



Practice Guidelines

ESTRO clinical practice guideline on radiotherapy for adult soft tissue sarcoma of the extremities and trunk wall – Endorsed by ASTRO



ARTICLE INFO

ABSTRACT

Purpose: This updated clinical practice guideline provides a practical, evidence-based approach for the management of adult soft tissue sarcoma of the extremity and trunk wall.

Materials and Methods: The European Society for Radiotherapy and Oncology (ESTRO) formed a task force of 13 European experts, alongside 3 experts from the American Society for Radiation Oncology (ASTRO), to analyze current evidence, provide recommendations and establish expert consensus in areas lacking strong evidence. Thirteen key questions were identified, encompassing indications for radiotherapy, pre- vs. postoperative radiotherapy, treatment preparation, patient positioning, target volume delineation, dose and fractionation, adverse events assessment, and dose guidance for organs of interest. Key recommendations were formulated and tabulated for each topic, addressing all identified key questions.

Results: Recommendations for 13 key questions were developed. Dosing for certain subtypes or clinical scenarios has evolved. Despite advancements in imaging, radiotherapy techniques, and personalized approaches, the core principles of treatment planning remain consistent with established practices. Innovative approaches, such as preoperative hypofractionation, radiotherapy combined with systemic therapies (immunotherapy, targeted therapies), and further histotype-specific dose tailoring, show promise; however, they should not be integrated into routine practice until further evidence is obtained.

Conclusion: Preoperative conventionally fractionated radiotherapy, delivered using highly conformal techniques and volumetric imaging, followed by surgery, remains the preferred sequencing strategy for localized soft tissue sarcoma. Multidisciplinary evaluation at expert sarcoma centers remains essential for determining the optimal treatment approach for each patient.

Introduction

Previous guidance for radiotherapy of extremity and truncal soft tissue sarcomas was published in the International Journal of Radiation Oncology, Biology, Physics in 2012 [1]. More recently, the American Society of Radiation Oncology (ASTRO) Clinical Practice Guideline was published in Practical Radiation Oncology in 2021 [2]. Multiple advances have occurred since these publications including the shift towards preoperative radiotherapy as standard of care, advancements in planning and delivery techniques (image-guided intensity-modulated

radiotherapy [IMRT] or volumetric modulated arc therapy [VMAT]), dose adjustments for histological subtypes, and ongoing investigations into preoperative hypofractionation [3–6]. This European Society for Radiotherapy and Oncology (ESTRO) guideline provides an updated perspective that incorporates results from recent trials published since the initial guidance article and complements the ASTRO guideline [1,2]. The authors stress the importance of treatment by experienced clinicians at sarcoma expert centers to ensure optimal patient care [7–11].

Abbreviations: 3D-CRT, Three-dimensional conformal radiation therapy; ASTRO, American Society for Radiation Oncology; CBCT, Cone beam computed tomography; CT, Computed tomography; CTCAE, Common Terminology Criteria for Adverse Events; CTV, Clinical target volume; EQD2, Equivalent doses in 2 Gy fractions; ESTRO, European Society for Radiotherapy and Oncology; Dmean, The average radiation dose received across the entire volume of the organ, expressed in Gray; Dmax, The highest dose of radiation delivered to any point within the organ, expressed in Gray; FNCLCC, Fédération Nationale des Centres de Lutte Contre; G1, Grade 1 (low-grade); G2, Grade 2 (intermediate-grade); G3, Grade 3 (high-grade); GTV, Gross tumor volume; Gy, Gray; IMRT, Intensity-modulated radiation therapy; IGRT, Image-guided radiation therapy; KQ, Key question; kV, Kilovolt; MPNST, Malignant peripheral nerve sheath tumor; MRI, Magnetic resonance imaging; MSKCC, Memorial Sloan Kettering Cancer Center; MSTs, Musculoskeletal Tumor Society Score; MV, Megavolt; PERSARC, PERSONALISED SARcoma Care; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PTV, Planning target volume; R0, Complete resection; R1, Microscopically positive margin; RTOG, Radiation Therapy Oncology Group; SIB, Simultaneous Integrated Boost; T1, T1-weighted (MRI sequence); T2, T2-weighted (MRI sequence); TESS, Toronto Extremity Salvage Score; VXGy, Percentage of the organ receiving at least X Gy; VMAT, Volumetric modulated arc therapy.

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Materials and Methods

ESTRO convened a task force of 13 European experts, alongside 3 experts from ASTRO, to analyze current evidence, provide recommendations for the use of pre- or postoperative radiotherapy for soft tissue sarcoma of the extremity or trunk wall in adults, and establish expert consensus in areas lacking strong evidence. The writing panel included an international team of 14 radiation oncologists (including one in training), 1 radiation therapist, and 1 medical physicist.

Thirteen key questions (KQs) were identified, encompassing indications for external beam radiotherapy, pre- vs. postoperative radiotherapy, treatment preparation, patient positioning, target volume delineation, dose and fractionation, adverse events assessment, and dose guidance for organs of interest. Key recommendations were formulated and tabulated for each topic, addressing all identified KQs. The strength of recommendations and quality of evidence were classified according to the ASTRO Clinical Practice Guideline Methodology Guide [12].

A systematic review was conducted following the current Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [13]. Literature searches were performed in PubMed and the Cochrane Library using the following search items: “radiotherapy,” “radiation therapy,” “preoperative,” “postoperative,” “surgery,” “soft tissue sarcoma,” “sarcoma,” “extremity,” “limb,” “trunk wall,” “high-volume,” “nomogram,” “myxoid liposarcoma,” “myxofibrosarcoma,” “MPNST,” “cancer syndromes,” “local control,” “survival,” “toxicities,” “outcomes,” “margins,” “hypofractionation,” “immobilization,” “positioning,” “IMRT,” “VMAT,” and “pembrolizumab”. All relevant retrospective and prospective studies in English language published before December 2024 were included. During the manuscript drafting process, additional relevant studies were published in 2025 and were incorporated to ensure the manuscript reflects the most current evidence.

All task force members contributed to the final writing of the manuscript and approved the final version of the manuscript. The guideline rationale, scope, writing panel, and reviewing panels were approved by the ESTRO Guideline Committee.

Indications

KQ1: What are general indications for perioperative radiotherapy in extremity and trunk wall soft tissue sarcoma?

Surgery is the mainstay of treatment in most soft tissue sarcomas. Radiotherapy delivered as an adjunct reduces the risk of local recurrence [14,15]. The indication for radiotherapy is primarily based on the risk of local recurrence, which is influenced by anatomical site, anticipated margin status, size, grade, depth, and histological subtype and is balanced against the morbidity of radiotherapy [16–21]. Treatment decisions should be discussed within a multidisciplinary expert sarcoma tumor conference [7–11]. The primary consideration is whether the surgeon can achieve oncologically appropriate wide resection to ensure optimal tumor control with minimal morbidity. If a close or microscopically positive margin is anticipated, perioperative radiotherapy is essential in targeting microscopic tumor cells, allowing for a more conservative resection that spares function while maintaining effective local control [22]. Microscopically positive surgical margins are generally the strongest risk factor for local recurrence [22–27]. Moreover, grade, assessed according to the most commonly used classification system, the Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC), is considered when assessing recurrence risk, with intermediate and high-grade tumors (G2-3) often at higher risk than low-grade tumors (G1) [26,28,29]. Some histological subtypes, especially myxofibrosarcoma, are at increased risk for local recurrence [17–22]. Other risk factors for recurrence include prior local recurrences, larger tumor size, site, and depth [17–20,27,30,31]. Published predictive nomogram tool may be helpful in assessing local recurrence risk and guide decision-making [16,26]. All factors

contribute to local recurrence risk and should be discussed in a personalized decision-making process within the multidisciplinary tumor conference.

