VIA MEDICA

NOWOTWORY Journal of Oncology
2020, volume 70, number 6, 288–295
DOI: 10.5603/NJO.2020.0056

ISSN 0029–540X
www.nowotwory.edu.pl

Conference addendum

Warsaw Sacroma Meeting
5th December 2020

Current advances in radiotherapy for soft tissue sarcomas

Mateusz J. Spałek, Aneta M. Borkowska

Department of Soft Tissue/Bone Sarcoma and Melanoma, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland

Radiotherapy (RT) is a part of the routine treatment of locally advanced or high-grade soft-tissue sarcomas (STS). However, RT has changed significantly over the last 20 years. Modern RT techniques have extended its potential application in STS treatment. That includes advances in contouring, fractionation regimens, RT techniques and combined treatment. This article summarizes the available data, current strategies and future research directions in RT for STS.

Key words: sarcoma, radiotherapy, intensity-modulated radiotherapy, image-guided radiotherapy, brachytherapy

Introduction

Perioperative radiotherapy (RT) combined with wide local excision enables over 90% of local control in patients with localized soft tissue sarcomas (STS) of extremities or the trunk wall. According to the National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) guidelines, RT is recommended as a part of the routine treatment of locally advanced or high-grade STS, depending on clinicopathological factors such as tumor size, grade and its resectability [1, 2]. NCCN recommends perioperative RT in selected patients with stage I and in all stage II, III extremity, superficial trunk, or head/neck STS. Likewise, ESMO recommends perioperative RT with wide excision in high-grade (G2–3), deep, large (>5 cm) STS. The role of RT in other clinical situations, such as superficial STS, high-grade <5 cm STS or low-grade >5 cm deep STS remains unclear; thus, the use of RT should be discussed at a multidisciplinary tumor board (MTB), given the risk of local recurrence, pathological diagnosis and potential toxicity. The issue of the treatment sequence is extensively discussed in literature. Currently, both neoadjuvant and adjuvant RT may be considered in localized STS, taking into account the risk of postoperative wound complications (tab. I) [3]. However, RT in STS has significantly changed over the last 20 years in many more aspects.

Moreover, contemporary RT may play an important role in the management of patients with metastatic STS. Modern RT techniques, such as stereotactic body RT (SBRT), allows the delivery of a high dose to target volume with minimal involvement of surrounding healthy tissues. The use of motion-management techniques enable the irradiation of moving tumors, for example, lung metastases that are the most frequent metastatic site of STS.

This article summarizes the available data, current strategies and future research directions in RT for STS. That includes advances in contouring, fractionation regimens, RT techniques, and combined treatment. The scope of the article does not cover selected STS subtypes with separate guidelines, namely Ewing sarcoma, rhabdomyosarcoma, gastrointestinal stromal tumors and dermatofibrosarcoma protuberans.

External beam radiotherapy

Contouring

Together with the evolution of RT techniques, RT planning in STS evolved from simple two-dimensions to complicated, volumetric shapes. Two-dimensional RT in STS required only the determination of field borders. Currently, a radiation oncologist delineates tumor volumes, elective margins and

How to cite:
Spałek MJ, Borkowska AM. ***Current advances in radiotherapy for soft tissue sarcomas.*** *NOWOTWORY J Oncol* 2020; 70: 288–295.

Table I. Comparison of neoadjuvant and adjuvant radiotherapy in soft tissue sarcomas

Issue	Adjuvant radiotherapy	Neoadjuvant radiotherapy
delineation	complicated (no GTV, fusion with preoperative imaging, postoperative changes)	easy (visible GTV)
target volume	larger (tumor bed, scars, drainage, operative route, and margins)	smaller (GTV + margin)
healthy tissues	move to the tumor bed	pushed away by the tumor
dose	higher (60–66 Gy EQD2)	lower (45–50.4 Gy EQD2)
treatment time	longer	shorter
hypofractionation	no/not known	possible
pathological assessment	unhindered	hindered
tumor response	none	possible
resection margins	no influence	could improve
tumor seeding during resection	no influence	possible reduction
risk of early toxicity[1]	lower	higher
risk of late toxicity[1]	higher	lower
combination with chemotherapy	possible	possible

