Adjuvant (%)	Significance
Pollack et al., 1998 [51]	MFH, synovial, and liposarcoma	Neoadjuvant 50Gy/25fx (n = 128), Adjuvant 60-66Gy/30–33fx (n = 165)	Acute	Wound complications	25%	6% *	p < 0.001
			Late	5-, 10-, and 15-year actuarial incidence	6, 7, and 7% respectively (Neoadjuvant & Adjuvant)		NS
O’Sullivan et al., 2002 [58]	Upper & Lower Extremities	Neoadjuvant 50Gy/25fx (n = 88),	Acute	Skin toxicity grade ≥2	36%	68% *	p < 0.0001

Reference	Disease Site	RT Course (# Patients)	Acute/ Late Toxicity	Measure	Neoadjuvant (%)	Adjuvant (%)	Significance
		Adjuvant 66Gy/33fx (<i>n</i> = 94)	Late	Wound complications	35%	17% *	<i>p</i> = 0.01
				MSTS (mean, scale 0–35)	21	25 *	<i>p</i> = 0.01
				TESS (mean, scale 0–100)	60	69 *	<i>p</i> = 0.01
				SF-36 bodily pain (mean, scale 0–100)	58	67 *	<i>p</i> = 0.03
Zagars et al., 2003 [52]	Head & Neck, Trunk, and Extremities	Neoadjuvant 50Gy (<i>n</i> = 271), Adjuvant 60Gy (<i>n</i> = 246)(1.8–2.0Gy/fx)	Late	10-year actuarial complication incidence	5%	9% *	<i>p</i> = 0.03
				Necrosis, fractures, edema, or fibrosis	4%	8.9%	NR
				Subcutaneous fibrosis	31.5%	48.2%	NS
Davis et al., 2005 [11]	Upper & Lower Extremities	Neoadjuvant 50Gy/25fx (<i>n</i> = 73), Adjuvant 66Gy/33fx (<i>n</i> = 56)	Late	Joint stiffness	17.8%	23.2%	NS
				Edema	15.1%	23.2%	NS
				TESS (mean, scale 0–100)	85.1	81.3	NS
				MSTS (mean, scale 0–35)	29.9	28.0	NS
O'Sullivan et al., 2013 [30]	Lower Extremities	Neoadjuvant 50Gy/25fx (<i>n</i> = 59), Compared to historical control of neoadjuvant from Davis et al., 2005 [11]	Acute		O'Sullivan 2013	Davis et al., 2005	
				Secondary operation	33%	43%	NS
				Seroma/hematoma drainage	8.4%	NR	
				Infection requiring debridement	5.0%	NR	
				Dressing changes/deep	6.7%	NR	

Reference	Disease Site	RT Course (# Patients)	Acute/ Late Toxicity	Measure	Neoadjuvant (%)	Adjuvant (%)	Significance
Folkert et al., 2014 [36]	Upper & Lower Extremities	Neoadjuvant 50Gy median (n = 39), Adjuvant 63Gy median (n = 280)	Late	packing. 4 months post-surgery			
				Total wound complications	30.5%	43%	NS
				Edema	11.1%	15.1%	NR
				Skin Toxicity	1.9%	NR	
				Subcutaneous fibrosis	9.3%	31.5%	NR
				Fracture	0%	NR	
				Joint Stiffness	5.6%	17.8%	NR
				TESS (mean, scale 0–100)	83.1	85.1	NR
				MSTS-87 (mean, scale 0–35)	31.5	29.9	NR
				MSTS-93 (mean, scale 0–100)	89.3	NR	
			Acute	Wound complications	17.5%	18.8%	NS
				Radiation dermatitis	48.7%	31.5%	p = 0.002
				Fracture	9.1%	4.8%	NS
				Joint stiffness	11.0%	14.5%	NS
Muller et al. 2016 [59]	Upper & Lower Extremities	Neoadjuvant 59Gy mean (n = 89), Adjuvant 71Gy mean (n = 365)	Late	Edema	14.9%	7.9% *	p = 0.05
				Nerve damage	1.6%	3.5%	NS
				Total	36.6% [4] [82]	30.7%	NR

fibrosis (48.2% vs. 31.5%), edema (23.2% vs. 15.1%) and fracture (23.2% vs. 17.8%) in adjuvant RT compared with neoadjuvant RT, respectively (all, $p < 0.05$) [11]. These late-stage complications may be related to increased total radiation dose (50 Gy in neoadjuvant vs. 60–66 Gy adjuvant) and larger treatment fields necessitated by surgical resection [52]. Most clinical studies regarding the timing of surgery and RT in STS use local control and

Abbreviations: a summary of significant but few studies have attempted to explain the mechanism of RT-induced histiocytosis in STS or wound-healing in STS. [11][39][36][51][52][58][59]
 Histocytosis in STS or wound-healing in STS. [11][39][36][51][52][58][59]
 Reported, NS = Not Significant, SF = Short Form, & TESS = Toronto Extremity Salvage Score.

