Radiotherapy of Soft tissue sarcomas

Subjects: Oncology

Contributor: Cameron Callaghan

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.

Keywords: 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), Adjuvant 66Gy/33fx (*n* = 94)	Acute	Skin toxicity grade ≥2	36%	68% *	*p* < 0.0001
				Wound complications	35%	17% *	*p* = 0.01
			Late	MSTS (mean, scale 0–35)	21	25 *	*p* = 0.01
				TESS (mean, scale 0–100)	60	69 *	*p* = 0.01
Zagars et al., 2003 [52]	Head & Neck, Trunk, and Extremities	Neoadjuvant 50Gy (*n* = 271), Adjuvant 60Gy (*n* = 246)(1.8–2.0Gy/fx)	Late	SF-36 bodily pain (mean, scale 0–100)	58	67 *	*p* = 0.03
				10-year actuarial complication incidence	5%	9% *	*p* = 0.03
				Necrosis, fractures, edema, or fibrosis	4%	8.9%	NR
Davis et al., 2005 [11]	Upper & Lower Extremities	Neoadjuvant 50Gy/25fx (*n* = 73), Adjuvant 66Gy/33fx (*n* = 56)	Late	Subcutaneous fibrosis	31.5%	48.2%	NS
				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

Reference	Disease Site	RT Course (# Patients)	Acute/ Late Toxicity	Measure	Neoadjuvant (%)	Adjuvant (%)	Significance
					O'Sullivan 2013	Davis et al., 2005	
O'Sullivan et al., 2013 [30]	Lower Extremities	Neoadjuvant 50Gy/25fx (*n* = 59), Compared to historical control of neoadjuvant from Davis et al., 2005 [11]	Acute	Secondary operation	33%	43%	NS
				Seroma/hematoma drainage	8.4%	NR	
				Infection requiring debridement	5.0%	NR	
				Dressing changes/deep packing. 4 months post-surgery	6.7%	NR	
				Total wound complications	30.5%	43%	NS
			Late	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	
Folkert et al., 2014 [36]	Upper & Lower Extremities	Neoadjuvant 50Gy median (*n* = 39), Adjuvant 63Gy median (*n* = 280)	Acute	Wound complications	17.5%	18.8%	NS
				Radiation dermatitis	48.7%	31.5%	*p* = 0.002
			Late	Fracture	9.1%	4.8%	NS
				Joint stiffness	11.0%	14.5%	NS
				Edema	14.9%	7.9% *	*p* = 0.05
				Nerve damage	1.6%	3.5%	NS
				Total	36.6%	30.7%	NR
Muller et al. 2016 [59]	Upper & Lower Extremities	Neoadjuvant 59Gy mean (*n* = 89), Adjuvant 71Gy mean (*n* = 365)	Acute	Surgical revision	9.0%	4.4%	NS
			Late	Wound necrosis, pathologic fractures, etc.	11.2%	15.2%	NS

Abbreviations: #= number, * = Significance at $p < 0.05$, fx = fractions, Gy = Gray, MFH = Malignant Fibrous Histiocytoma, MSTS = Musculoskeletal Tumor Society Rating Scale (with updates -87 and -93), NR = Not Reported, NS = Not Significant, SF = Short Form, & TESS = Toronto Extremity Salvage Score.

2.2.2. Adjuvant Radiotherapy

Adjuvant RT is typically delivered via EBRT to a total dose of 60–66 Gy in 1.8–2 Gy fractions usually 2–4 months after surgical resection to eliminate microscopic residual disease [4][82] but can also be delivered via brachytherapy as discussed in the above section [57]. Compared with neoadjuvant RT, adjuvant radiation allows for better staging of tumor grade and appropriate surgical margins to be achieved without any impact of prior RT on tumor [13]. Additionally, adjuvant RT has reduced the incidence of acute wound complications which require additional surgical procedures [30][31][58][59].

Several studies have confirmed lower acute radiation toxicity in the adjuvant setting (Table 1). In a prospective, randomized trial, Davis et al. showed a significantly higher incidence of 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 wound morbidity as primary endpoints, but few studies have attempted to explain the mechanism of RT-induced normal tissue injury or wound complications in STS [11][30][36][51][52][58][59].

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.