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[1]In conventionally fractionated radiotherapy. EQD2 – equivalent total dose in 2-Gy fractions; GTV – gross tumor volume

the volumes of organs at risk. The contouring process varies depending on the treatment sequence. However, the main rule remains the same – the elective margin should follow the most probable path of local spread – namely areas of least resistance. In neoadjuvant RT, gross tumor volume (GTV) should be delineated on T1 contrast-enhanced magnetic resonance imaging (MRI) fusion with planning CT. The clinical target volume (CTV) should cover GTV, tumor-associated edema in T2 MRI and the elective margin of healthy tissues. In deeply-seated STS, it is recommended to add 1.5–2.0 cm to GTV radially and 4 cm longitudinally, stopping at anatomical barriers (for example bones, major vessels, fascias) [4]. In superficially-spreading STS, it is suggested to extend GTV by at least 4 cm in each direction, except the deep margin that should end at the nearest non-involved anatomical border. The delineation of organs at risk depends on the irradiated site, including large joints, skin, subcutaneous tissue and contralateral extremity. Due to the large volumes of primary tumors and extensive margins, the protection of organs at risk is challenging. However, the evidence from two clinical trials does not support a reduction of target volumes. In a phase III Randomised Trial of Volume of Post-operative Radiotherapy Given to Adult Patients With eXtremity Soft Tissue Sarcoma (VORTEX, NCT00423618), patients with STS were randomly assigned into postoperative RT with conventional and postoperative RT with reduced margins (2 cm in each direction) [5]. The small number of events did not allow conclusions to be drawn regarding local relapse-free survival. Moreover, the authors found no difference between arms in limb function at 2 years. Thus, reduced margins cannot be recommended as a standard of care. Another phase II Radiation Therapy Oncology Group (RTOG) 0630 non-randomized single-arm clinical trial indicated that modern image-guided RT with simultaneous margin reduction enabled a low rate of late toxicity with good local control [6]. However, it was a single-arm clinical trial and it was not possible to conclude which factors (image-guided RT or margin reduction or both) contributed to the aforementioned results. Thus, conventional extensive margins remain a standard of STS contouring.

Fractionation regimen

The recommended perioperative RT fractionation regimens for STS delivers 2.0 Gy per day, 5 times weekly, up to 50 Gy in preoperative radiotherapy and 60–66 Gy in postoperative radiotherapy [7]. In hypofractionated regimens, the total dose is divided into fewer fractions with an increased fraction dose. Hypofractionated RT in STS has a radiobiological rationale. The alpha/beta ratio of STS seems to be lower than 10 Gy [8]. Thus, a higher dose per fraction should result in better tumor control. Furthermore, hypofractionated RT may allow for a reduction of the delivered total dose without compromising tumor control. This may lead to healthy tissues being spared close to the target volume. Moreover, it can be combined with chemotherapy or targeted therapy [9]. Hypofractionated RT for STS was investigated in many prospective phase I or phase II clinical trials and prospective registries (tab. II); however there is no evidence from phase III trials to support its use in routine clinical practice [9–15]. Nevertheless, it may be used individually in selected patients upon the decision of the MTB.

Table II. Preoperative hypofractionated radiotherapy regimens in soft tissue sarcomas in major published studies

First author	Evidence	Number of patients	Dominant preoperative regimen	Surgery after RT	R0 %	@years local control	Reported late toxicity	@years estimated survival
Temple 1997 [52]	prospective register	42	doxorubicin 30 Gy/10 fr.	delayed (4–6 weeks)	ND	@5y 97%	ND	@5y OS 79%
Ryan 2008 [53]	retrospective cohort	25	EI 28 Gy/8 fr.	delayed (4–5 weeks)	88	@2y 88%	ND	@2y DRFS 78% OS 84%
MacDermed 2009 [54]	retrospective cohort	34 included 6 patients with DM	ifosfamide 28 Gy/8 fr.	delayed (4–8 weeks)	100	@5y 89%	fibrosis 14% edema 17%	@5y (no DM) DRFS 53% OS 45%
Meyer 2013 [55]	phase I single arm CT	16 included 2 patients with DM	sorafenib EI 28 Gy/8 fr.	delayed	94	@2y 100%	ND	@2y PFS 86%
Kosela 2014 [11]	prospective register	272 61 CHT + RT 211 RT	CHT*& 25 Gy/5 fr.	immediate (3–7 days)	79	@3y 81%	15% all 23% CHT+RT 12% RT	@5y OS 60%
Pennington 2018 [56]	retrospective cohort	116	CHT* 28 Gy/8 fr.	delayed (2–3 weeks)	93	@3y 89% @6y 83%	4%	@3y DRFS 75% OS 82% @6y DRFS 65% OS 67%
Spalek 2019 [14]	phase II single arm CT	30 marginally resectable or unresectable	1x AI 25 Gy/5 fr. 2x AI	delayed (6–8 weeks)	73	@1y 97%	ND	@1y DRFS 74%
Parsai 2020 [57]	retrospective cohort	16 3 CHT+RT 13 RT	CHT* 30 Gy /5 fr.	immediate (0–7 days)	63	@1y 100%	ND	ND
Kalbasi 2020 [10]	phase II single arm CT	50	30 Gy/5 fr.	delayed (2–6 weeks)	82	@2y 94%	G1: fibrosis 24% JS 11% edema 4% G2: fibrosis 11% JS 11% edema 4%	@2y DRFS 79%
Kosela 2020 [12]	phase II single arm CT	29 MLPS only	25 Gy /5 fr.	delayed (6–8 weeks)	93	@1y 100%	ND	@1y DRFS 86%

