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Pre- or postoperative radiotherapy for soft tissue sarcomas

Radiothérapie pré- ou postopératoire pour les sarcomes des tissus mous

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Abstract

Sarcomas are rare tumours arising from mesenchymal tissue. A multimodal management in an expert centre combining surgery and radiotherapy is the current standard of care for localized soft-tissue sarcomas of the extremities, to enable limb-sparing strategies. The delivery of pre- radiotherapy or postoperative radiotherapy offers similar local control and survival rates but the toxicity profile is quite different: preoperative radiotherapy increases the risk of wound complications and postoperative radiotherapy affects long-term functional outcomes. While postoperative radiotherapy has long been the rule, especially in Europe, technical improvements with image-guided- and intensity-modulated radiotherapy associated with a better management of postoperative wounds has tended to change practices with more frequent preoperative radiotherapy. More recently the possibilities of a hypofractionated regimen or potentiation by nanoparticles to increase the therapeutic index plead in favour of a preoperative delivery of radiotherapy. The aim of this paper is to report pros and cons of pre- and post-operative radiotherapy for soft-tissue sarcomas.

Keywords

Soft-tissue sarcomas, surgery, biopsy, imaging, radiotherapy; preoperative; postoperative

Résumé

Les sarcomes sont des tumeurs rares survenant à partir des tissus mésenchymateux. La prise en charge multimodale en centre expert associant chirurgie et radiothérapie est le standard thérapeutique actuel des sarcomes des tissus mous des membres de plus de 5 cm localisés, permettant une stratégie de préservation de membres. La délivrance de la radiothérapie pré- ou postopératoire offre des taux de contrôle local et de survie similaires mais avec un profil de toxicité différent : la radiothérapie préopératoire augmente le taux de complications de cicatrice et la radiothérapie postopératoire altère les capacités fonctionnelles sur le long terme. Alors que la radiothérapie postopératoire a longtemps été la règle, les améliorations techniques avec la radiothérapie conformationnelle avec modulation d'intensité guidée par l'image associées à une meilleure prise en charge de la cicatrisation postopératoire a permis d'observer un changement de pratiques avec davantage de recours à la

radiothérapie préopératoire. Plus récemment la possibilité de réalisation de schémas hypofractionnés ou la potentialisation par des nanoparticules afin d'augmenter l'index thérapeutique plaident en faveur d'une délivrance préopératoire de la radiothérapie. Cet article rapporte les principaux arguments en faveur de la radiothérapie pré- ou postopératoire pour les sarcomes des tissus mous.

Mots clés

Sarcomes des tissus mous, chirurgie, biopsie, imagerie, radiothérapie ; préopératoire ; postopératoire

1. Introduction

Sarcomas are rare tumours of mesenchymal cell origin. They represent 1 to 3% of adult cancers and have an incidence of approximately 6 per 100 000 per year in France. They are heterogeneous in terms of age distribution, site of presentation, histology, molecular biology, and prognosis. Mainstay of treatment is surgery. Quality of resection with initial complete resection is a major prognostic factor for survival. If amputation was the standard treatment for limb sarcomas 50 years ago, the combination of surgery and radiotherapy has progressively become the standard treatment with studies showing equivalent outcome and better functional outcome. Based on two randomized studies, postoperative radiotherapy has been the rule for several reasons [1, 2]: in the era before systematic biopsy, histological diagnosis was key. Moreover, the notion that sarcomas were radioresistant was against radiotherapy for macroscopic disease. However, radiotherapy of sarcomas can be delivered pre- or postoperatively; and like the switch observed in the last twenty years for rectal cancer, the therapeutic landscape is changing towards the use of preoperative radiotherapy. While this is mainly for soft tissue sarcoma, preliminary data suggest that some subtypes and locations may benefit more than others from this strategy. The following article addresses the pros and cons as well as evidence-based data regarding these two strategies.

2. Overview of main practice and main results (literature review)

Oncologic toxicity and functional outcomes according to timing of radiotherapy:

Surgery has historically been the sole treatment of soft tissue sarcomas. Radiotherapy was later introduced for soft tissue sarcoma of the extremities associated to conservative surgery to avoid amputation and improve quality of life while maintaining survival rates [3, 4]. Changes in quality of diagnostic imaging by the introduction of CT scan and most particularly MRI, have also contributed to the improvement of soft tissue sarcoma combined treatment. This has been mostly with postoperative radiotherapy (external beam or brachytherapy) but in North America, combined modality treatments integrating preoperative radiotherapy have also been conducted during this period [5, 6].

According to several retrospective studies, pre- and postoperative radiotherapy yielded similar local control ($83 \pm 12\%$ vs. $91 \pm 8\%$; $P = 0.41$) and overall survival rates ($75 \pm 15\%$ vs. $79 \pm 11\%$; $P = 0.94$). Higher rates of wound complications were observed after preoperative radiotherapy (31% vs.