References

1. Wang, D.; Abrams, R.A. Radiotherapy for Soft Tissue Sarcoma: 50 Years of Change and Improvement. Am. Soc. Clin. Oncol. Educ. Book 2014, 34, 244–251, doi:10.14694/edbook_am.2014.34.244.
2. Stinson, S.F.; Delaney, T.F.; Greenberg, J.; Yang, J.C.; Lampert, M.H.; Hicks, J.E.; Venzon, D.; White, D.E.; Rosenberg, S.A.; Glatstein, E.J. Acute and long-term effects on limb function of combined modality limb sparing therapy for extremity soft tissue sarcoma. Int. J. Radiat. Oncol. 1991, 21, 1493–1499, doi:10.1016/0360-3016(91)90324-w.
3. Wilson, A.; Davis, A.; Bell, R.; O'Sullivan, B.; Catton, C.; Madadi, F.; Kandel, R.; Fornasier, V. Local control of soft tissue sarcoma of the extremity: The experience of a multidisciplinary sarcoma group with definitive surgery and radiotherapy. Eur. J. Cancer 1994, 30, 746–751, doi:10.1016/0959-8049(94)90286-0.
4. Yang, J.C.; E Chang, A.; Baker, A.R.; Sindelar, W.F.; Danforth, D.N.; Topalian, S.L.; Delaney, T.; Glatstein, E.; Steinberg, S.M.; Merino, M.J.; et al. Randomized prospective study of the benefit of adjuvant radiation therapy in the treatment of soft tissue sarcomas of the extremity. J. Clin. Oncol. 1998, 16, 197–203, doi:10.1200/jco.1998.16.1.197.
5. Alektiar, K.; Velasco, J.; Zelefsky, M.J.; Woodruff, J.; Lewis, J.; Brennan, M.F. Adjuvant radiotherapy for margin-positive high-grade soft tissue sarcoma of the extremity. Int. J. Radiat. Oncol. 2000, 48, 1051–1058, doi:10.1016/s0360-3016(00)00753-7.
6. Alektiar, K.M.; Leung, D.H.Y.; Zelefsky, M.J.; Healey, J.H.; Brennan, M.F. Adjuvant brachytherapy for primary high-grade soft tissue sarcoma of the extremity. Ann. Surg. Oncol. 2002, 9, 48–56, doi:10.1245/aso.2002.9.1.48.
7. Davis, A.; O'Sullivan, B.; Bell, R.; Turcotte, R.; Catton, C.; Wunder, J.; Chabot, P.; Hammond, A.; Benk, V.; Isler, M.; et al. Function and Health Status Outcomes in a Randomized Trial Comparing Preoperative and Postoperative Radiotherapy in Extremity Soft Tissue Sarcoma. J. Clin. Oncol. 2002, 20, 4472–4477, doi:10.1200/jco.2002.03.084.
8. Edmonson, J.H.; Petersen, I.A.; Shives, T.C.; Mahoney, M.R.; Rock, M.G.; Haddock, M.G.; Sim, F.H.; Maples, W.J.; O'Connor, M.I.; Gunderson, L.L.; et al. Chemotherapy, irradiation, and surgery for function-preserving therapy of primary extremity soft tissue sarcomas: initial treatment with ifosfamide, mitomycin, doxorubicin, and cisplatin plus granulocyte macrophage-colony-stimulating factor. Cancer 2002, 94, 786–792.
9. Delaney, T.F.; Spiro, I.J.; Suit, H.D.; Gebhardt, M.C.; Hornicek, F.J.; Mankin, H.J.; Rosenberg, A.L.; I Rosenthal, D.; Miryousefi, F.; Ancukiewicz, M.; et al. Neoadjuvant chemotherapy and radiotherapy for large extremity soft-tissue sarcomas. Int. J. Radiat. Oncol. 2003, 56, 1117–1127, doi:10.1016/s0360-3016(03)00186-x.
10. O'Sullivan, B. Five-year results of a randomized phase III trial of pre-operative versus postoperative radiotherapy in extremity soft tissue sarcoma. J. Clin. Oncol. 2004, 22 (Suppl. 14), 9007.
11. Davis, A.; O'Sullivan, B.; Turcotte, R.; Bell, R.; Catton, C.; Chabot, P.; Wunder, J.; Hammond, A.; Benk, V.; Kandel, R. Late radiation morbidity following randomization to preoperative versus postoperative radiotherapy in extremity soft tissue sarcoma. Radiother. Oncol. 2005, 75, 48–53, doi:10.1016/j.radonc.2004.12.020.
12. Holt, G.E.; Griffin, A.M.; Pintilie, M.; Wunder, J.S.; Catton, C.; O'Sullivan, B.; Bell, R.S.; Fractures following radiotherapy and limb-salvage surgery for lower extremity soft-tissue sarcomas. A comparison of high-dose and low-dose radiotherapy. J. Bone. Jt. Surg. Am. 2005, 87, 315–319.
13. Wolfson, A.H. Preoperative vs postoperative radiation therapy for extremity soft tissue sarcoma: controversy and present management. Curr. Opin. Oncol. 2005, 17, 357–360, doi:10.1097/01.cco.0000161745.24887.82.
14. Cannon, C.P.; Ballo, M.T.; Zagars, G.K.; Mirza, A.N.; Lin, P.P.; Lewis, V.O.; Yasko, A.W.; Benjamin, R.S.; Pisters, P.W. Complications of combined modality treatment of primary lower extremity soft-tissue sarcomas. Cancer 2006, 107, 2455–2461, doi:10.1002/cncr.22298.
15. Oertel, S.; Treiber, M.; Zahlten-Hinguranage, A.; Eichin, S.; Roeder, F.; Funk, A.; Hensley, F.W.; Timke, C.; Niethammer, A.G.; Huber, P.E.; et al. Intraoperative electron boost radiation followed by moderate doses of external beam radiotherapy in limb-sparing treatment of patients with extremity soft-tissue sarcoma. Int. J. Radiat. Oncol. 2006, 64, 1416–1423, doi:10.1016/j.ijrobp.2005.10.009.
16. Tran, Q.N.H.; Kim, A.C.; Gottschalk, A.R.; Wara, W.M.; Phillips, T.L.; O'Donnell, R.J.; Weinberg, V.; Haas-Kogan, D.A. Clinical Outcomes of Intraoperative Radiation Therapy for Extremity Sarcomas. Sarcoma 2006, 2006, 1–6, doi:10.1155/SRCM/2006/91671.
17. Griffin, A.M.; Euler, C.I.; Sharpe, M.B.; Ferguson, P.C.; Wunder, J.S.; Bell, R.S.; Chung, P.W.M.; Catton, C.N.; O'Sullivan, B. Radiation planning comparison for superficial tissue avoidance in radiotherapy for soft tissue sarcoma of the lower extremity. Int. J. Radiat. Oncol. 2007, 67, 847–856, doi:10.1016/j.ijrobp.2006.09.048.
18. Temple, C.; Ross, D.; Magi, E.; DiFrancesco, L.; Kurien, E.; Temple, W. Preoperative chemoradiation and flap reconstruction provide high local control and low wound complication rates for patients undergoing limb salvage surgery for upper extremity tumors. J. Surg. Oncol. 2007, 95, 135–141, doi:10.1002/jso.20629.