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AI – doxorubicin, ifosfamide; EI – epirubicin, ifosfamide; CHT – chemotherapy; CT – clinical trial; DM – distant metastases; DRFS – distant recurrence-free survival; JS – joint stiffness; MLPS – myxoid liposarcomas; ND – no data; OS – overall survival; PFS – progression-free survival; RT – radiotherapy; STS – soft tissue sarcomas; * – various regimens were used; & – only part of a group received chemotherapy

Techniques

At the beginning of the 2000s, the vast majority of STS patients were irradiated with 2D and 3D-conformal RT that was reflected in the most important STS clinical trials [16–18]. Radiation oncologists who are experienced in STS slowly adapted modern highly-conformal RT techniques. This was caused by the risk of delivery of small doses to high volumes of healthy tissues, including the whole extremity circumference

Theoretically, that may translate into a high occurrence of significant late toxicities. However, the results of two clinical trials do not confirm this hypothesis. In the RTOG-0630 trial, the authors found a significant reduction of late toxicities in patients with extremity STS who had been treated with preoperative image-guided highly conformal RT with reduced margins when compared with the results of the CAN-NCIC--SR2 trial with 3D-conformal RT [6, 17]. In another phase II clinical trial, O'Sullivan et al. investigated the use of intensity-modulated RT (IMRT) in reducing wound complications after preoperative RT for lower extremity STS [19]. IMRT was used to protect healthy tissues (skin flaps for wound closure, bone, or other uninvolved soft tissues). The incidence of wound complications in the investigated group irradiated with IMRT was lower (30.5%) than in the aforementioned CAN-NCIC-SR2 trial (43%). However, this difference was not statistically significant. Additionally, preoperative RT significantly decreased the need for tissue transfer. Due to the high probability of tumor volume size changes during preoperative RT, an image-guided approach is recommended [20]. An

interesting option for reducing the risk of errors could be the introduction of adaptive RT [21].

Other RT techniques

Stereotactic body radiotherapy

Modern diagnostic tools and the growing number of available options for effective systemic treatment introduced the terms oligometastatic and oligoprogressive disease in STS patients. For many years, surgery remained the only curative modality in the case of isolated countable metastases, mostly to the lungs. Existing data suggest an improvement in overall survival after the resection of a limited number of metastases in STS patients. The development of dynamic RT techniques with motion-management enabled precise treatment of small volumes with high-dose radiation accompanied by concomitant sparing of the surrounding healthy tissues. Thus, SBRT could be offered to patients who are not suitable candidates or refuse surgery. This kind of treatment may provide high local control with short overall treatment time and a good toxicity profile. A Swedish group analyzed the outcomes of 46 patients with 136 distant STS metastases treated with SBRT between 1994 and 2005 using a 3D-conformal multifield RT and a stereotactic body-frame. The majority of treated lesions were lung metastases. The authors described an excellent overall response rate that reached almost 90% with acceptable treatment tolerance; only two serious non-lethal adverse events were observed. In a recently designed prospective phase III international randomized clinical trial (Stereotactic Body Radiotherapy in Patients With Rare Oligometastatic Cancers, OligoRARE, NCT04498767), the authors aim to investigate the effect of adding SBRT to the standard of care treatment on overall survival in patients with rare oligometastatic cancers, including STS. SBRT will be given to all metastatic sites as an additional modality to the current standard of care. Patients will be randomly allocated to one of two arms: standard of care or standard of care with SBRT to all metastatic lesions. Full results will be available within 10 years.