KQ2: What are the indications for preoperative versus postoperative radiotherapy in soft tissue sarcoma of the extremities and trunk wall?

Preoperative radiotherapy is recommended over postoperative radiotherapy due to its more favorable late adverse events profile i.e. lower risk of fibrosis, lymphedema, and joint stiffness, and equivalent oncological outcomes [32–35]. However, postoperative radiotherapy may be preferred in certain clinical scenarios such as, but not limited to: evidence of rapid tumor growth, clinical situations where the elevated risk of wound complications from preoperative radiotherapy would present a greater risk to the patient than the increased risk of late effects from postoperative radiotherapy, significant bleeding, fungating, or infected tumors, and an inability to maintain the therapeutic position due to tumor-related pain not responding sufficiently to conventional measures. Additionally, radiotherapy may be considered following unplanned non-oncological excisions (whoops procedures) to improve local tumor control when secondary wide re-resections are not feasible and active surveillance is not pursued [36].

KQ3: What specific considerations exist for certain subtypes of soft tissue sarcomas?

The following section outlines selected examples of soft tissue sarcoma subtypes and clinical scenarios requiring specific considerations for radiotherapy. This list is not exhaustive, and treatment decisions should be individualized and discussed within a multidisciplinary sarcoma team at an expert center.

Myxoid liposarcoma

Due to distinct radiosensitivity, myxoid liposarcomas can be downsized with radiotherapy, thereby facilitating surgical resection [37–42]. Therefore, preoperative radiotherapy is recommended (see also dose & treatment planning paragraph for further details).

Myxofibrosarcoma

Myxofibrosarcomas have an exceptionally infiltrative growth pattern and carry a high risk of local recurrence [18,19]. Radiotherapy is recommended in this patient population, and the use of more generous clinical target volume (CTV) margins may be appropriate (see Section 6: Target volume delineation and margins).

Low grade soft tissue sarcoma

In certain low-grade (G1) soft tissue sarcomas with a higher risk of local recurrence—such as cases with previous local recurrence(s)—radiotherapy may be considered [14,43]. This is particularly relevant when a subsequent salvage surgery for local recurrence would result in significant morbidity.

Radiation-associated sarcoma

Perioperative radiotherapy remains a treatment option for select cases of radiation-associated soft tissue sarcomas, with careful consideration of prior irradiation to normal tissues. The decision regarding the use of radiotherapy, and preoperative or postoperative radiotherapy sequencing should be individualized and discussed within a multidisciplinary tumor conference.

Soft tissue sarcoma associated with genetic cancer predisposition syndromes

Sarcoma patients with hereditary cancer predisposition syndromes, such as Li-Fraumeni or other germline TP53-related syndromes, or neurofibromatosis type 1, have an increased risk of developing secondary malignancies following radiotherapy [44,45]. There is no absolute contraindication to the use of radiotherapy in this population.

However, the risk–benefit ratio should be carefully evaluated on a case-by-case basis weighing the potential risk of radiation-associated malignancies with current clinical presentation and need for radiotherapy for optimal local control and consideration of alternative treatment approaches not including radiotherapy. It is recommended to consult the current evidence on radiotherapy in genetic syndromes for further guidance [44].

KQ4: What is the recommended time interval between the completion of preoperative radiotherapy and surgery or between surgery and the initiation of postoperative radiotherapy?

Although no definitive evidence supports a specific timeframe, a time window of 4 to 8 weeks between completion of preoperative radiotherapy and surgery is generally considered appropriate [46]. For postoperative radiotherapy, it should commence within 4 to 8 weeks following surgery. If delays occur due to factors such as wound healing or diagnostic assessments, postoperative radiotherapy should not be omitted and should proceed as soon as possible. Delays of up to 4 months after surgery (or the final surgery in the case of re-resection) can still be considered acceptable, and radiation treatment should proceed as planned. Radiotherapy is discouraged if delays beyond 4 months arise (Table 1).

Treatment preparation

KQ5: What are the key requirements prior to planning radiotherapy for soft tissue sarcomas of the extremities and trunk wall?

Patient assessment

Prior to recommendation for and initiation of radiotherapy, a thorough diagnostic workup with appropriate staging, histopathological review by a pathologist experienced in soft tissue sarcomas, and a dedicated multidisciplinary soft tissue sarcoma team evaluation should be conducted to ensure and confirm suitability and optimal treatment planning [47]. Evaluation at a sarcoma center by an experienced multidisciplinary team leads to optimal treatment recommendations and patient outcomes [7–11]. Clinically, it must be assessed whether the patient can lie on the treatment table and tolerate immobilization of the tumor region (trunk wall or extremity) for the required duration and over multiple fractions of treatment. Any discomforting symptoms, such as pain, shortness of breath, or mental health issues, that may hinder immobilization should be managed accordingly (see section on patient positioning, planning CT and image guidance).

Imaging of the primary tumor

A recent contrast-enhanced diagnostic MRI scan of the primary site, preferably obtained within the preceding two weeks, when possible, is recommended, unless contraindicated. In cases of suspected tumor growth since diagnostic investigations, a repeat MRI should be conducted. The diagnostic MRI should include both T1-weighted sequences with post-gadolinium contrast and T2-weighted sequences to assess edema that may harbor microscopic extension of sarcoma cells [48]. Ideally, the diagnostic MRI should be performed in the treatment position. Alternatively, a planning MRI with T1 post-gadolinium and T2 sequences can be used, as it is equally valid. If a diagnostic MRI has been used, it should be registered with the planning computed tomography (CT) scan. If registration is possible, a non-contrast planning CT may be used. If registration is not possible or contraindications for MRI exist, a contrast-enhanced planning CT is recommended (Table 2).

Table 1

Key recommendations for indications.