19. Alektiar, K.M.; Brennan, M.F.; Healey, J.H.; Singer, S. Impact of Intensity-Modulated Radiation Therapy on Local Control in Primary Soft-Tissue Sarcoma of the Extremity. J. Clin. Oncol. 2008, 26, 3440–3444, doi:10.1200/jco.2008.16.6249.

20. Cahlon, O.; Spierer, M.; Brennan, M.F.; Singer, S.; Alektiar, K.M. Long-term outcomes in extremity soft tissue sarcoma after a pathologically negative re-resection and without radiotherapy. Cancer 2008, 112, 2774–2779, doi:10.1002/cncr.23493.

21. Jebsen, N.L.; Trovik, C.S.; Bauer, H.C.; Rydholm, A.; Monge, O.R.; Hall, K.S.; Alvegård, T.; Bruland, Øyvind S. Radiotherapy to Improve Local Control Regardless of Surgical Margin and Malignancy Grade in Extremity and Trunk Wall Soft Tissue Sarcoma: A Scandinavian Sarcoma Group Study. Int. J. Radiat. Oncol. 2008, 71, 1196–1203, doi:10.1016/j.ijrobp.2007.11.023.

22. Dickie, C.I.; Parent, A.; Griffin, A.M.; Fung, S.; Chung, P.W.M.; Catton, C.; Ferguson, P.C.; Wunder, J.S.; Bell, R.S.; Sharpe, M.B.; et al. Bone Fractures Following External Beam Radiotherapy and Limb-Preservation Surgery for Lower Extremity Soft Tissue Sarcoma: Relationship to Irradiated Bone Length, Volume, Tumor Location and Dose. Int. J. Radiat. Oncol. 2009, 75, 1119–1124, doi:10.1016/j.ijrobp.2008.12.006.

23. Kim, B.; Chen, Y.-L.; Kirsch, D.G.; Goldberg, S.I.; Kobayashi, W.; Kung, J.H.; Wolfgang, J.A.; Doppke, K.; E Rosenberg, A.; Nielsen, G.P.; et al. An Effective Preoperative Three-Dimensional Radiotherapy Target Volume for Extremity Soft Tissue Sarcoma and the Effect of Margin Width on Local Control. Int. J. Radiat. Oncol. 2010, 77, 843–850, doi:10.1016/j.ijrobp.2009.06.086.

24. Alektiar, K.M.; Brennan, M.F.; Singer, S. Local control comparison of adjuvant brachytherapy to intensity-modulated radiotherapy in primary high-grade sarcoma of the extremity. Cancer 2011, 117, 3229–3234, doi:10.1002/cncr.25882.

25. Wang, D.; Bosch, W.; Roberge, D.; Finkelstein, S.E.; Petersen, I.; Haddock, M.; Chen, Y.-L.E.; Saito, N.G.; Kirsch, D.G.; Hitchcock, Y.J.; et al. RTOG Sarcoma Radiation Oncologists Reach Consensus on Gross Tumor Volume and Clinical Target Volume on Computed Tomographic Images for Preoperative Radiotherapy of Primary Soft Tissue Sarcoma of Extremity in Radiation Therapy Oncology Group Studies. Int. J. Radiat. Oncol. 2011, 81, e525–e528, doi:10.1016/j.ijrobp.2011.04.038.

26. Haas, R.L.M.; Delaney, T.F.; O'Sullivan, B.; Keus, R.B.; Le Pechoux, C.; Olmi, P.; Poulsen, J.-P.; Seddon, B.; Wang, D. Radiotherapy for Management of Extremity Soft Tissue Sarcomas: Why, When, and Where? Int. J. Radiat. Oncol. 2012, 84, 572–580, doi:10.1016/j.ijrobp.2012.01.062.

27. Mullen, J.T.; Kobayashi, W.; Wang, J.; Harmon, D.C.; Choy, E.; Hornicek, F.J.; Rosenberg, A.E.; Chen, Y.-L.; Spiro, I.J.; Delaney, T.F. Long-term follow-up of patients treated with neoadjuvant chemotherapy and radiotherapy for large, extremity soft tissue sarcomas. Cancer 2011, 118, 3758–3765, doi:10.1002/cncr.26696.

28. Bahig, H.; Roberge, D.; Bosch, W.; Levin, W.; Petersen, I.; Haddock, M.; Freeman, C.; Delaney, T.F.; Abrams, R.A.; Indelicato, D.; et al. Agreement among RTOG sarcoma radiation oncologists in contouring suspicious peritumoral edema for preoperative radiation therapy of soft tissue sarcoma of the extremity. Int. J. Radiat. Oncol. 2013, 86, 298–303, doi:10.1016/j.ijrobp.2013.01.032.

29. Hong, N.J.L.; Hornicek, F.J.; Harmon, D.C.; Choy, E.; Chen, Y.-L.; Yoon, S.S.; Nielsen, G.P.; Szymonifka, J.; Yeap, B.Y.; Delaney, T.F.; et al. Neoadjuvant chemoradiotherapy for patients with high-risk extremity and truncal sarcomas: a 10-year single institution retrospective study. Eur. J. Cancer 2012, 49, 875–83, doi:10.1016/j.ejca.2012.10.002.