Particle therapy

Particle therapy (PT), such as proton and carbon ion therapy, has several potential advantages compared to conventional photon based therapy, which, due to the Bragg curve, can provide better dose distribution. Based on these unique features, PT may allow escalation of the dose to the tumor while reducing the dose to the surrounding organs at risk. Moreover, charged particles, such as carbon ions, deposit the radiation dose in a way that causes complex DNA damage at multiple sites which is challenging for a single DNA damage response pathway to repair; this makes their usage in RT potentially effective in the management of radio- and chemo-resistant tumors like STS. The dose of PT is measured in Gray-equivalents, calculated as a carbon physical dose in Gy, multiplied by relative biological effectiveness (RBE). It is assumed that the RBE of protons is 1.1, whereas in carbon ions RBE equals 2.5-3. PT was used to irradiate sarcomas of the base of the skull and spine. It could be also considered in selected patients with extremity STS [22]. The vast majority of data concerning PT in STS, describes its efficacy in rhabdomyosarcomas and Ewing sarcomas [23]. One study was conducted to assess the effectiveness and safety of PT for unresectable or incomplete resected bone sarcomas and STS of the pelvis [24]. 91 patients, mostly with a primary tumor (90%) were treated with proton and carbon ion therapy. Results showed 83% of them with 3-year overall survival, 72% with 3-year progression-free survival, and 92% with 3-year local control. All patients completed therapy; however, acute grade ≥3 toxicities were observed in 22 patients (24%). Late grade ≥3 toxicities were observed in 23 patients (25%). Another study of 128 patients with unresectable localized axial STS, treated with carbon ion therapy, showed 65% 5-year local control and 49% 5-year overall survival [25]. Yang et al used carbon ion RT to treat patients with locally recurrent or radiation-induced second primary STS of the head and neck [26]. Among the 19 patients, 1-year local control and 1-year overall survival reached 75% and 87%, respectively. A Japanese group conducted a phase I/II trial that aimed to determine the effectiveness of carbon ion therapy for localized primary sarcomas of the extremities [27]. Nine patients had primary diseases and eight had recurrent diseases. In 65% of patients, a radiological response was observed. The 5-year overall survival and 5-year local control was 56% and 76%, respectively. Local recurrences were observed in four patients, three died due to systemic diseases and one was salvaged by repeated carbon ion RT. The aforementioned results indicate the good local efficacy and tolerance of PT in STS. However, further research on that topic is required to establish clear indications for PT in STS.

Brachytherapy

The effectiveness of interstitial brachytherapy in STS has been confirmed in several studies. Brachytherapy in STS is usually applied intraoperatively or postoperatively. Either sole brachytherapy or as a boost after external beam RT were investigated [28–31]. In selected clinical situations, brachytherapy may be superior to external beam RT due to the reduction of treatment time, higher dose intensity and better sparing of surrounding healthy tissues. However, brachytherapy and external beam RT were not directly compared in any prospective study. Moreover, the majority of available data describe the use of low dose rate brachytherapy whereas data regarding high dose rate brachytherapy are limited [32–35]. The American Brachytherapy Society summarized the available evidence on brachytherapy in STS and published a consensus statement regarding indications, techniques, implantation, fractionation regimens and special considerations [36]. Importantly, it is suggested that brachytherapy as monotherapy can be consi-

dered in low-risk STS or in situations of re-irradiation whereas a brachytherapy boost may be applied in high-risk STS or in cases of larger target volumes.