2.2.3. Intraoperative and Adjuvant Boosts

Radiation field boosts in STS are generally delivered to smaller volumes consider to be at higher risk for recurrence. Whether EBRT is delivered neoadjuvant or adjuvantly, the boost may be delivered via IORT, adjuvant brachytherapy, or additional EBRT fractions. Recommended boost RT doses vary following neoadjuvant RT, and are determined by RT modality and surgical margin status (16–18 Gy for microscopically positive and 20–26 Gy for grossly positive margins when using an EBRT boost; 16–26 Gy LDR or 14–24 Gy HDR for brachytherapy boost; and typically 10–12.5 Gy for microscopically positive, and ~15 Gy for grossly positive margins for an IORT boost) [16][66].

If there is an indication for RT boost prior to or during surgery, IORT may be delivered (~10–16 Gy) or catheters placed for an adjuvant BT boost (~16–20 Gy LDR or HDR equivalent for positive margins). If an IORT or BT boost were delivered, post-operative EBRT would usually be initiated 3–8 weeks after surgery. An alternative to BT or IORT boost following neoadjuvant RT is to boost tissues via EBRT (10–16 Gy delivered over 5 to 8 fractions) in the post-op setting. However, some studies demonstrated no local control benefit of an adjuvant boost for positive surgical margins [89][90].

2.3. Anatomic Disease Site

STS are classified into different staging groups by the American Joint Committee on Cancer (AJCC) 8th edition into categories of “Head and Neck”, “Trunk and Extremities”, “Abdomen and Thoracic Visceral Organs”, and “Retroperitoneum”, while the National Comprehensive Cancer Network (NCCN) guidelines split STS anatomically into groups of ‘Extremity/Body wall/Head and Neck’ and “Retroperitoneal/Intraabdominal”, with Rhabdomyosarcoma, Desmoid, and Gastrointestinal Stromal Tumors being treated as separate entities.

2.3.1. Extremity, Head and Neck, and Superficial Trunk

In AJCC stage IA-IB, low-grade disease-RT is typically reserved for cases in which appropriate margins were not achieved during surgery, though re-resection (if feasible) or observation (for IA) are also management options. In patients with resectable, stage II-III disease, which would be likely to have acceptable functional outcomes after surgery-RT can be delivered neoadjuvantly or adjuvantly, possibly with chemotherapy for stage III disease. Chemotherapy is not the standard of care in STS. There is currently no Category 1 evidence to suggest an overall survival benefit by treating STS patients with chemotherapy alone or in combination with RT in the non-metastatic, locally advanced setting. However, chemotherapy has been employed in select patients and can be considered in unresectable stage II-III disease or cases in which acceptable functional outcomes would not be expected after surgery. Management options in these cases include RT, chemotherapy, chemoradiation, or amputation (extremity). Once the patient receives RT and/or chemotherapy, they can then be re-evaluated to assess whether they have become a suitable candidate for surgery.

In general, there are studies that are specific to STS of the extremities [40][41][42][43], but most that include STS of the Head and Neck or Trunk/Torso/Body wall are combined with extremity STS cases [51][52][91][92][93]. There are indications that extremity STS (especially lower extremities) have higher rates of wound complications as well as unique considerations/options involving amputation vs. limb preservation. Additionally, certain RT modalities are used more or less frequently based on anatomic location (e.g., the use of IORT is relatively common in the retroperitoneum, whereas adjuvant BT in the upper abdomen is not recommended) [66].

2.3.2. Retroperitoneal/Intra-Abdominal

For retroperitoneal STS, adjuvant RT is typically not administered for patients that have negative or microscopically positive margins unless local recurrence would cause significant morbidity [50]. If a patient underwent neoadjuvant RT and ultimately had microscopically positive margins, a 10–16 Gy boost may be considered per current NCCN guidelines [94]. Studies typically separate retroperitoneal STS from those of the Superficial Trunk/Head and Neck/Extremities, with or without “Intra-abdominal” or “Visceral Organ” STSs included.

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