30. O'Sullivan, B.; Griffin, A.M.; Dickie, C.I.; Sharpe, M.B.; Chung, P.W.M.; Catton, C.N.; Ferguson, P.C.; Wunder, J.S.; Deheshi, B.M.; White, L.M.; et al. Phase 2 study of preoperative image-guided intensity-modulated radiation therapy to reduce wound and combined modality morbidities in lower extremity soft tissue sarcoma. Cancer 2013, 119, 1878–1884, doi:10.1002/cncr.27951.

31. Alamanda, V.K.; Song, Y.; Shinohara, E.; Schwartz, H.S.; Holt, G.E. Postoperative radiation boost does not improve local recurrence rates in extremity soft tissue sarcomas. J. Med Imaging Radiat. Oncol. 2014, 58, 633–640, doi:10.1111/1754-9485.12184.

32. Beane, J.D.; Yang, J.C.; White, D.; Steinberg, S.M.; Rosenberg, S.A.; Rudloff, U. Efficacy of adjuvant radiation therapy in the treatment of soft tissue sarcoma of the extremity: 20-year follow-up of a randomized prospective trial. Ann. Surg. Oncol. 2014, 21, 2484–9, doi:10.1245/s10434-014-3732-4.

33. Call, J.A.; Stafford, S.L.; Petersen, I.A.; Haddock, M.G. Use of Intraoperative Radiotherapy for Upper-extremity Soft-tissue Sarcomas. Am. J. Clin. Oncol. 2014, 37, 81–85, doi:10.1097/coc.0b013e31826b9b3d.

34. Calvo, F.A.; Sole, C.V.; Polo, A.; Cambeiro, M.; Montero, A.; Álvarez, A.; Cuervo, M.; Julian, M.S.; Martínez-Monge, R. Limb-sparing management with surgical resection, external-beam and intraoperative electron-beam radiation therapy boost for patients with primary soft tissue sarcoma of the extremity. Strahlenther. und Onkol. 2014, 190, 891–898, doi:10.1007/s00066-014-0640-2.

35. Cassier, P.A.; Kantor, G.; Bonvalot, S.; Lavergne, E.; Stoeckle, E.; Le Pechoux, C.; Meeus, P.; Sunyach, M.- P.; Vaz, G.; Coindre, J.- M.; et al. Adjuvant radiotherapy for extremity and trunk wall atypical lipomatous tumor/well-differentiated LPS (ALT/WD-LPS): a French Sarcoma Group (GSF-GETO) study. Ann. Oncol. 2014, 25, 1854–1860, doi:10.1093/annonc/mdu202.

36. Folkert, M.R.; Singer, S.; Brennan, M.F.; Kuk, D.; Qin, L.-X.; Kobayashi, W.K.; Crago, A.M.; Alektiar, K.M. Comparison of Local Recurrence With Conventional and Intensity-Modulated Radiation Therapy for Primary Soft-Tissue Sarcomas of the Extremity. J. Clin. Oncol. 2014, 32, 3236–3241, doi:10.1200/jco.2013.53.9452.

37. Davis, L.E.; Ryan, C.W. Preoperative Therapy for Extremity Soft Tissue Sarcomas. Curr. Treat. Options Oncol. 2015, 16, 1–12, doi:10.1007/s11864-015-0346-4.

38. Griffin, A.M.; Dickie, C.I.; Catton, C.N.; Chung, P.W.M.; Ferguson, P.C.; Wunder, J.S.; O'Sullivan, B. The Influence of Time Interval Between Preoperative Radiation and Surgical Resection on the Development of Wound Healing Complications in Extremity Soft Tissue Sarcoma. Ann. Surg. Oncol. 2015, 22, 2824–2830, doi:10.1245/s10434-015-4631-z.

39. Tseng, W.W.; Zhou, S.; To, C.A.; Thall, P.F.; Lazar, A.J.; Pollock, R.E.; Lin, P.P.; Cormier, J.N.; Lewis, V.O.; Feig, B.W.; et al. Phase 1 adaptive dose-finding study of neoadjuvant gemcitabine combined with radiation therapy for patients with high-risk extremity and trunk soft tissue sarcoma. Cancer 2015, 121, 3659–67, doi:10.1002/cncr.29544.

40. Wang, D.; Zhang, Q.; Eisenberg, B.L.; Kane, J.M.; Li, X.A.; Lucas, D.; Petersen, I.A.; Delaney, T.F.; Freeman, C.R.; Finkelstein, S.E.; et al. Significant Reduction of Late Toxicities in Patients With Extremity Sarcoma Treated With Image-Guided Radiation Therapy to a Reduced Target Volume: Results of Radiation Therapy Oncology Group RTOG-0630 Trial. J. Clin. Oncol. 2015, 33, 2231–2238, doi:10.1200/jco.2014.58.5828.

41. Roeder, F.; Lehner, B.; Saleh-Ebrahimi, L.; Hensley, F.W.; Ulrich, A.; Alldinger, I.; Mechtersheimer, G.; Huber, P.E.; Krempien, R.; Bischof, M.; et al. Intraoperative electron radiation therapy combined with external beam radiation therapy and limb sparing surgery in extremity soft tissue sarcoma: a retrospective single center analysis of 183 cases. Radiother. Oncol. 2016, 119, 22–29, doi:10.1016/j.radonc.2015.11.014.