8%; $P = 0.0014$) [7, 8]. However, other teams have integrated preoperative radiotherapy in their current practice after having demonstrated an advantage in terms of local control without excess toxicity [9-11].

Owing to discrepancies in practices and lack of strong evidence in favour of pre- or postoperative radiotherapy, within the National Cancer Institute of Canada O'Sullivan et al. conducted a randomized trial (SR2 trial) of preoperative radiotherapy (50 Gy with or without a postoperative 16-20 Gy boost in case of positive margins after resection) or postoperative radiotherapy of 66 Gy. Complete resection (83% preoperative radiotherapy vs. 85% postoperative radiotherapy), local recurrence, regional or distant failure rates and progression free survival were similar between the two groups [12]. The study was finished prematurely due to a significantly worse rate of wound complications in the group receiving preoperative radiotherapy (35% vs. 17%; $P=0.001$) and it was observed that this risk varied according to anatomical site, lower extremity having the highest risk for wound complications (upper leg 45% preoperative radiotherapy vs. 28% postoperative radiotherapy; lower leg 38% preoperative radiotherapy vs. 5% postoperative radiotherapy). Subcutaneous fibrosis grade 2 or above was however more frequent in the group receiving postoperative radiotherapy (48.2 vs. 31.5%, $P= 0.07$, 95% confidence interval [95% CI]: 0.0002-0.3) as well as joint stiffness (23.2 vs. 17.8%, $P=0.51$, 95%CI: 0.09-0.19) and oedema (23.2 vs. 15.1%, $P=0.26$, 95%CI: 0.05-0.22). Functional outcomes were more impaired in patients who had grade 2 or above fibrosis, joint stiffness, and oedema. Only field size was found to be a risk factor for subcutaneous fibrosis ($P=0.002$) and joint stiffness ($P=0.006$) [13]. An update of this study showed that the timing of radiotherapy was unlikely to affect patient survival.

Considering that the SR2 trial focused on wound complications and that comparative retrospective series yielded inconsistent results in terms of local control and survival, a meta-analysis of 1098 patients from five studies was conducted [14]. This study pointed out a statistically non-significant higher overall survival in the preoperative group (76% vs. 67%) despite a higher number of large tumours in this group; the delay in surgical resection in patients with preoperative radiation did not seem to increase the risk of lethal metastatic spread. The authors conclude that their results should be interpreted with caution because of the heterogeneity and bias in the available studies [11]. Results from these studies are summarized in Table 1.

Because all the above studies used bidimensional or conformal three-dimensional radiotherapy techniques with large radiation fields even in the preoperative setting (5cm in the longitudinal axis around the gross tumour volume or the virtual gross tumour volume), their usability in the current context is limited. Non-comparative results of contemporary radiotherapy series using reduced field image-guided, intensity-modulated irradiation techniques suggest that most toxicity can be reduced while maintaining locoregional control. In the preoperative setting, 5-year locoregional failure free

survival rates were maintained above 85% [15, 16] despite smaller preoperative margins (2 to 3 cm in the longitudinal axis and 1.5 to 1 cm axial) and intensity-modulated, image-guided radiotherapy (75% intensity-modulated radiotherapy/25% three-dimensional radiotherapy) in the RTOG 0630 trial. The preliminary results of the Vortex trial show similar 5-year locoregional failure free survival (86% vs. 84%), survival (72% vs. 67%) with a reduction of postoperative margins from 5 cm to 2 cm [17]. The Toronto team showed a reduction of late fibrosis (9.3%), joint stiffness (5.6%) and oedema (11%) with preoperative intensity-modulated radiotherapy [15]. Wound complications in the lower extremity remained frequent (30.5%, vs. 43% in the SR2-trial). Similar improvements were achieved in the postoperative setting by Alektiar *et al* using intensity-modulated radiotherapy [18]. The rate of bone fracture was 4.9%, joint stiffness 17.1% and oedema 12%. These results were better than the postoperative arm of the SR2 trial and comparable to its preoperative arm.

Further analysis of risk factors for wound complications suggests that proximal lower extremity, especially the internal side, tumour size (greater than 10 cm vs. below 10cm; odds ratio [OR]: 1.11; 95% CI: 1.05-1.18) and large surgical defect are more at risk for wound complications [12, 19,20]. Another independent factor for wound complication is the tumour proximity to skin surface below 3 mm [21]. Skin protection can be achieved with intensity-modulated radiotherapy but does not translate into fewer wound complications in the preoperative setting when compared to historical series [22, 23]. The recruiting PREMISS study (Trial registration: NCT01552239) evaluates the use of preoperative intensity-modulated image-guided radiotherapy and reduction of safety margins to prevent wound complications [24]. Results from these studies are summarized in tables 2 and 3.