Recommendations	Strength of recommendation	Level of evidence
<i>KQ1: What are general indications for perioperative radiotherapy in extremity and trunk wall soft tissue sarcoma?</i>		
Radiotherapy indication should be based on local recurrence risk and reviewed by a multidisciplinary tumor conference.	Strong	High [14,22,28,48–49]
Radiotherapy is recommended for tumors with anticipated microscopically positive margins or after resection with positive margins.	Strong	Moderate [22–24,26,28]
Radiotherapy is recommended for patients with intermediate or high-grade tumors (G2–G3), and certain histological subtypes (e.g., myxofibrosarcoma, MPNST).	Strong	Moderate [18–21]
Predictive nomograms can assist in guiding decision-making based on recurrence risk.	Strong	Moderate [16,26]
<i>KQ2: What are the indications for preoperative versus postoperative radiotherapy in soft tissue sarcoma of the extremities and trunk wall?</i>		
Preoperative radiotherapy is recommended over postoperative radiotherapy.	Strong	Moderate [33,34]
Postoperative radiotherapy may be preferred in select cases (e.g., rapid tumor growth, high wound complication risk, positioning challenges), or when the risk of wound complications represents a greater risk to the patient than the increased rate of late toxicities.	Conditional	Expert Opinion
Postoperative radiotherapy may be considered after unplanned non-oncological excision (whoops procedure) when secondary re-resections are not feasible and active surveillance is not pursued.	Conditional	Expert Opinion
<i>KQ3: What specific considerations exist for certain subtypes of soft tissue sarcomas?</i>		
Due to distinct radiosensitivity of myxoid liposarcoma, preoperative radiotherapy is recommended to facilitate resection.	Strong	Moderate [37–42]
For myxofibrosarcoma, radiotherapy is generally recommended, with consideration of larger CTV margins due to its infiltrative growth pattern.	Strong	Low [18,19]
Radiotherapy may be considered in low-grade (G1) soft tissue sarcomas with an increased risk of local recurrence (e.g., previous recurrence(s)), particularly when salvage surgery for further recurrences would entail significant morbidity.	Conditional	Moderate [14,43]
In radiation-associated sarcomas, perioperative radiotherapy remains a treatment option, with decision individualized according to prior irradiation.	Conditional	Expert Opinion
In soft tissue sarcomas associated with genetic cancer predisposition syndromes, radiotherapy is not absolutely contraindicated, but benefits and risks should be carefully evaluated.	Conditional	Low [44]
<i>KQ4: What is the recommended time interval between the completion of preoperative radiotherapy and surgery or between surgery and the initiation of postoperative radiotherapy?</i>		
<u>Preoperative radiotherapy to surgery:</u> A treatment window of 4–8 weeks is considered appropriate. <u>Surgery to</u>	Strong	Expert Opinion

(continued on next page)

Table 1 (continued)

Recommendations	Strength of recommendation	Level of evidence
postoperative radiotherapy: Start within 4–8 weeks; proceed once healing and assessments are complete. Delays up to 4 months may be acceptable, but radiotherapy is discouraged beyond this.		
Delays due to factors such as wound healing or diagnostics should not preclude radiotherapy.	Strong	Expert Opinion

Abbreviations.

CTV = Clinical Target Volume; G1 = Grade 1 (low-grade); G2 = Grade 2 (intermediate-grade); G3 = Grade 3 (high-grade); KQ = Key question; MPNST = Malignant peripheral nerve sheath tumor; MSKCC = Memorial Sloan Kettering Cancer Center; PERSARC = PERSONALISED SARcoma Care.

Table 2
Key recommendations for treatment preparation.

Recommendations	Strength of recommendation	Level of evidence
KQ5: What are the key requirements prior to planning radiotherapy for soft tissue sarcomas of the extremities and trunk wall?		
Thorough diagnostic workup and dedicated multidisciplinary soft tissue team evaluation are recommended before initiation of radiotherapy.	Strong	Low [7–11,50]
A recent MRI of the primary site, preferably within the preceding two weeks, is recommended for treatment planning, unless contraindicated.	Strong	Expert Opinion
MRI should include T1-weighted sequences with post-gadolinium contrast to assess gross tumor and T2-weighted sequences to assess peritumoral edema.	Strong	Expert Opinion
MRI should be performed in the treatment position, if feasible.	Strong	Expert Opinion
Accurate registration of the non-contrast planning CT with MRI is essential for reliable target delineation.	Strong	Expert Opinion
If MRI is contraindicated or registration is inadequate, a contrast-enhanced planning CT is recommended.	Strong	Expert Opinion

Abbreviations.

CT = Computed tomography; KQ = Key question; MRI = Magnetic resonance imaging.

Patient positioning, planning CT and image guidance

KQ6: What is the optimal patient positioning for radiotherapy in soft tissue sarcomas of the extremities and trunk wall?

Personalized planning is essential for delivering radiotherapy to extremity and truncal soft tissue sarcomas. Patient positioning should account for tumor location, beam entry and exit, mobility limitations, and overall comfort. Comfort must be balanced with reproducibility and should remain a key consideration in all immobilization strategies. Immobilization should be tailored to each patient and tumor site. A neutral limb position should be the default goal unless clinically contraindicated, while limb rotation should be stabilized. Thermoplastic shells or customized rigid devices are recommended to reduce intra- and interfraction motion. Vacuum bags may be used when rigid options are not feasible, but they should ideally be combined with additional support devices, such as cushions or thermoplastic shells, to enhance reproducibility [49–52]. Vacuum bags are less preferred due to potential shape deformation or perforation over time, which can compromise

setup stability [49]. Materials used for immobilization should be positioned outside of the tumor volume to avoid dose build-up and associated skin toxicities and discomfort [53].

In proximal lower extremity sarcomas, patients may benefit from having the extremities separated using distal thermoplastic shells or other immobilization techniques. For upper extremity sarcomas, arm abduction may be beneficial for proximal tumors and distal tumors may benefit from forearm support with a hand rest and/or thermoplastic shells. The unaffected limb should be positioned as far as comfortably possible from the treatment field to maintain a neutral, reproducible setup. It can be abducted or elevated as far away as possible to optimize beam clearance. For male patients, genitalia should be appropriately displaced to minimize radiation dose to the region. For patients desiring fertility preservation, referral for reproductive counseling and appropriate interventions (e.g., sperm banking, oocyte preservation) should occur before radiotherapy. For trunk wall sarcomas, standard positioning should follow established protocols used for thoracic or abdominal tumors including respiratory management, based on tumor location and extent. Generally, for truncal tumors, supine positioning is preferred for set-up reproducibility, however for some patients with tumors located on the posterior chest wall or back who are uncomfortable lying flat, treatment in the prone position may be used with close attention to displacement due to respiratory motion.

Stable positioning is critical for defining planning target volume (PTV) margins [51,54]. Photographic documentation at CT simulation is recommended to serve as a visual reference for setup reproducibility. Strict adherence to institutional positioning protocols is essential to ensure consistency and minimize acute and late treatment-related toxicities.

KQ7: How should the planning CT be performed to ensure accurate target delineation?

Patient positioning at the planning CT for proximal thigh tumors should be head-first toward the gantry, whereas for tumors of the distal lower extremity, patients should be positioned feet-first toward the gantry. Surgical scars should be marked with radiopaque material. A planning CT with 2–3 mm slice thickness is recommended, extending from the most proximal to the most distal joint to include the full bone, tumor bed, surgical scar, biopsy or drain sites, and organs of interest. When possible, the planning CT should be registered with the MRI to aid target delineation [55,56]. Particular attention should be paid to tumor laterality, ensuring that the full diameter of the limb is captured within the field-of-view of the CT, with the limb centered on the table to minimize collision risks during treatment. Skin markings should be placed on stable anatomical landmarks to improve reproducibility.

KQ8: What are the best practices for image guidance during treatment delivery?