Hyperthermia

Hyperthermia is a cancer treatment in which a heated volume is exposed to temperatures between 41–43°C. It works through the application of electromagnetic energy for a defined period of time. Heat can be delivered using an electromagnetic field, ultrasound or perfusion method. Hyperthermia in oncology comprises three subgroups: whole body hyperthermia, regional hyperthermia and local hyperthermia. It is widely used in combination with RT or chemotherapy in various cancers, including STS. The effectiveness of hyperthermia combined with chemotherapy in locally advanced STS was confirmed in a phase III randomized clinical trial [37, 38]. However, there is no such data on the combination of hyperthermia with radiotherapy in STS. Currently, the Polish Sarcoma Group conducts a prospective phase II clinical trial with neoadjuvant hyperthermia with radiotherapy (3.25 Gy to 32.5 Gy, SINDIR, NCT03989596) in patients with locally advanced STS. Moreover, a combination of RT with hyperthermia may be offered to patients with radiation-induced or in-field recurrent STS. De Jong et al. retrospectively assessed a cohort of patients who received RT with hyperthermia as a treatment for STS which grew in previously irradiated volumes within the thoracic region [39]. Two hypofractionated regimens with hyperthermia twice a week were used (3 Gy to 36 Gy; or 4 Gy to 32 Gy). Thirteen patients underwent treatment with curative intent. The remaining three patients received RT with hyperthermia postoperatively. In seven patients the complete response was observed, whereas partial response was found in two patients. Despite the previous irradiation, both early and late toxicities were acceptable. The authors described only one severe late toxicity, namely arm ischemia that required limb amputation, occurring several years after treatment. Nevertheless, no prospective evidence on RT with hyperthermia in this clinical situation exists. Recently, the Polish Sarcoma Group started a phase II clinical trial with hyperthermia combined with hypofractionated RT in radiation-induced or in-field recurrent STS (HOT, NCT04398095).

Tailored radiotherapy

STS are very heterogeneous and present a wide spectrum of radiosensitivity. Some STS subtypes are considered to be especially radiosensitive compared with other STS. In a prospective phase II single arm clinical trial conducted by the Polish Sarcoma Group, patients with locally advanced myxoid liposarcomas received one-week RT (25 Gy in five fractions) followed by a 6–8 weeks gap before surgery [12]. 29 patients were enrolled on the trial. The investigated method did not increase the wound complication rate (37.9%) compared to other STS trials, whereas in all analyzed surgical specimens a significant response to RT was observed. An interesting approach could be the implementation of radiogenomics models in predicting response to the radiation of selected STS. A research group from the H. Lee Moffitt Cancer Center and Research Institute (Tampa, Florida, USA) and the Netherlands Cancer Institute (Amsterdam, the Netherlands) developed and validated a robust multigene expression model of intrinsic tumor radiosensitivity [40]. To predict the response to treatment, scientists created a model of radiosensitivity as a function of gene expression and other factors in a form of a rank-based linear regression algorithm to establish the radiosensitivity index (RSI). This model was used in further research to calculate the RSI of 113 resected STS samples [41]. The study investigated a predictive value of RSI for locoregional control with preoperative RT in STS. The whole group was divided into two cohorts based on RSI, radiosensitive and radioresistant STS. The four-year locoregional control was better in the radiosensitive STS cohort than in the cohort of the radioresistant tumor (95% *vs.* 79.3%, $p = 0.021$). The genomic-adjusted RT may be an important direction for further research in STS radiation oncology.

Nanoparticles

Using agents to radiosensitize tumor cells has been tested for many years. A multicenter, randomized, II/III phase clinical trial aimed at investigating the efficacy of hafnium oxide nanoparticles (NBTXR3) as a local radiosensitizer added to neoadjuvant RT. Patients with locally advanced resectable STS of extremities or the trunk wall, requiring preoperative RT, were enrolled. The control group received preoperative RT (2 Gy to 50 Gy) alone, whereas the study group received a single intratumoral administration of NBTXR3 before preoperative RT. The primary endpoint was the proportion of patients with a complete pathological response. Analysis of 176 patients – 87 in the study group and 89 in the control group – showed a statistically significant difference in the pathological complete response between the study group (14 patients) and the control group (7 patients) ($p = 0.044$). R0 resection was achieved more frequently in the NBTXR3 group compared to the RT alone group ($p = 0.042$). Serious adverse events occurred in 39% of patients in the NBTXR3 group and 30% of patients in the RT alone group. In both groups, the postoperative wound complication was according to Common Terminology Criteria for Adverse Events v 4.0. The most common grade ≥3 adverse event related to NBTXR3 injection was pain (4%) and hypotension (7%). The administration of NBTXR3 does not increase RT-related toxicities. The most common grade ≥3 adverse event related to RT was skin injuries in both groups: 6% in the NBTXR3 group and 4% in the RT alone group. An NBTXR3 injection before neoadjuvant RT may be a promising radioenhancer that improves the effectiveness of locally advanced STS treatment with no increase in RT-related toxicities. However, there are no long-term results, therefore the late toxicity profile and efficacy of nanoparticles with RT in STS are still unknown.