Besides, the timing of radiotherapy (pre- vs. postoperative radiotherapy [OR: 3.08; 95%CI: 1.43-6.64]) is independently associated with more wound complications. Overall, it is unclear whether better long-term toxicity results are due to lower dose, smaller radiation fields used in the preoperative setting or to radiotherapy timing. Despite better long-term toxicity with preoperative radiotherapy and similar local control and overall survival rates in the preoperative setting, wound complications remain a concern that limits insufficiently trained teams to expand preoperative radiotherapy as an alternative to postoperative radiotherapy. Moreover, inadequate upfront management is often performed in peripheral hospitals, which restrains the use of changing strategies. However, management in tertiary sarcoma-expert centres should be encouraged since it has been shown to improve survival [25]. Patients treated out of higher volume sarcoma centres are at higher risk of having initial “whoops surgery” or unplanned positive margins, that are known to be at higher risk of relapse even if they receive adjuvant radiotherapy.

3. Pros and cons of preoperative radiotherapy

As in oesophageal, pancreatic or rectal cancer, preoperative radiotherapy is thought to confer several theoretical advantages over postoperative radiotherapy. Treatment strategy for soft tissue sarcomas

should always be discussed upfront within a multidisciplinary sarcoma board with recent limb MRI and biopsy result. If better results in terms of local control are observed after preoperative radiotherapy and surgery, it is because such strategy is more frequently performed in high volume centres.

3.1. Radiation oncologist arguments in favour of preoperative radiotherapy

3.1.1. Easier definition of target volumes and smaller target volumes in the preoperative setting

Preoperative radiotherapy allows accurate definition of smaller target volumes based on preoperative T1-gadolinium-enhanced MRI and 3 to 4 cm longitudinal margins and 1.5 cm of radial margins from gross tumour volume to clinical target volume to cover T2-hypersignal oedema. Clinical target volume margins can be reduced to the anatomic compartment limits [26, 27]. Reduced margins have shown excellent local control and better acute and late tolerance [23, 28].

Postoperative radiotherapy induces larger irradiation fields to cover the tumour bed as well as all contaminated tissues during the surgical procedure. It also takes into account the possible uncertainty of target volume definition due to the fact that communication with surgeons is not always possible and in some cases there is a lack of preoperative information (for example: after whoops surgery or surgery performed without preoperative MRI and biopsy).

3.1.2. Easier target volume definition goes with reduced interobserver and intraobserver variability

Reproducibility in target volume definition is a major issue for quality assurance in radiotherapy for soft tissue sarcomas. Sargos et al. evaluated target volume contouring variability among expert radiation oncologists of the French sarcoma group (GSF–Geto) [29]. Agreement in the preoperative setting was excellent for all target volumes (Kappa values between 0.675 and 0.768), which is consistent with results from Wang et al. [27]. In contrast, agreement on the postoperative case was “fair” to “moderate” (kappa values between 0.38 and 0.42). The most important conflict between experts was the difficulty to create a reconstructed gross tumour volume definition, which explained the poor agreement in this postoperative setting (kappa: 0.383); For the planning target volume, both pre- and postoperative discrepancies were clearly dependent on the multimodal image-guidance used. Moreover, the precautionary principle implies that uncertainties associated with the geometry of potentially contaminated surgical scars are responsible for increase in irradiated volumes in the postoperative setting. In that respect, preoperative radiotherapy may improve tolerance due to higher accuracy and smaller irradiated volumes as well as lower doses.

Another advantage of the preoperative setting is the lack of metallic material in the surgical bed which could favour infection, due to a fibrosis induced less vascularized environment. Furthermore, the presence of metallic material could artefact with the radiotherapy beam, resulting in a higher dose distribution heterogeneity, not always predictable that could be translated into cold or hot spots.

3.1.3. Parameters impacting radiation response

Hypoxia can be increased in the postoperative setting due to disruption of the normal microvasculature [30]. Preservation of tumour oxygenation with radiotherapy before surgery, leads to a higher sensitivity to radiation due to the oxygen enhancement ratio, which might explain same local control rates with lower doses [31].

Dissection of a high-grade sarcoma from a fixed structure such as an artery or nerve more likely achieves negative margins or planned positive margins (which have similar prognosis) after preoperative radiotherapy [32,33]. Cytoreduction of tumour boundaries to facilitate resection and histological response that could be a disease-free survival prognostic argument [31]. Resection margin status being the most important prognostic factor for local recurrence, translation of preoperative irradiation into clinical benefits should be high.

However, significant dimensional radiologic responses after preoperative radiotherapy are rare events, and it is frequent to observe improvement in tumour size during preoperative radiotherapy secondary to histopathological changes including necrosis, cystic changes, haemorrhage, hyalinization and fibrosis but this does not seem to influence on local control or overall survival rates [34,35].