Daily image guidance is essential for all patients. At minimum, orthogonal kilovolt (kV) imaging is recommended, with cone-beam computed tomography (CBCT) preferred when feasible [51,54]. All translational and rotational shifts should be corrected where possible. Generally, tolerances of up to 5 mm (translation) and 3° (rotation) are accepted [50]. Any set-up error exceeding 1 cm should trigger a reassessment of positioning and immobilization. Institutions should audit their verification protocols, define consistent CBCT matching regions, and establish site-specific PTV margins to ensure high-quality and standardized practice [57]. Daily image-guided radiotherapy (IGRT) using orthogonal 2D kV and megavolt (MV) electronic images or CBCT is strongly advised to ensure accurate positioning [51,52,54]. A specific ESTRO guideline on limb positioning, immobilization and verification for radiotherapy is in preparation which will complement this paper (Table 3).

Table 3

Key recommendations for patient positioning, planning CT and image guidance.

Recommendations	Strength of recommendation	Level of evidence
<i>KQ6: What is the optimal patient positioning for radiotherapy in soft tissue sarcomas of the extremities and trunk wall?</i>		
Patient positioning should account for tumor location, beam entry and exit, mobility limitations, and overall comfort, balancing reproducibility.	Strong	Expert Opinion
A neutral limb position is preferred unless clinically contraindicated, while limb rotation should be stabilized.	Strong	Expert Opinion
Thermoplastic shells or customized rigid devices are recommended to minimize intra- and interfraction motion.	Strong	Moderate [53–55]
Vacuum bags may be used if rigid devices are not feasible, ideally combined with additional supports (e. g., cushions, thermoplastic shells), to enhance reproducibility.	Strong	Low [52]
Immobilization materials should be placed outside the tumor volume to avoid dose build-up and skin side effects.	Strong	Low [56]
For proximal lower extremity sarcomas, extremities should be separated using distal thermoplastic shells or other immobilization techniques.	Strong	Expert Opinion
In upper extremity sarcomas, arm abduction is recommended for proximal tumors, while distal tumors may benefit from forearm support with a hand rest and/or thermoplastic shells.	Strong	Expert Opinion
The unaffected limb should be positioned as far as comfortably possible from the treatment field to maintain a neutral, reproducible setup and optimize beam clearance.	Strong	Expert Opinion
Male genitalia should be appropriately displaced to minimize radiation exposure.	Strong	Expert Opinion
Positioning for trunk wall sarcomas should follow standard thoracic or abdominal protocols, including respiratory management, depending on tumor location and extent. Posterior chest wall or back tumors may be treated in prone position if comfortable for the patient and such positioning does not introduce set up uncertainty.	Strong	Expert Opinion
Stable positioning is recommended to ensure accurate PTV margin definition.	Strong	Moderate [54,57]
Photographic documentation at CT simulation is recommended to ensure setup reproducibility.	Strong	Expert Opinion
<i>KQ7: How should the planning CT be performed to ensure accurate target delineation?</i>		
For proximal thigh tumors, head-first CT scanning toward the gantry is recommended; for distal lower extremities, feet-first scanning toward the gantry is recommended.	Strong	Expert Opinion
Surgical scars should be marked with radiopaque material.	Strong	Expert Opinion
Planning CT should use a 2–3 mm CT slice thickness and cover from the most proximal to most distal joint, including the full bone, tumor bed, surgical scar, biopsy or drain sites, and organs of interest.	Strong	Expert Opinion

Table 3 (continued)

Recommendations	Strength of recommendation	Level of evidence
Planning CT should be registered with diagnostic MRI to aid target delineation	Strong	Low [58,59]
<i>KQ8: What are the best practices for image guidance during treatment delivery?</i>		
Daily image guidance should be used to ensure setup reproducibility. At a minimum, use orthogonal kV imaging; CBCT is preferred when feasible and safe.	Strong	Moderate [54,55,57,61]
Setup tolerances should be maintained within 5 mm (translation) and 3° (rotation), errors greater than 1 cm should prompt reassessment.	Strong	Expert Opinion
Institutions should audit verification protocols, define CBCT matching regions, and set site-specific PTV margin expansions.	Strong	Expert Opinion

Abbreviations.

CBCT = Cone-beam computed tomography; CT = Computed tomography; KQ = Key question; MRI = Magnetic resonance imaging; PTV = Planning target volume.

Target volume delineation and margins

KQ9: How should target volumes and margins be delineated for soft tissue sarcomas of the extremities and trunk wall?

Preoperative radiotherapy

The gross tumor volume (GTV) is defined by the visible tumor on T1-weighted contrast-enhanced MRI, registered to the planning CT. The CTV is created by adding a minimum of 3 cm longitudinal margin along the tumor's axis following muscle fibers with a minimum of 1.5 cm radial margin, with expansion as needed to include peritumoral edema on T2-weighted MRI (see Fig. 1). In myxofibrosarcomas, which have an exceptionally infiltrative growth pattern, a longitudinal margin of up to 4 cm may be more appropriate. CTV margins should respect anatomical barriers such as fascia, bone, and skin and should be cropped at these structures when there is no evidence of tumor invasion (see Fig. 2); if infiltration is suspected, margins may need to be extended accordingly. Inclusion of the biopsy tract is encouraged whenever feasible. Bolus should be used routinely only if the skin is clearly infiltrated on clinical examination and/or diagnostic imaging, and if this skin will not be resected at surgery.

Postoperative radiotherapy

Target delineation for postoperative radiotherapy delivery remains the same as originally defined in the 2012 guidance article by Haas et al. [1]. To revisit and summarize, the “GTV” should be reconstructed by registering the preoperative MRI with the planning CT and reviewing the postoperative pathology and operative notes. To construct the CTV elective, the “GTV” is expanded with a 4 cm longitudinal margin along the muscle fibers, while respecting surgically non-disrupted structures such as fascia and bones if not infiltrated. The tumor bed/seroma, surgical clips, scar and drain sites are routinely included. In the radial direction, a 1.5 cm margin should be applied. The CTV does not include the skin surface and may be cropped 1–5 mm from the skin surface depending on the anatomical site. The use of bolus is not recommended if the skin was not infiltrated on preoperative imaging or in the pathological specimen. In circumstances with a close or positive superficial margin at the skin, the use of bolus can be considered. For the CTV boost volume, the CTV elective volumes are used, but the longitudinal margin along the muscle fibers is reduced to 2 cm, while the radial margin remains 1.5 cm. The same anatomical structures are respected in the CTV