42. Gingrich, A.A.; Bateni, S.B.; Monjazeb, A.M.; Darrow, M.A.; Thorpe, S.W.; Kirane, A.R.; Bold, R.J.; Canter, R.J. Neoadjuvant Radiotherapy is Associated with R0 Resection and Improved Survival for Patients with Extremity Soft Tissue Sarcoma Undergoing Surgery: A National Cancer Database Analysis. Ann. Surg. Oncol. 2017, 24, 3252–3263, doi:10.1245/s10434-017-6019-8.

43. Ramey, S.; Yechieli, R.; Zhao, W.; Kodiyan, J.; Asher, D.; Chinea, F.M.; Patel, V.; Reis, I.M.; Wang, L.; Wilky, B.A.; et al. Limb-sparing surgery plus radiotherapy results in superior survival: an analysis of patients with high-grade, extremity soft-tissue sarcoma from the NCDB and SEER. Cancer Med. 2018, 7, 4228–4239, doi:10.1002/cam4.1625.

44. Sole, C.V.; Calvo, F.A.; Cambeiro, M.; Polo, A.; Montero, A.; Hernanz, R.; Gonzalez, C.; Cuervo, M.; Pérez, D.; Julian, M.S.; et al. Intraoperative radiotherapy-containing multidisciplinary management of trunk-wall soft-tissue sarcomas. Clin. Transl. Oncol. 2014, 16, 834–842, doi:10.1007/s12094-014-1157-y.

45. Musat, E.; Kantor, G.; Caron, J.; Lagarde, P.; Laharie, H.; Stoeckle, E.; Angles, J.; Gilbeau, L.; Bui, B.N.; Comparison of intensity-modulated postoperative radiotherapy with conventional postoperative conformal radiotherapy for retroperitoneal sarcoma. Cancer Radiother. 2004, 8, 255–261.

46. Dziewirski, W.; Rutkowski, P.; Nowecki, Z.I.; Sałamacha, M.; Morysiński, T.; Kulik, A.; Kawczyńska, M.; Kasprowicz, A.; Łyczek, J.; Ruka, W. Surgery Combined With Intraoperative Brachytherapy in the Treatment of Retroperitoneal Sarcomas. Ann. Surg. Oncol. 2006, 13, 245–252, doi:10.1245/aso.2006.03.026.

47. Tzeng, C.-W.D.; Fiveash, J.B.; Popple, R.A.; Arnoletti, J.P.; Russo, S.M.; Urist, M.M.; Bland, K.I.; Heslin, M.J. Preoperative radiation therapy with selective dose escalation to the margin at risk for retroperitoneal sarcoma. Cancer 2006, 107, 371–379, doi:10.1002/cncr.22005.

48. Swanson, E.L.; Indelicato, D.; Louis, D.; Flampouri, S.; Li, Z.; Morris, C.G.; Paryani, N.; Slopsema, R. Comparison of Three-Dimensional (3D) Conformal Proton Radiotherapy (RT), 3D Conformal Photon RT, and Intensity-Modulated RT for Retroperitoneal and Intra-Abdominal Sarcomas. Int. J. Radiat. Oncol. 2012, 83, 1549–1557, doi:10.1016/j.ijrobp.2011.10.014.

49. Baldini, E.H.; Abrams, R.A.; Bosch, W.; Roberge, D.; Haas, R.L.; Catton, C.N.; Indelicato, D.J.; Olsen, J.R.; Deville, C.; Chen, Y.-L.; et al. Retroperitoneal Sarcoma Target Volume and Organ at Risk Contour Delineation Agreement Among NRG Sarcoma Radiation Oncologists. Int. J. Radiat. Oncol. 2015, 92, 1053–1059, doi:10.1016/j.ijrobp.2015.04.039.

50. Trans-Atlantic RPS Working Group Management of Primary Retroperitoneal Sarcoma (RPS) in the Adult: A Consensus Approach From the Trans-Atlantic RPS Working Group. Ann. Surg. Oncol. 2014, 22, 256–263, doi:10.1245/s10434-014-3965-2.

51. Pollack, A.; Zagars, G.K.; Goswitz, M.S.; A Pollock, R.; Feig, B.W.; Pisters, P.W.T. Preoperative vs. postoperative radiotherapy in the treatment of soft tissue sarcomas: a matter of presentation. Int. J. Radiat. Oncol. 1998, 42, 563–572, doi:10.1016/s0360-3016(98)00277-6.

52. Zagars, G.K.; Ballo, M.T.; Pisters, P.W.T.; E Pollock, R.; Patel, S.R.; Benjamin, R.S. Preoperative vs. postoperative radiation therapy for soft tissue sarcoma: A retrospective comparative evaluation of disease outcome. Int. J. Radiat. Oncol. 2003, 56, 482–488, doi:10.1016/s0360-3016(02)04510-8.

53. Smith, G.; Johnson, G.; Grimer, R.; Wilson, S. Trends in presentation of bone and soft tissue sarcomas over 25 years: little evidence of earlier diagnosis. Ann. R. Coll. Surg. Engl. 2011, 93, 542–547, doi:10.1308/147870811X13137608455055.

54. White, L.M.; Wunder, J.S.; Bell, R.S.; O'Sullivan, B.; Catton, C.; Ferguson, P.; Blackstein, M.; Kandel, R.A. Histologic assessment of peritumoral edema in soft tissue sarcoma. Int. J. Radiat. Oncol. 2005, 61, 1439–1445, doi:10.1016/j.ijrobp.2004.08.036.