A possible advantage of the postoperative setting is that radiation dose level can be more easily tailored to the risk of local recurrence, which is greatly affected by the quality of resection and surgical margins. It has been shown that preoperative radiotherapy, at the dose of 50 Gy, and postoperative radiotherapy, at the dose of 60 to 66 Gy, provide similar rates of local control [36, 37].

3.2. Surgical concerns about preoperative and postoperative radiotherapy

3.2.1. Surgery of irradiated tissues

The higher risk of wound complications with preoperative radiotherapy has likely been the major obstacle to expansion of preoperative radiotherapy in soft tissue sarcomas.

However, preoperative radiotherapy could allow for an easier resection due to the thickening and acellular modification of the pseudo capsule allowing a higher rate of complete resection after preoperative radiotherapy (89.73% vs. 75.50%; $P < 0.0001$), which is a major oncological prognostic factor [33, 38]. When the tumour grows close to a fixed, critical structure such as a major motor nerve, vessel or bone, the margins will be unavoidably close if function is to be preserved. Preoperative radiotherapy is particularly interesting in case of planned R1 surgery since it has indeed similar local recurrence rates as R0 surgery [32]. Nevertheless, it is impossible to predict if those structures will be easily resected after preoperative radiotherapy or not (for example vascular resections that may need vascular reconstruction or nerve graft). Generally, preoperative radiotherapy should be favoured in

case of large soft tissue sarcoma needing nerve graft, vascular reconstruction, or muscle flaps. Surgery after preoperative radiotherapy may need contribution of vascular or plastic surgeon.

It is interesting to note that historical rates of complete pathological responses after preoperative radiotherapy including all histologic types are about 8-10% [34, 39, 40]. However, these rates are dependent on histologic subtype, such as myxoid liposarcoma, which are generally considered more radiosensitive [41]. Preoperative radiotherapy can achieve major histological response in these cases with up to 65 to 100% of non-viable cells (depending on the chosen cut-off for pathological complete response). [42]. It has been suggested that patients with a complete pathological response (tumour necrosis) have a better disease-free survival than patients with poor tumour necrosis [39, 43]. The dose de-escalation DOREMY trial (NCT02106312 trial) in myxoid liposarcomas aims to reduce toxicity, especially wound complications while conserving the same rate of local control.

3.2.2. Better management of wound complications allows development of preoperative radiotherapy

Some surgeons may still be reluctant to preoperative radiotherapy because of the higher risk of wound complication which might entail higher need of reoperation and prolonged hospitalization. For this reason, several factors able to impact the development of wound complications have been investigated to try to prevent them.

Time interval between preoperative radiotherapy and surgical resection has been evaluated but seems to be of minimal impact on the development of wound complications [44]. A recent phase II study evaluating hypofractionated preoperative radiotherapy in soft tissue sarcomas identified that some germline biomarker profile showed a possible individual predisposition for wound complications. If confirmed, genomics-based patient selection could improve the safety of preoperative radiotherapy [45].

The use of vascularized tissue transfer may lower wound complication rates after preoperative radiotherapy, as shown in a prospective non-randomized study [46]. It is well accepted that wound complications are more frequent after preoperative radiotherapy, with an incidence of 30%, even after intensity-modulated radiotherapy with limited field and lower doses. However, several teams have demonstrated that the use of tissue transfers after preoperative radiotherapy prevents wound complications [47]. It is of note that when tissue transfers are used with upfront surgery they tolerate radiotherapy well in 95.5% of cases [48, 49].

Patients with tumours of the lower extremity involving major neurovascular structures should be considered for immediate simultaneous vascularized tissue transfer, regardless of radiotherapy timing [50]. The use of flaps or skin grafts in 60% of patients after preoperative radiotherapy for locally advanced tumours with exposure of vessels or bone, lowered wound complications rates down to 20%

of cases in a team dedicated to soft tissue sarcoma. It is interesting to note that the use of tissue transfer in the SR-2 trial was 34% (with 35% of major wound complications) [47]. Teams using preoperative chemoradiotherapy also used tissue transfers in 48-56% of cases and have shown low rates of major wound complications (6-23%) [51, 52]. This has been confirmed by Bonvalot et al., in a randomized trial evaluating the association of NBTXB3 nanoparticles to preoperative radiotherapy finding a rate of wound complication of 20% in the control arm and of 21% in the combined arm [53]. However, when tissue transfer is not feasible in those high-risk situations, because of patient's comorbidities, postoperative radiotherapy should be favoured.