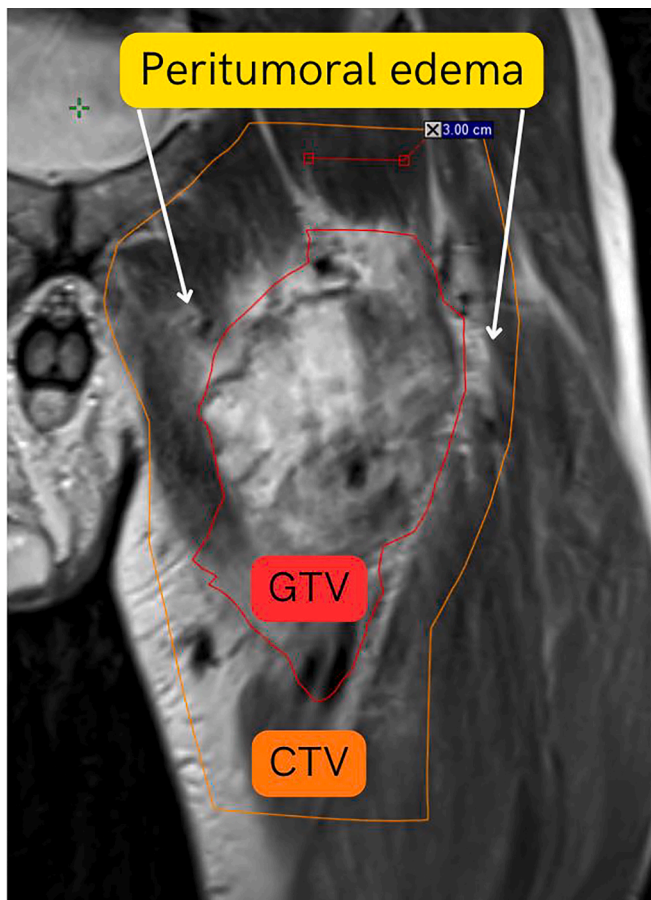


Fig. 1. Soft tissue sarcoma with peritumoral edema. Coronal T2-weighted magnetic resonance imaging (MRI) of the proximal lower extremity in a patient with a grade 3 leiomyosarcoma of the left thigh. The gross tumor volume (GTV) corresponds to the tumor delineated on contrast-enhanced T1-weighted MRI. The clinical target volume (CTV) includes axial and longitudinal expansions of the GTV and encompasses the peritumoral edema visible on T2-weighted imaging, in accordance with recommended radial (approximately 1.5 cm) and longitudinal (3–4 cm) margins.

boost volume as in the CTV elective volume.

Planning target volumes

For preoperative and postoperative treatment volumes, a minimum CTV-to-PTV margin of 5 mm should be applied if daily image guidance is utilized, with adjustments made according to institutional set-up error measurements and protocols [51] (Table 4).

Dose & treatment planning

KQ10: What is the recommended radiation dose prescription for treating soft tissue sarcomas?

Standard dosing regimens

Preoperative radiotherapy. The standard preoperative radiotherapy regimen consists of daily fractions of 1.8–2 Gy, up to 50–50.4 Gy over 5–6 weeks [33,34,54,58,59]. The addition of a postoperative boost following preoperative radiotherapy after resection with microscopically positive margins (R1) is not recommended, even if residual microscopic disease is anticipated [60,61]. Importantly, this applies in particular to situations where positive margins after preoperative radiotherapy are located at neurovascular bundles or the periosteum. In

these settings, multiple series have demonstrated local recurrence rates comparable to those achieved after preoperative radiotherapy and resections with negative margins [25,62]. Therefore, a postoperative boost does not provide additional local control benefit in these scenarios and should not be administered.

Postoperative radiotherapy

In the postoperative setting, the standard protocol includes daily fractions of 1.8–2 Gy to 50–50.4 Gy for the larger target volume (PTV elective), with a sequential boost or simultaneous integrated boost (SIB, see below) to a smaller volume (PTV boost) up to 60 Gy after resection with clear surgical margins (R0) or up to 66 Gy for R1 resections. This corresponds to an overall treatment duration of approximately 6–7 weeks for R0 resections and 7–8 weeks for R1 resections (see also alternative regimens paragraph as well as target volume delineation and margins paragraph for details) [33,34].

Alternative regimens

Preoperative radiotherapy with dose reduction for myxoid liposarcoma

Prospective and retrospective data have demonstrated excellent radiosensitivity for myxoid liposarcoma [37–39]. Preoperative radiotherapy is preferred, as it can effectively downsize the tumor and improve resectability. A recent study indicated, that a dose reduction to 36 Gy, delivered in 2 Gy daily fractions, does not compromise local control. Use of this regimen is investigational and can be considered in select patients.

Preoperative hypofractionated radiotherapy

Numerous promising trials have investigated preoperative hypofractionation with daily radiation doses of 2.85 Gy to ≥ 6 Gy, and ongoing studies will clarify its impact, especially on late effects [4,5,64–74]. Until optimal regimens are validated against conventional fractionation in randomized trials, preoperative hypofractionation cannot be considered standard of care [75,76]. For a detailed discussion on preoperative hypofractionation, see Future perspectives paragraph.

Postoperative radiotherapy with simultaneous integrated boost

For R0-resected tumors, postoperative SIB radiotherapy over 5–6 weeks can be used achieving an equivalent dose in 2 Gy fractions (EQD2) of 50–50.4 Gy ($\alpha/\beta = 4$ Gy) in 25–28 daily fractions to the larger volume (PTV elective) and simultaneously 25–28 daily fractions to an EQD2 of 60 Gy to the smaller boost volume (PTV boost) [58,69]. For R1-resected tumors, EQD2 of 66 Gy in 25–28 daily fractions to the smaller boost volume (PTV boost), along with EQD2 of 50–50.4 Gy in 25–28 daily fractions to the larger volume (PTV elective), may be delivered [58].

KQ11: How should treatment for soft tissue sarcomas be planned?

In general, highly conformal photon-based radiation techniques like IMRT or VMAT are preferred over 3D conformal approaches due to their improved side effect profile while maintaining equivalent local tumor control [54,58,59,77,78]. However, in select cases, comparison plans of static three-dimensional conformal radiation therapy (3D-CRT) may offer superior normal tissue sparing over IMRT-based techniques and a thorough individual plan comparison is recommended. Proton beam radiotherapy is an alternative highly conformal radiation technique that can be considered for extremity and trunk wall soft tissue sarcoma [79–81] (Table 5).

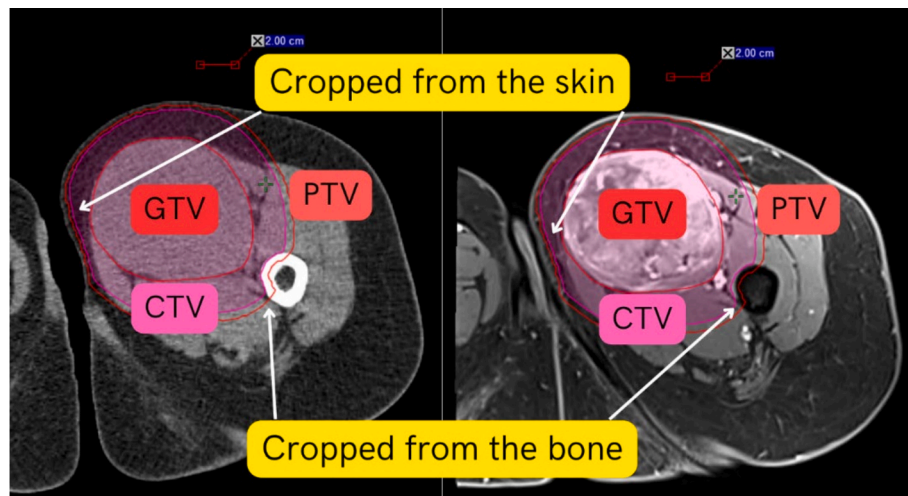


Fig. 2. Cropping of the clinical target volume at anatomical barriers. Axial planning computed tomography (CT, left image) without contrast and co-registered post-contrast T1-weighted magnetic resonance imaging (MRI, right image) of the proximal lower extremity in a patient with an undifferentiated pleomorphic sarcoma (FNCLCC grade 3) of the left thigh adductor compartment. The gross tumor volume (GTV) corresponds to the tumor delineated on contrast-enhanced T1-weighted MRI. The clinical target volume (CTV) is generated by applying standard radial expansions (1.5 cm) and is appropriately cropped at uninvolved anatomical barriers, including bone and skin, where no radiological evidence of tumor infiltration is present. The CTV is subsequently expanded using institution-specific margins to generate the planning target volume (PTV) to account for setup uncertainties and patient motion. This figure illustrates modification of CTV margins to respect physical boundaries while maintaining oncologically adequate coverage.