55. Pisters, P.W.T.; O'Sullivan, B.; Maki, R. Evidence-Based Recommendations for Local Therapy for Soft Tissue Sarcomas. J. Clin. Oncol. 2007, 25, 1003–1008, doi:10.1200/jco.2006.09.8525.

56. Rosenberg, S.A.; Tepper, J.; Glatstein, E.; Costa, J.; Baker, A.; Brennam, M.; Demoss, E.V.; Seipp, C.; Sindelar, W.F.; Sugarbaker, P.; et al. The Treatment of Soft-tissue Sarcomas of the Extremities. Ann. Surg. 1982, 196, 305–315, doi:10.1097/00000658-198209000-00009.

57. Pisters, P.W.; Harrison, L.B.; Leung, D.H.Y.; Woodruff, J.M.; Casper, E.S.; Brennan, M.F. Long-term results of a prospective randomized trial of adjuvant brachytherapy in soft tissue sarcoma. J. Clin. Oncol. 1996, 14, 859–868, doi:10.1200/jco.1996.14.3.859.

58. O'Sullivan, B.; Davis, A.M.; Turcotte, R.; Bell, R.; Catton, C.; Chabot, P.; Wunder, J.; Kandel, R.; Goddard, K.; Sadura, A.; et al. Preoperative versus postoperative radiotherapy in soft-tissue sarcoma of the limbs: a randomised trial. Lancet 2002, 359, 2235–2241, doi:10.1016/s0140-6736(02)09292-9.

59. A Müller, D.; Beltrami, G.; Scoccianti, G.; Frenos, F.; Capanna, R. Combining limb-sparing surgery with radiation therapy in high-grade soft tissue sarcoma of extremities – Is it effective? Eur. J. Surg. Oncol. (EJSO) 2016, 42, 1057–1063, doi:10.1016/j.ejso.2016.02.004.

60. A Rosenberg, S.; Kent, H.; Costa, J.; Webber, B.L.; Young, R.; Chabner, B.; Baker, A.R.; Brennan, M.F.; Chretien, P.B.; Cohen, M.H.; et al. Prospective randomized evaluation of the role of limb-sparing surgery, radiation therapy, and adjuvant chemoimmunotherapy in the treatment of adult soft-tissue sarcomas. Surg. 1978, 84, 62–9.

61. Hong, L.; Alektiar, K.M.; Hunt, M.; Venkatraman, E.; A Leibel, S. Intensity-modulated radiotherapy for soft tissue sarcoma of the thigh. Int. J. Radiat. Oncol. 2004, 59, 752–759, doi:10.1016/j.ijrobp.2003.11.037.

62. Folkert, M.R.; Casey, D.L.; Berry, S.L.; Crago, A.; Fabbri, N.; Singer, S.; Alektiar, K.M. Femoral Fracture in Primary Soft-Tissue Sarcoma of the Thigh and Groin Treated with Intensity-Modulated Radiation Therapy: Observed versus Expected Risk. Ann. Surg. Oncol. 2019, 26, 1326–1331, doi:10.1245/s10434-019-07182-5.

63. Delannes, M.; Thomas, L.; Martel, P.; Bonnevialle, P.; Stöckle, E.; Chevreau, C.; Bui, B.N.; Daly-Schveitzer, N.; Pigneux, J.; Kantor, G. Low-dose-rate intraoperative brachytherapy combined with external beam irradiation in the conservative treatment of soft tissue sarcoma. Int. J. Radiat. Oncol. 2000, 47, 165–169, doi:10.1016/s0360-3016(99)00548-9.

64. Llácer, C.; Delannes, M.; Minsat, M.; Stoeckle, E.; Votron, L.; Martel, P.; Bonnevialle, P.; Bui, B.N.; Chevreau, C.; Kantor, G.; et al. Low-dose intraoperative brachytherapy in soft tissue sarcomas involving neurovascular structure. Radiother. Oncol. 2006, 78, 10–16, doi:10.1016/j.radonc.2005.12.002.

65. Pohar, S.; Haq, R.; Liu, L.; Koniarczyk, M.; Hahn, S.; Damron, T.; Aronowitz, J.N. Adjuvant high-dose-rate and low-dose-rate brachytherapy with external beam radiation in soft tissue sarcoma: A comparison of outcomes. Brachytherapy 2007, 6, 53–57, doi:10.1016/j.brachy.2006.11.004.

66. Naghavi, A.; Fernandez, D.; Mesko, N.; Juloori, A.; Martinez, A.; Scott, J.; Shah, C.; Harrison, L. American Brachytherapy Society consensus statement for soft tissue sarcoma brachytherapy. Brachytherapy 2017, 16, 466–489, doi:10.1016/j.brachy.2017.02.004.

67. Nag, S.; Shasha, D.; Janjan, N.; Petersen, I.; Zaider, M. The American Brachytherapy Society recommendations for brachytherapy of soft tissue sarcomas. Int. J. Radiat. Oncol. 2001, 49, 1033–1043, doi:10.1016/s0360-3016(00)01534-0.

68. Petera, J.; Soumarova, R.; Ruzickova, J.; Neumanová, R.; Dušek, L.; Sirák, I.; Macingova, Z.; Paluska, P.; Kašaová, L.; Hodek, M.; et al. Perioperative Hyperfractionated High-Dose Rate Brachytherapy for the Treatment of Soft Tissue Sarcomas: Multicentric Experience. Ann. Surg. Oncol. 2009, 17, 206–210, doi:10.1245/s10434-009-0684-1.