Spatially-fractionated radiotherapy

In some STS, the utilization of RT is greatly limited by the bulky size and tolerance of surrounding healthy tissue. Advances in RT has led to the development of special techniques of treating bulky tumors. One of them is spatially fractionated radiation therapy applied through sieve-like collimators, namely GRID therapy [42]. A modern adaptation of GRID, 3D-lattice RT, uses highly conformal RT techniques to emulate grid-like patterns within the tumor volume [43]. The aforementioned techniques showed promising results in the treatment of large abdominal gynecological tumors [44, 45]. In the analysis performed at the University of Kentucky (Lexington, Kentucky, USA), 37 patients with locally advanced STS were treated with single fraction 3D-lattice RT (12–20 Gy) before standard conventionally-fractionated RT (1.8–2 Gy to 50–60 Gy) or moderately hypofractionated RT (2.25–3 Gy to 30–40 Gy) [46]. The average tumor size was 14x14 cm. Among those patients who underwent surgery (15/37), a complete pathological response was observed in seven patients (47%), whereas a partial response was seen in eight patients (53%). Among those 15 patients, two experienced grade 3 skin toxicity and three presented delayed wound healing. The median survival of patients who underwent surgery was 18.6 months with a low local failure rate (20%) and high occurrence of distant metastases (74%). Among patients without surgery, two presented a complete clinical response, ten had a partial response, five showed stable disease and five were not evaluable. In another study with spatially-fractionated RT, 14 patients with bulky STS received a single dose of 18 Gy followed by conventionally fractionated RT (2 Gy to 50 Gy) with concomitant ifosfamide-based chemotherapy [47]. They were subsequently referred to surgery. Twenty patients completed the whole protocol; treatment was prematurely stopped for one patient due to grade 3 skin toxicity. One patient underwent a foot amputation, the others underwent limb-sparing surgery. In 12/13 patients, negative margins were achieved. Two patients experienced delayed wound healing. Interestingly, in 9/14 patients >90% tumor necrosis in surgical specimens was present. No local recurrences were observed. To summarize, spatially-fractionated RT may be a valuable treatment option of locally advanced STS; however, prospective trials are awaited.

Retroperitoneal soft tissue sarcomas

Particular attention should be paid to retroperitoneal STS. Perioperative RT is a part of routine treatment in extremity or trunk wall STS, whereas its role in retroperitoneal STS remains uncertain. The main limitations are large target volumes and their localization within the abdominal cavity, close to at risk radiosensitive organs. In recently published results from a phase III randomized study of preoperative radiotherapy plus surgery versus surgery alone for patients with retroperitoneal STS (STRASS, EORTC 62092), the addition of preoperative RT to surgery did not improve the abdominal relapse-free survival [48]. Moreover, a large retrospective study performed by the Trans-Atlantic Retroperitoneal Sarcoma Working Group, showed multivariate analysis indicated no benefit in local control of perioperative RT in retroperitoneal STS [49]. In turn, another study presented prolonged local recurrence-free survival in patients with retroperitoneal STS who received preoperative RT [50]. Additionally, the Surveillance, Epidemiology, and End Results analysis showed a benefit to overall survival by adding adjuvant RT after resection of high-grade retroperitoneal STS [51]. To sum up, the current evidence does not support the routine use of perioperative RT in patients with retroperitoneal STS; however, it could be used in selected patients depending on the decision of the MTB. The role of RT in the management of residual or recurrent retroperitoneal STS is unknown. Contemporary RT techniques, such as MR-based RT or particle therapy, may open up new possibilities for this group of patients.

Summary

Multiple innovations in RT have been introduced over the last 20 years. The vast majority of them are used to improve the results of multidisciplinary treatment of STS. This includes advances in external beam RT as well as more widespread use of existing experimental methods and the introduction of new approaches. Further evaluation of new strategies is warranted, but a part of them could be currently used in selected STS patients depending on the decision of the MTB.

Conflict of interest: none declared

Mateusz Spałek
Maria Sklodowska-Curie National Research Institute of Oncology
Department of Soft Tissue/Bone Sarcoma and Melanoma
ul. Roentgena 5
02-781 Warszawa, Poland
e-mail: mateusz.spalek@pib-nio.pl

Received and accepted: 15 Nov 2020

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