Adverse events assessment and dose guidance

KQ12: How should radiotherapy treatment-related adverse events be assessed and documented?

Standardized adverse events grading systems, such as the Common Terminology Criteria for Adverse Events (CTCAE), are essential for accurately assessing and reporting treatment-related adverse events in radiation therapy for soft tissue sarcoma of the extremities and trunk wall and should be used for consistent adverse events evaluation [82]. The Radiation Therapy Oncology Group (RTOG) criteria also offer guidelines for radiotherapy-induced toxicities [83]. In addition, acute adverse events up to 120 days after surgery in the form of wound complications, as reported in the CAN-NCIC-SR2 trial, should be recorded [33,34]. Stern's scale is recommended for lymphedema assessment, while the Toronto Extremity Salvage Score (TESS) and the Musculoskeletal Tumor Society Score 87 (MSTS 87) and 93 (MSTS 93) are valuable for evaluating functional outcomes measurement [84–86]. Adverse events assessments, which should be routinely and consistently measured and reported, should include at a minimum joint stiffness, lymphedema, fractures, subcutaneous fibrosis, wound healing delay beyond 180 days after surgery, and pain. Furthermore, amputation of a treated limb for reasons other than local recurrence and salvage should be recorded. We recommend a standardized timeline for adverse events assessment, including evaluations at pre-treatment, 4–6 weeks post-treatment, and at 3, 6, 12, and 24 months, to ensure consistency in reporting and comparability across studies.

KQ13: What dose guidance and additional considerations should be applied for organs of interest in treatment planning?

Precise contouring of organs of interest and the application of specific dose guidance are essential for delivering the prescribed target dose while minimizing acute and late toxicities in radiotherapy for extremity and trunk wall soft tissue sarcomas [35,54,88–90]. Depending on tumor location, organs of interest may include weight-bearing bones, skin and subcutaneous tissue, joints, peripheral nerves and others [87–89]. Table 6 summarizes the recommended dose guidance and contouring guidelines for specific organs of interest. It is worth highlighting that

generally PTV dose coverage should be prioritized over organ of interest constraints, except for vital organs of interest (e.g., spinal cord).

Weight-bearing bones

The entire circumferential volume of weight-bearing bones (including the femur, tibia and humerus) should be contoured, extending 2 cm above and below the PTV [35,91]. Dose guidance should be maintained at V40Gy < 64%, Dmean < 37 Gy, and Dmax < 59 Gy to reduce fracture risk, if achievable without compromises in target dose coverage. Fracture risk increases with radiation dose: each 1 Gy above a maximum dose of 59 Gy raises fracture risk by 10%, and each 1 Gy above a mean dose of 37 Gy raises fracture odds by 9%. Additionally, V50Gy should be kept below 50% and delivery of 50 Gy to whole bone circumference should be avoided if possible [35,90]. The femoral head and neck should be contoured from the top of the femoral head to the most inferior aspect of the lesser trochanter. The mean dose should be kept below 40 Gy [88]. If dose guidance cannot be maintained and the patient has additional fracture risk factors—such as older age, female sex, large tumor size, or anticipated periosteal stripping—a discussion with an orthopedic oncologist regarding prophylactic surgical interventions should be undertaken [90,92]. Dose to adjacent joints should be minimized without compromising target volume coverage.

Brachial plexus and other major peripheral nerves

The brachial plexus and other major peripheral nerves should be contoured according to institutional guidelines. The maximum dose (Dmax) should be kept below 60–66 Gy while prioritizing target volume coverage [89].

Genitalia and fertility

Dose exposure to the genitalia and reproductive organs should be minimized by contouring and sparing the specific organs wherever possible. For patients wishing to preserve fertility, referral for reproductive counseling and appropriate interventions should occur before radiotherapy to the pelvis or genitalia, and external genitalia should be displaced from the treatment fields whenever possible.

Circumferential extremity dose

Dose to the extremity circumference should be carefully evaluated

Table 4

Key recommendations for target volume delineation and margins.

Recommendations	Strength of recommendation	Level of evidence
<i>KQ9: How should target volumes and margins be delineated for soft tissue sarcomas of the extremities and trunk wall?</i>		
<i>Preoperative radiotherapy</i>		
GTV should be defined based on T1-weighted post-gadolinium MRI.	Strong	Expert Opinion
GTV-to-CTV expansion: Minimum 3 cm longitudinal margin along muscle fibers and 1.5 cm radial margin.	Strong	Moderate [37,57]
CTV should include peritumoral edema on T2-weighted MRI (see Fig. 1; Appendix).	Strong	Moderate [25,51,57]
CTV should be restricted to anatomical borders (fascia, bone, and skin) unless there is evidence of tumor infiltration (see Fig. 2, Appendix).	Strong	Moderate [57,62,63]
Inclusion of the biopsy tract is encouraged whenever feasible.	Conditional	Expert Opinion
Routine use of bolus is not recommended, except when diagnostic imaging shows skin infiltration and that skin will not be resected en bloc with the tumor.	Strong	Moderate [57,62,63]
<i>Postoperative radiotherapy</i>		
CTV elective should be defined using reconstructed preoperative MRI-based GTV with a 4 cm longitudinal margin and 1.5 cm radial margin, including the tumor bed/seroma, surgical scars or clips, and drain sites.	Strong	Expert Opinion
CTV elective should be limited to surgically non-disrupted (intact) anatomical boundaries.	Strong	Low [62]
Routine inclusion of the skin surface and use of bolus is not recommended, unless skin infiltration is evident on preoperative imaging or pathology (close or positive superficial margins at skin).	Strong	Low [62]
CTV boost should follow the same principles and anatomical boundaries as CTV elective, with a reduced longitudinal margin of 2 cm.	Strong	Moderate [33,62]
<i>Planning target volumes</i>		
When daily image guidance is employed, the minimum recommended CTV-to-PTV margin is 5 mm.	Strong	Moderate [54,55,57,61]

Abbreviations.

CTV = Clinical target volume; GTV = Gross tumor volume; KQ = Key question; MRI = Magnetic resonance imaging; PTV = Planning target volume.

during treatment planning and plan review to minimize the risk of soft tissue toxicity, fibrosis, and lymphedema. While contouring a dedicated skin or subcutaneous tissue strip as an organ at risk is not routinely required with modern IMRT or VMAT techniques, treatment plans should aim to avoid delivery of intermediate or high doses circumferentially around the entire limb. As a practical planning objective, dose distributions should be optimized such that the full extremity circumference does not receive approximately 20 Gy or greater, where achievable without compromising target coverage.

Other organs of interest

Other organs of interest located near the target volume should be managed according to institutional guidelines for the respective anatomical site (Table 6).