3.3. Histological assessment of response to preoperative radiotherapy

The increasing use of neoadjuvant treatments in the management of soft tissue sarcomas has substantially impacted the histological evaluation of the surgical specimen, in particular tumour grading is no longer possible after preoperative treatments as necrosis and nuclear atypia are influenced by chemotherapy and radiotherapy [54]. Tumour grading should therefore be performed on the pretreatment biopsy. Pathological assessment of response to therapy currently remains the gold standard. guidelines have pointed out the importance of selecting representative tumour slabs based on findings made on gross examination. The pathology report should mention necrosis, cystic change, haemorrhage, hyalinization, and fibrosis [54]. Moreover, tumour size does not correlate with response to therapy and none of the histopathological changes observed in post-therapy specimens are specific to radiotherapy [35]. Necrosis is a marker of tumour aggressiveness and prognosis rather than of response to therapy [55]. It should be noted that specific patterns of response are observed in some sarcoma subtypes, such as adipocytic maturation in myxoid liposarcomas and myogenic maturation in rhabdomyosarcomas. High grade and stroma-poor sarcomas have been associated with better response rates but they actually vary from one subtype to another, in particular some stroma-poor high grade sarcoma such as those with *CIC* gene rearrangement are notoriously resistant to radiation [42,56,57]. Furthermore, no universal cut-off or threshold of therapy response correlating with prognosis has been established across all sarcoma types, and a descriptive semi-quantitative report indicating the percentage of viable cells (such as 0%, below 1%, between 1 and 10%, between 10 and 50%, 50% or more) is favoured [58].

3.4. How preoperative radiotherapy impacts on evaluation of radiologic response

Soft tissue sarcomas have a high inter and intratumoral heterogeneity, and some considerations should be considered when evaluating response after preoperative radiotherapy. It is rare to observe radiological response after neoadjuvant treatment except with myxoid liposarcoma (see **Fig 1.**), furthermore it is frequent to observe up to 10% improvement in tumour size in about 31% of cases without impact on outcome [35]. This lack of response or pseudoprogression could significantly influence dimension-based assessments of response. Imaging should therefore be performed as close

to the date of surgery as possible (4-6 weeks). The RECIST classification does not seem to be well adapted to evaluate pathologic response in soft tissue sarcomas nor to predict the evolution of disease [47]. CHOI criteria considering tumour attenuation changes could be useful in evaluating some soft tissue sarcomas and some histologic types like synovial sarcoma could benefit from functional imaging. However, functional parameters are still confined to clinical research and its development is limited by the technical heterogeneity of acquisition in the MRI parc. This leads to a lack of robust validated criteria for morphologic evaluation of response in soft tissue sarcomas. Despite the difficulties in having a good interpretation of response after preoperative radiotherapy or chemoradiotherapy of soft tissue sarcomas, in the absence of metastatic evolution, imaging evaluation will not change the decision to operate.

Image-based radiomics use algorithm-based large-scale quantitative analysis of imaging features as an alternative tool to characterize tissue. This does not allow to evaluate response but to evaluate prognostic factors since Radiomics has been associated with survival, tumour progression and molecular changes (genetic mutations and expression profiles). The advantage of radiomics is that they can analyse the whole tumour before therapy rather than focal analysis with biopsy and that this analysis can be done based on daily clinical practice tools as proven by Peeken et al who showed the prognostic potential of radiotherapy planning CT-based radiomic models in terms of overall-, local and distant progression-free survival [59]. High risk patients identified by radiomic model could be administered to additional systemic therapies whereas low-risk patients could be spared unnecessary toxicities. However, for the development of radiomics in soft-tissue sarcomas, it would be necessary a deep learning and implementation of automatic contouring tools.

4. Additional questions or perspectives

4.1. Do we need an additional dose if positive margins after resection following preoperative radiotherapy?

Positive surgical margins have been consistently reported to adversely correlate with outcome. Local inadequacy apparently correlates with local relapse and late metastases. The adequacy of surgical margins after preoperative radiotherapy and the impact of a postoperative radiotherapy boost has been the focus of several studies. In a 317-patient series undergoing preoperative radiotherapy, patients undergoing marginal excision after preoperative radiotherapy had excellent local control (95% at 5 years) and amputation-free survival rates (97% at 5 years) similar to that of patients undergoing radical or wide excisions (95% and 92% respectively) [19]. Such data suggested that 50 Gy of preoperative radiotherapy may effectively sterilize microscopic disease within the reactive zone and surrounding at-risk tissues. Alternately, patients having positive or contaminated margins experienced decreased local control (65% at 5 years) and limb preservation rates (64% to 83% at 5 years). Thus, 50 Gy of preoperative radiotherapy may not adequately overcome the increased risk of local recurrence for