69. Itami, J.; Sumi, M.; Beppu, Y.; Chuman, H.; Kawai, A.; Murakami, N.; Morota, M.; Mayahara, H.; Yoshimura, R.; Ito, Y.; et al. High–dose rate brachytherapy alone in postoperative soft tissue sarcomas with close or positive margins. Brachytherapy 2010, 9, 349–353, doi:10.1016/j.brachy.2009.07.012.

70. Emory, C.L.; Montgomery, C.O.; Potter, B.K.; Keisch, M.E.; Conway, S.A. Early Complications of High-dose-rate Brachytherapy in Soft Tissue Sarcoma: A Comparison With Traditional External-beam Radiotherapy. Clin. Orthop. Relat. Res. 2011, 470, 751–758, doi:10.1007/s11999-011-2106-5.

71. Sharma, D.N.; Deo, S.S.; Rath, G.K.; Shukla, N.K.; Bakhshi, S.; Gandhi, A.K.; Julka, P.K. Perioperative high-dose-rate interstitial brachytherapy combined with external beam radiation therapy for soft tissue sarcoma. Brachytherapy 2015, 14, 571–577, doi:10.1016/j.brachy.2015.03.002.

72. Miguel, I.S.; San-Julian, M.; Cambeiro, M.; Sanmamed, M.F.; Vázquez-García, B.; Pagola, M.; Gaztañaga, M.; Martin-Algarra, S.; Martínez-Monge, R. Determinants of Toxicity, Patterns of Failure, and Outcome Among Adult Patients With Soft Tissue Sarcomas of the Extremity and Superficial Trunk Treated With Greater Than Conventional Doses of Perioperative High-Dose-Rate Brachytherapy and External Beam Radiotherapy. Int. J. Radiat. Oncol. 2011, 81, e529–e539, doi:10.1016/j.ijrobp.2011.04.063.

73. Beroukas, E.; Peponi, E.; Soulimioti, G.; Kalaitzi, Z.; Potamianou, A.; Skarlatos, I.; Economou, G.; E Athanassiou, A.; Beroukas, K. Intraoperative electron beam radiotherapy followed by moderate doses of external beam radiotherapy in the treatment of resected soft tissue sarcomas of the extremities. J. B.U.ON.: Off. J. Balk. Union Oncol. 2007, 9, 391–398.

74. Sindelar, W.F.; Kinsella, T.J.; Chen, P.W.; Delaney, T.F.; Tepper, J.E.; Rosenberg, S.A.; Glatstein, E. Intraoperative Radiotherapy in Retroperitoneal Sarcomas. Arch. Surg. 1993, 128, 402–410, doi:10.1001/archsurg.1993.01420160040005.

75. Gieschen, H.L.; Spiro, I.J.; Suit, H.D.; Ott, M.J.; Rattner, D.W.; Ancukiewicz, M.; Willett, C.G. Long-term results of intraoperative electron beam radiotherapy for primary and recurrent retroperitoneal soft tissue sarcoma. Int. J. Radiat. Oncol. 2001, 50, 127–131, doi:10.1016/s0360-3016(00)01589-3.

76. Krempien, R.; Roeder, F.; Oertel, S.; Weitz, J.; Hensley, F.W.; Timke, C.; Funk, A.; Lindel, K.; Harms, W.; Büchler, M.W.; et al. Intraoperative electron-beam therapy for primary and recurrent retroperitoneal soft-tissue sarcoma. Int. J. Radiat. Oncol. 2006, 65, 773–779, doi:10.1016/j.ijrobp.2006.01.028.

77. Pawlik, T.M.; Pisters, P.W.T.; Mikula, L.; Feig, B.W.; Hunt, K.K.; Cormier, J.N.; Ballo, M.T.; Catton, C.N.; Jones, J.J.; O'Sullivan, B.; et al. Long-Term Results of Two Prospective Trials of Preoperative External Beam Radiotherapy for Localized Intermediate- or High-Grade Retroperitoneal Soft Tissue Sarcoma. Ann. Surg. Oncol. 2006, 13, 508–517, doi:10.1245/aso.2006.05.035.

78. Roeder, F.; Ulrich, A.; Habl, G.; Uhl, M.; Saleh-Ebrahimi, L.; Huber, P.E.; Schulz-Ertner, D.; Nikoghosyan, A.V.; Alldinger, I.; Krempien, R.; et al. Clinical Phase I/II trial to Investigate Preoperative Dose-Escalated Intensity-Modulated Radiation Therapy (IMRT) and Intraoperative Radiation Therapy (IORT) in patients with retroperitoneal soft tissue sarcoma: interim analysis. BMC Cancer 2014, 14, 1–12, doi:10.1186/1471-2407-14-617.

79. Roeder, F.; Krempien, R. Intraoperative radiation therapy (IORT) in soft-tissue sarcoma. Radiat. Oncol. 2017, 12, 20, doi:10.1186/s13014-016-0751-2.

80. Kunos, C.; Colussi, V.; Getty, P.; Kinsella, T.J. Intraoperative Electron Radiotherapy for Extremity Sarcomas Does Not Increase Acute or Late Morbidity. Clin. Orthop. Relat. Res. 2006, 446, 247–252, doi:10.1097/01.blo.0000203470.43184.8c.

81. Roeder, F.; Lehner, B.; Schmitt, T.; Kasper, B.; Egerer, G.; Sedlaczek, O.; Grüllich, C.; Mechtersheimer, G.; Wuchter, P.; Hensley, F.W.; et al. Excellent local control with IOERT and postoperative EBRT in high grade extremity sarcoma: results from a subgroup analysis of a prospective trial. BMC Cancer 2014, 14, 350, doi:10.1186/1471-2407-14-350.