Future perspectives

Numerous emerging topics have the potential to significantly

Table 5

Key recommendations for dose & treatment planning.

Recommendations	Strength of recommendation	Level of evidence
<i>KQ10: What is the recommended radiation dose prescription for treating soft tissue sarcomas?</i>		
<i>Preoperative radiotherapy</i>		
A regimen of 25–28 daily fractions of 1.8–2 Gy, totaling 50–50.4 Gy over 5–6 weeks is recommended.	Strong	Moderate [33,34,57,62,63]
A postoperative boost after preoperative radiotherapy and R1 resection is not recommended.	Strong	Low [64,65]
For myxoid liposarcoma, a preoperative dose reduction to 36 Gy in 18 fractions can be considered in select patients.	Conditional	Moderate [37–42]
The routine clinical use of preoperative hypofractionated regimens is not recommended.	Strong	Expert Opinion [80]
<i>Postoperative radiotherapy</i>		
For PTV-elective, a regimen of 25 daily fractions of 2 Gy (total 50 Gy over 5 weeks) is recommended. For PTV boost, additional daily fractions of 2 Gy up to 60 Gy for R0 resection or 66 Gy for R1 resection are recommended.	Strong	Moderate [33]
Simultaneous integrated boost (SIB) may be used as an alternative to sequential boost. The target dose to PTV elective should correspond to an EQD2 of 50 Gy ($\alpha/\beta = 4$ Gy) in 28 daily fractions, while the target dose to PTV boost should correspond to an EQD2 of 60 Gy for R0 resection or 66 Gy for R1 resection in 28 daily fractions.	Conditional	Low [62,87]
<i>KQ11: How should treatment for soft tissue sarcomas be planned?</i>		
Highly conformal radiation techniques, such as IMRT or VMAT, are preferred over other radiotherapy techniques.	Strong	Moderate [57,62,63,82,83]
3D-CRT may be considered in select cases to improve healthy tissue sparing.	Conditional	Expert Opinion
Proton beam radiotherapy is an alternative radiation technique that can be considered.	Conditional	Low [84–86,88]

Abbreviations.

3D-CRT = Three-Dimensional Conformal Radiation Therapy; CBCT = Cone-beam computed tomography; EQD2 = Equivalent dose in 2 Gy fractions; IGRT = Image-Guided Radiation Therapy; IMRT = Intensity-Modulated Radiation Therapy; KQ = Key question; kV = Kilovolt; MV = Megavolt; R0 = Complete resection; R1 = Microscopically positive margin; SIB = Simultaneous integrated boost; VMAT = Volumetric Modulated Arc Therapy.

influence the field of extremity and trunk wall soft tissue sarcoma radiotherapy in the future, although they have not yet been widely adopted in clinical practice.

The optimal management after non-oncological excision (“whoops” procedure) with microscopically negative margins and no residual disease on postoperative MRI remains under debate [93–95]. In particular, the respective roles of secondary surgery and neoadjuvant radiotherapy are unclear, as robust prospective data addressing this clinically relevant scenario are currently lacking. Addressing this gap represents an important priority for future research.

While concurrent chemotherapy use was outside the scope of this guideline, several systemic therapies given concomitantly with radiotherapy for localized extremity and trunk wall soft tissue sarcoma hold promise and are being investigated. The use of concomitant radiochemotherapy has been investigated in several trials combining preoperative radiotherapy with established drugs such as trabectedin or

Table 6

Key recommendations for adverse events assessment and dose guidance.

<i>KQ12: How should radiotherapy treatment-related adverse events be assessed and documented?</i>			
Recommendations	Strength of recommendation	Quality of evidence	
<i>Adverse events assessment</i>			
Assessment and reporting of radiotherapy-related adverse events using established grading systems (e.g., CTCAE, RTOG, Stern's scale), wound complications (CAN-NCIC-SR2 trial), and functional outcomes (TESS, MST5 87, MST5 93) is strongly recommended.	Strong	Moderate [32–35,91–94]	
A standardized adverse events evaluation schedule is recommended, including assessments pre-treatment, at 4–6 weeks post-treatment, and at 3-, 6-, 12-, and 24-month.	Strong	Expert Opinion	
Sarcoma treatment-specific toxicities should be measured and reported at a minimum for joint stiffness, lymphedema, fractures, subcutaneous fibrosis, amputation of the treated limb for reasons other than local recurrence, delayed wound healing beyond 180 days after surgery, and pain.	Strong	Moderate [32–35]	
<i>KQ13: What dose guidance and additional considerations should be applied for organs of interest in treatment planning?</i>			
Organ of interest	Contouring guidelines	Dose guidance (EQD2)	Quality of evidence
Femur, tibia, and humerus	Contour the bone 2 cm above and below the PTV.	V40Gy < 64% Dmean < 37 Gy Dmax < 59 Gy Full bone circumference < 50 Gy	Low [35,97,98]
Femoral head and neck	Contour from the top of the femoral head to the most inferior aspect of the lesser trochanter.	Dmean < 40 Gy	Low [95]
Brachial plexus and other major peripheral nerves	Contour the brachial plexus and major peripheral nerves as per institutional guidelines.	Dmax < 60–66 Gy	Moderate [96]
Circumferential extremity soft tissue	Routine contouring of a dedicated skin/subcutaneous strip is not required. Circumferential dose should be carefully evaluated during plan optimization and review.	Circumferential dose < 20 Gy	Expert opinion
<i>Additional considerations</i>			
Recommendations	Strength of recommendation	Quality of evidence	
Delineation of extremity-specific organs of interest is recommended.	Strong	Moderate [35,57,95,96]	
PTV dose coverage should be prioritized over organ of interest dose guidance, except for vital organs of interest (e.g., spinal cord).	Strong	Expert Opinion	
Fertility preservation strategies should always be considered in patients of childbearing age prior to radiotherapy near the genitalia.	Strong	Expert Opinion	
Dose exposure to genitalia and reproductive organs should be minimized, and institutional protocols for displacing the scrotum during treatment are recommended.	Strong	Expert Opinion	

Table 6 (continued)

<i>KQ12: How should radiotherapy treatment-related adverse events be assessed and documented?</i>		
Recommendations	Strength of recommendation	Quality of evidence
Management of other organs of interest near the target volume should follow institutional guidelines for the specific anatomical site.	Strong	Expert Opinion

Abbreviations.

CTCAE = Common Terminology Criteria for Adverse Events; Dmax = The highest dose of radiation delivered to any point within the organ, expressed in Gray (Gy); Dmean = The average radiation dose received across the entire volume of the organ, expressed in Gray (Gy); KQ = Key question; MST5 = Musculoskeletal Tumor Society Score; PTV = Planning target volume; RTOG = Radiation Therapy Oncology Group; TESS = Toronto Extremity Salvage Score; VXGy = Percentage of the organ receiving at least X Gy.

epirubicin/ifosfamide as well as other targeted drugs with various results [96–98]. The SU2C-SARC032 randomized phase II trial demonstrated a significant disease-free survival benefit by combining anti-PD-1 immunotherapy with preoperative radiotherapy for high-grade undifferentiated pleomorphic sarcoma and dedifferentiated liposarcoma. Notably, this trial marked a significant step in integrating immunotherapy into the management of localized soft tissue sarcoma [99].