those patients with contaminated or intralesional margins. O'Sullivan et al., in their randomized SR-2 trial, delivered a postoperative radiotherapy boost of 16 to 20 Gy after preoperative radiotherapy in case of positive margins [12]. This policy was followed up in the RTOG 0630 study. However, an increased risk of bone fracture and an inferior functional outcome was observed with higher radiation doses [13, 60]. Post hoc analysis of 93 patients with positive margins (52 treated only with 50 Gy and 41 with 50 + 16 Gy) showed that the 5-year local relapse free survival in the "preoperative only" group was 90.4% and in the "preoperative radiotherapy and postoperative boost" group 73.8%, but this difference was not statistically significant (log rank 2.32; P=0.13). There was no local relapse in the "preoperative only" group for low grade tumours and for planned positive margins. Overall, postoperative radiation boost did not improve local control (9 cases out of 41 and 6 cases out of 52 respectively; P=0.256). Similar conclusions were provided in the study by Sadoski et al. (N=132), with five-year actuarial local control of 82% in patients with positive margins and 97% in patients with negative margins (P=0.02) [61]. Twenty-four percent of patients did not receive a postoperative boost because of wound complications or medical reasons, and in this group local control remained excellent with no local recurrences, even for patients with positive margins.

Based on above studies we can conclude that there is no clear benefit to adding a postoperative boost in case of positive margins after preoperative radiotherapy.

4.2. Preoperative radiochemotherapy or radiotherapy

In some high grade rapidly progressive sarcomas, preoperative treatments can be critical to avoid rapid metastatic dissemination and optimize locoregional response. Indeed, there is little evidence in favour of preoperative chemoradiotherapy or radiotherapy or chemotherapy and practice is highly centre-dependent. Gronchi et al. analysed 252 patients from a phase III randomized trial [62]. One-hundred and thirty-five patients received preoperative chemoradiotherapy (50 Gy) and 117 patients underwent preoperative chemotherapy and postoperative radiotherapy (60 Gy). In patients treated preoperatively, positive surgical margins were not associated with an increased risk of distant spread or local failure when associated preoperative radiotherapy combined with chemotherapy was used. This reflects some protection of both local and distant spread by preoperative chemoradiotherapy.

Even if local control is satisfying in most soft tissue sarcomas resected with negative margins, there is a group of high-risk patients (high grade, size over 8 cm, inadequate surgery, recurrent) who would need more aggressive strategies to improve local and distant control. Several teams have provided interesting results associating chemoradiotherapy. They reported pathologic complete response rates of 27 to 40% with a rate of complete resection of 80 to 91% at the price of higher toxicity with 5% of treatment-related deaths and grade 4 toxicity of 83%. Furthermore, the excellent rate of pathologic complete response and complete resection rates did not translate into a survival benefit in this study showing a local relapse rate of 22% at 5 years [63-66].

The idea of combining targeted therapies with radiotherapy is interesting due to the expression of angiogenic factors by the sarcomas. The association of radiotherapy to bevacizumab, sorafenib, sunitinib and pazopanib has been evaluated in phase I-II studies. Promising rates of pathologic complete response have been reported ranging between 40 and 45%, nevertheless acute toxicity was non-negligible. However longer follow-up is necessary to confirm those encouraging results [67-70]. Recently, Aaron et al. have reported in an abstract form, the results of a phase II randomized study (ARST1321) evaluating in children and young adults the association of a doxorubicin–ifosfamide-based chemoradiotherapy (irradiation dose of 45 Gy) to pazopanib versus the same chemoradiotherapy protocol. Pathologic complete response in the combined arm was almost 60% vs. 22% in the chemoradiotherapy arm, but grade 3-4 toxicity was extremely high (74% vs. 29%) [71].

4.3. Intratumoral nanoparticles

Another strategy to improve local control has been the association of nanoparticles to preoperative radiotherapy. The association of hafnium oxide nanoparticles (NBTXR3) to preoperative radiotherapy (50 Gy) by intratumoral injection has been compared in a phase II-III randomized trial. For this first analysis, 176 patients were evaluable. With a median follow-up of 9.7 months (range: 0.2-28.9 months) the rate of pathological complete response was 16% in the combined arm and 8% in the preoperative alone arm (P=0.044). It is interesting to note that historical rates of complete pathological responses after preoperative radiotherapy alone ranged between 8 and 10% [34, 39, 40]. Patients having received the combined treatment had more complete resections (77% vs. 64%; P=0.042) and tumour necrosis or infarction (P=0.014). There was no significant difference in terms of toxicity between the two groups and grade 3-4 reactions due to intratumoral injection were rare. The advantage of the use of nanoparticles in association with radiotherapy instead of drugs is the absence of systemic toxicity. Long term results about toxicity and local and distant control are expected to establish if this advantage in radiosensitivity and pathologic complete response is translated in clinical benefit. If those results are confirmed, this study could change practices [53]. It is interesting to note that participation in this study has induced a switch towards preoperative radiotherapy in many centres.