82. Hoefkens, F.; Dehandschutter, C.; Leskelä, H.-V.; Meijnders, P.; Van Gestel, D. Soft tissue sarcoma of the extremities: pending questions on surgery and radiotherapy. Radiat. Oncol. 2016, 11, 136, doi:10.1186/s13014-016-0668-9.

83. Al-Absi, E.; Farrokhyar, F.; Sharma, R.; Whelan, K.; Corbett, T.; Patel, M.; Ghert, M. A Systematic Review and Meta-Analysis of Oncologic Outcomes of Pre- Versus Postoperative Radiation in Localized Resectable Soft-Tissue Sarcoma. Ann. Surg. Oncol. 2010, 17, 1367–1374, doi:10.1245/s10434-009-0885-7.

84. Sampath, S.; Schultheiss, T.E.; Hitchcock, Y.J.; Randall, R.L.; Shrieve, D.C.; Wong, J.Y. Preoperative Versus Postoperative Radiotherapy in Soft-Tissue Sarcoma: Multi-Institutional Analysis of 821 Patients. Int. J. Radiat. Oncol. 2011, 81, 498–505, doi:10.1016/j.ijrobp.2010.06.034.

85. Kuklo, T.R.; Temple, H.T.; Owens, B.D.; Juliano, J.; Islinger, R.B.; Andejeski, Y.; A Frassica, D.; Berrey, B.H. Preoperative versus postoperative radiation therapy for soft-tissue sarcomas. Am. J. Orthop. (Belle Mead, N.J.) 2005, 34, 75–80.

86. Albertsmeier, M.; Rauch, A.; Roeder, F.; Hasenhütl, S.; Pratschke, S.; Kirschneck, M.; Gronchi, A.; Jebsen, N.L.; Cassier, P.A.; Sargos, P.; et al. External Beam Radiation Therapy for Resectable Soft Tissue Sarcoma: A Systematic Review and Meta-Analysis. Ann. Surg. Oncol. 2017, 25, 754–767, doi:10.1245/s10434-017-6081-2.
87. Cheng, E.Y.; Dusenbery, K.E.; Winters, M.R.; Thompson, R.C. Soft tissue sarcomas: Preoperative versus postoperative radiotherapy. J. Surg. Oncol. 1996, 61, 90–99, doi:10.1002/(sici)1096-9098(199602)61:23.0.co;2-m.
88. Nielsen, O.; Cummings, B.; O'Sullivan, B.; Catton, C.; Bell, R.; Fornasier, V. Preoperative and postoperative irradiation of soft tissue sarcomas: Effect on radiation field size. Int. J. Radiat. Oncol. 1991, 21, 1595–1599, doi:10.1016/0360-3016(91)90337-4.
89. Al Yami, A.; Griffin, A.M.; Ferguson, P.C.; Catton, C.; Chung, P.W.M.; Bell, R.S.; Wunder, J.S.; O'Sullivan, B. Positive Surgical Margins in Soft Tissue Sarcoma Treated With Preoperative Radiation: Is a Postoperative Boost Necessary? Int. J. Radiat. Oncol. 2010, 77, 1191–1197, doi:10.1016/j.ijrobp.2009.06.074.
90. Pan, E.; Goldberg, S.I.; Chen, Y.-L.; Giraud, C.; Hornick, J.L.; Nielsen, G.P.; Hornicek, F.J.; Raut, C.P.; Delaney, T.F.; Baldini, E.H. Role of post-operative radiation boost for soft tissue sarcomas with positive margins following pre-operative radiation and surgery. J. Surg. Oncol. 2014, 110, 817–822, doi:10.1002/jso.23741.
91. Jakob, J.; Wenz, F.; Dinter, D.J.; Ströbel, P.; Hohenberger, P. Preoperative Intensity-Modulated Radiotherapy Combined with Temozolomide for Locally Advanced Soft-Tissue Sarcoma. Int. J. Radiat. Oncol. 2009, 75, 810–816, doi:10.1016/j.ijrobp.2008.11.032.
92. Bramwell, V.; Rouesse, J.; Steward, W.; Santoro, A.; Schraffordt-Koops, H.; Buesa, J.; Ruka, W.; Priario, J.; Wagener, T.; Burgers, M. Adjuvant CYVADIC chemotherapy for adult soft tissue sarcoma--reduced local recurrence but no improvement in survival: a study of the European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group. J. Clin. Oncol. 1994, 12, 1137–1149, doi:10.1200/jco.1994.12.6.1137.
93. Fakhrai, N.; for the Austrian Cooperative Soft Tissue Sarcoma Study Group; Ebm, C.; Köstler, W.J.; Jantsch, M.; Abdolvahab, F.; Dominkus, M.; Pokrajac, B.; Kauer-Dorner, D.; Zielinski, C.C.; et al. Intensified adjuvant IFADIC chemotherapy in combination with radiotherapy versus radiotherapy alone for soft tissue sarcoma: long-term follow-up of a prospective randomized feasibility trial. Wien. Klin. Wochenschr. 2010, 122, 614–619, doi:10.1007/s00508-010-1472-4.
94. Von Mehren, M.; Randall, R.L.; Benjamin, R.S.; Kane, J.M.; Bui, M.M.; Choy, E.; Connelly, M.; Ganjoo, K.N.; George, S.; Gonzalez, R.J.; et al. Soft tissue sarcoma, version 2.2020. J. Natl. Compr. Canc. Netw. 2020, 2, 'EXTSARC-1 - RETSARC-4′, and 'MS-4—MS-80′