The EORTC 62961-ESHO 95 randomized clinical trial reported an overall survival benefit with the addition of regional hyperthermia to neoadjuvant chemotherapy in a pooled cohort of retroperitoneal and extremity soft tissue sarcoma [100,101]. Specifically for extremity and trunk wall soft tissue sarcoma, the role of additional regional hyperthermia has not reached level 1 evidence yet. A well-designed randomized trial investigating the role of regional hyperthermia in addition to radiotherapy for extremity and trunk wall soft tissue sarcoma is warranted [102].

Building on evidence from prostate, breast, and rectal cancers, where hypofractionation at specific daily radiation doses has proven at least non-inferior to conventional fractionation, a similar trend can be observed in extremity and trunk wall soft tissue sarcomas [103–107]. Hypofractionation offers possible radiobiological advantages alongside practical benefits such as fewer treatment sessions, shorter overall treatment times (key considerations for frail, immobile patients and in low-resource settings with limited access to radiotherapy) [5,69,70,109–111]. However, the long-term side effects of hypofractionation must be rigorously evaluated before it becomes a standard of care.

Prospective published and ongoing single-arm studies have explored and are exploring, moderate preoperative hypofractionation (e.g., 2.85 Gy × 15 fractions) and ultra-hypofractionation (5 Gy to 8 Gy × 5 fractions) using photon and proton radiation and achieving EQD2 values ranging from 37.5 Gy to 80 Gy ($\alpha/\beta = 4$ Gy) [4,64–74]. While local tumor control appears equivalent to conventional fractionation for most hypofractionated regimens investigated, the risk of early and late adverse events to normal tissue rises substantially with increasing EQD2 of either the total or daily fractional dose [112–114]. Until optimal dosing regimens are established and validated for local control and late effects in head-to-head comparisons with conventional fractionation, preoperative hypofractionation cannot yet be considered standard of care [75]. The results of the completed randomized phase II trial from the Netherlands Cancer Institute (NCT04425967) comparing 25 × 2 Gy to 14 × 3 Gy are highly anticipated [76].

Concluding remarks

Despite advances in imaging modalities, radiotherapy techniques, and personalized radiotherapy approaches, the core principles of treatment planning remain largely consistent with historical practices.

Preoperative conventionally fractionated radiotherapy, delivered using highly conformal techniques and volumetric imaging, followed by surgery, remains the preferred sequencing strategy for localized soft tissue sarcoma.

Innovative approaches, including moderate and ultra-hypofractionation, combination of radiotherapy with systemic therapies such as immunotherapy, and further histological subtype-specific dose individualization, are promising and under investigation. However, these strategies require further evidence before adoption into routine clinical practice. Multidisciplinary evaluation and discussion at expert sarcoma centers and shared decision-making with the patient remain essential to determine the optimal treatment approach for each patient to optimize patient outcomes.

CRediT authorship contribution statement

Siyer Roohani: Conceptualization, Data curation, Investigation, Methodology, Writing – original draft. **Mateusz Jacek Spalek:** Conceptualization, Investigation, Methodology, Visualization, Writing – original draft. **Ninna Aggerholm-Pedersen:** Investigation, Writing – original draft. **Franziska Eckert:** Investigation, Writing – original draft. **B. Ashleigh Guadagnolo:** Investigation, Writing – review & editing. **David G. Kirsch:** Investigation, Writing – review & editing. **Cécile Le Péchoux:** Investigation, Writing – original draft. **Aisha B. Miah:** Investigation, Writing – original draft. **Kilian E. Salerno:** Investigation, Writing – review & editing. **Claudia Sangalli:** Investigation, Writing – original draft. **Rita Simões:** Investigation, Writing – original draft. **Renate Walter:** Investigation, Writing – original draft. **Lisette M. Wiltink:** Investigation, Writing – original draft. **Shane Zaidi:** Investigation, Writing – original draft. **Beate Timmermann:** Conceptualization, Investigation, Supervision, Writing – original draft. **Rick L. Haas:** Conceptualization, Investigation, Supervision, Writing – original draft.

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Siyer Roohani^{a,b,1,*}, Mateusz Jacek Spalek^{c,d,1},
 Ninna Aggerholm-Pedersen^e, Franziska Eckert^f,
 B. Ashleigh Guadagnolo^g, David G. Kirsch^{b,h}, Cécile Le Péchouxⁱ,
 Aisha B. Miah^j, Kilian E. Salerno^k, Claudia Sangalli^l,
 Rita Simões^{j,m,n}, Renate Walter^o, Lisette M. Wiltink^{p,q},
 Shane Zaidi^r, Beate Timmermann^{s,1}, Rick L. Haas^{p,q,1}

^a Department of Radiotherapy and Radiation Oncology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

^b Radiation Medicine Program, Princess Margaret Cancer Centre, University Health Network, Toronto, Ontario, Canada

^c Department of Radiotherapy I, Maria Skłodowska-Curie National Research Institute of Oncology, Warsaw, Poland

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

- ^e Department of Oncology, Department of Clinical Medicine, Aarhus University Hospital, Aarhus, Denmark
- ^f Department of Radiation Oncology, Comprehensive Cancer Center, Medical University Vienna, Währinger Gürtel 18-20, 1090 Vienna, Austria
- ^g Department of Radiation Oncology, MD Anderson Cancer Center, Houston, TX, USA
- ^h Department of Radiation Oncology and Department of Medical Biophysics, University of Toronto, Toronto, Ontario, Canada
- ⁱ Department of Radiation Oncology, Gustave Roussy, Villejuif 94850, France
- ^j Department of Radiotherapy and Physics, The Royal Marsden Hospital and The Institute of Cancer Research, London, the United Kingdom of Great Britain and Northern Ireland
- ^k Radiation Oncology Branch, National Cancer Institute, Bethesda, MD, USA
- ^l Department of Radiation Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy
- ^m Radiotherapy and Proton Beam Therapy Departments, University College London Hospitals NHS Foundation Trust, London NW1 2BU, the United Kingdom of Great Britain and Northern Ireland
- ⁿ UK Radiotherapy Trials Quality Assurance (RTTQA) Group, Radiotherapy Physics, Mount Vernon Cancer Centre, Northwood, the United Kingdom of Great Britain and Northern Ireland
- ^o Department of Medical Physics, Universitätsklinikum Augsburg, Stenglinstr 2, 86156 Augsburg, Germany
- ^p Department of Radiation Oncology, Leiden University Medical Center, Leiden, the Netherlands
- ^q Department of Radiotherapy, Netherlands Cancer Institute, Amsterdam, the Netherlands
- ^r Department of Clinical Oncology, The Royal Marsden Hospital and The Institute of Cancer Research, London, the United Kingdom of Great Britain and Northern Ireland
- ^s Department of Particle Therapy, University Hospital Essen, West German Proton Therapy Centre Essen (WPE), West German Cancer Center (WTZ), German Cancer Consortium (DKTK), Essen, Germany
- ^{*} Corresponding author at: Department of Radiotherapy and Radiation Oncology, University Clinic Hamburg-Eppendorf, Martinistrasse 52, O26, Sockelgeschoss, 20246 Hamburg, Germany.
E-mail address: s.roohani@uke.de (S. Roohani).

¹ Contributed equally.