4.4. Need of adaptive radiotherapy in the preoperative setting

It has been admitted in the past that any volumetric variations may happen during radiotherapy for soft tissue sarcomas. Recently, several investigators have observed volumetric variations under preoperative radiotherapy of soft tissue sarcomas, which could involve a miss in volume coverage with possible consequences on local control and toxicity. Haas et al. showed that soft tissue sarcoma volumes may change substantially during preoperative radiotherapy in 59% of patients, leading to plan adaptations resulting from increased volumes in 8% [72]. Daily critical observation of these patients is mandatory to avoid geographic misses because of increases in size and overdosing of normal tissues

when masses shrink. Those results have been confirmed by Dickie et al. [73]. Implementation in routine practice is quite demanding. Cases requiring systematic adaptive may be selected based on their radiosensitivity, such as myxoid liposarcomas.

4.4. Cost analysis of pre and postoperative radiotherapy

Qu et al. carried out a cost-effectiveness analysis of preoperative versus postoperative radiotherapy based on the SR-2 randomized trial and assuming similar patient and disease characteristics [74]. Preoperative radiotherapy would be more cost-effective because of the higher incidence of chronic adverse events with radiotherapy in the postoperative setting. In a second study, cost-effectiveness of three-dimensional conformal- and intensity-modulated conformal radiotherapy of soft-tissue sarcomas was evaluated. Intensity-modulated radiotherapy was the preferred technique as it lowered local recurrences rates, severe toxicity and improved the quality of life [75].

Main indications of preoperative and postoperative radiotherapy following sarcoma expert's recommendations are summarized in Table 4.

5. Conclusion

Preoperative radiotherapy shows benefits in terms of long-term toxicity and function with at least similar local control and survival when compared to postoperative radiotherapy. However, the rate of wound complications remains high despite technical progress. Use of tissue transfers during surgical procedure after preoperative radiotherapy has shown to decrease the risk of wound complications. This requires multidisciplinary surgical teams with plastic, vascular and sarcoma surgeons. Furthermore some “prerequisites” are necessary for the implementation of preoperative radiotherapy. Preoperative radiotherapy requires careful planning of the strategy by a multidisciplinary team, as well as access to radiotherapy teams trained in soft tissue sarcoma volume definition and able to practice image-guided radiotherapy for the daily follow-up of tumour volume variation that occurs during the course of radiotherapy.

There are still many indications for postoperative radiotherapy. Patients with significant comorbidities who are at risk of major wound complications are good candidates for postoperative radiotherapy as are some tumoral locations, such as the internal side of the proximal lower limb, when there is no possibility to practice a tissue transfer, or when faced with difficulties in obtaining a pathological diagnosis.

Author contributions

CLM: manuscript writing; JT: supervision of the development of this work. All the authors verified the contents of this manuscript.

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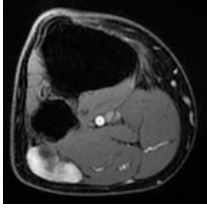
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Figure legend

Fig 1. Pre- or postoperative radiotherapy of soft tissue sarcomas: example of a myxoid liposarcoma. a: before radiotherapy; b: evaluation after 50 Gy irradiation and before surgery.



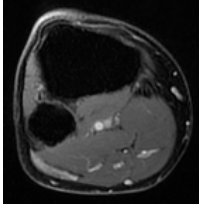


Table 1. Summary of results from series comparing pre- and postoperative radiotherapy of soft tissue sarcomas.

Reference	Number of patients	Follow-up (months)	Number of pre-/postoperative radiotherapy	Tumour grade	Size >10 cm (%)	Radiation dose (Gy)	Chemotherapy (%)	R1 resection (%)	Local control rate pre-/postoperative radiotherapy (%)	Survival rate pre-/postoperative radiotherapy (%)	Late toxicity rate pre-/postoperative radiotherapy (%)	Wound complications rate (%)
Kuklo et al., 2005 [9]	117	73 /100	59/58	nd	35/26	51/63	23/20	nd	Locoregional 5 / 12 (P=0.19)	83.1/82.8	nd	32/29 (P=0.89)
Zagars et al., 2003 [8]	517	72	271/246	nd	42/21	50/60	53/42	24/12	5 year: 81 10-year: 78 83 / 72	62 / 41	10-year Gx 5 / 9 (P=0.03)	nd not analysed
Suitet al., 1985 [10]	170	-	60/110	nd	43/18	50-52/60-64	nd	nd	Locoregional 18.1 /18.3	73 / 62	nd	nd
Cheng et al., 1996 [7]	112	-	48/64	nd	nd	48/62	nd	40/42	83±12/91±8 (P=0.41)	75 / 79	nd	31/8 (P=0.0014)
O'Sullivan et al., 2002 (phase III randomized) [12]	182	39,6	88/44	-	35/33	50/66	no	17/15	P=0.7911	88 / 72 (P=0.048)	-	35/17
Sampath et al., 2011 [11]	821	63	293/528	nd	nd	50.4/60	17	40/40	preoperative radiotherapy associated with better local relapse-free survival	65/60 (P=0.07)	nd	nd

									(HR : 0.5; 95% CI : 0.28-0.88; P<0.05)			
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Nd: not disclosed; HR : hazard ratio ; CI : confidence interval.

Table 2. Summary of results from modern series comparing pre- and postoperative radiotherapy of soft tissue sarcomas: local control.

Reference	Number of patients	Follow-up (months)	Chemotherapy	Irradiation technique	Dose (Gy)	Timing of radiotherapy	Field size (long axis)	Grade	Tumour size	Quality of resection	Local control/recurrence rate (%)
O'Sullivan et al., 2013 (phase II) [15]	59	49	no	Intensity-modulated radiotherapy	50	preoperative	4 cm	93% grade 2-3	9.5 cm 44% > 10 cm	nd	Local recurrence: 6.8 5-year local recurrence-free survival: 88.2
Wang and Abrams, 2015 (RTOG 0630) [16]	86	43	no	25% 3D conformal radiotherapy/75% intensity-modulated radiotherapy	50 +/- 16	preoperative	2-3cm	74% grade 2-3	62% ≥8 cm	76% R0 20% R1	Local recurrence: 6.8
Alektiar et al., 2008 [18]	41	35	nd	Intensity-modulated radiotherapy	63/50	82% postoperative/17% preoperative	Clinical target volume 3 cm Planning target volume 2 cm	83% grade 2-3	68% ≥10 cm	51% R1	5-year local control: 94
Robinson et al., 2016 (Vortex, phase III R) [17]	216	57	no	3D conformal radiotherapy	50 +16= 66 Gy	postoperative	A : 5cm+2cm B : 2 cm	nd	nd	nd	5-year local recurrence-free survival: 86 5-year local recurrence-free survival: 84

Nd: not disclosed

Table 3. Summary of results from series comparing pre- or postoperative radiotherapy of soft tissue sarcomas: wound complications and late toxicity.

Reference	Number of patients	Follow-up	Chemotherapy	Radiation dose (Gy)	Irradiation technique	Field size (cm)	Tissue transfer rate (%)	Wound complication rate (%)	Fibrosis grade ≥ 2 rate (%)	Joint stiffness grade ≥ 2 rate (%)	Oedema grade ≥ 2 rate (%)	Bone fracture rate (%)
O'Sullivan, et al., 2013 [15]	59	49	No	50	Preoperative intensity-modulated radiotherapy	4	7	30.5	Grade ≤ 2 : 9.3	G ≤ 2 5.6	G ≤ 2 11	0
Wang and Abrams, 2015 (RTOG0630) [16]	86	43	No	50 \pm 16	Preoperative 25%: 3D conformal radiotherapy 75%: intensity-modulated radiotherapy	2-3	33.7	36.6	5.3	3.5	5.3	nd
Alektiar et al., 2008 [18]	41	35	No	63 Gy/50 Gy	Postoperative 82% Preoperative 18% Intensity-modulated radiotherapy	5	nd	19.5	nd	17.1	12	4.8
Robinson et al., 2016 (Vortex, phase III) [17]	216	58	No	66 Gy	Postoperative 3D conformal radiotherapy	5	nd	nd	47	18	nd	11
						2			41	18		15
									P=0.39			P=0,48
Bonvalot et al., 2019 (phase II/III) [53]	90	nd	No	50 Gy	Preoperative 3D conformal /intensity-	3	nd	20	nd	nd	nd	nd

					modulated radiotherapy											
Levy et al., 2014 [47]	54	42	50%	50±16	Preoperative	nd	60	22	Grade 3: 2	Grade 3 5.5	7.4	2%				
O'Sullivan et al., 2002 (SR-2 trial) [12]	129	nd	no	50±16	Preoperative Postoperative 3D conformal radiotherapy	5	34	35	31.5	17.8	15.1	nd				
				50+16			23						17	48.2	23.2	23.2
													P=0.01	P=0.07	P=0.51	P=0.26

Nd: not disclosed.

Table 4. Clinical and tumour factors favouring pre- or postoperative radiotherapy for soft tissue sarcomas.

Factors favouring preoperative radiotherapy	Factors favouring postoperative radiotherapy
	Difficulty to obtain a certain pathologic diagnosis with percutaneous biopsy before surgery
	Entire pathological specimen available without any neoadjuvant treatment to characterize soft tissue sarcoma and evaluating grade
	Uncertainty on the added value of radiotherapy
Young patients without comorbidities (atheroma, skin trophic state)	Eldery patients or with comorbidities: - skin trophicity - tobacco - diabetes - vascular disease
High risk location for wound complication (internal side of proximal lower limb) when a muscular flap is possible	High risk location for wound complication (internal side of proximal lower limb) when a muscular flap is not possible
Large sarcoma needing muscle flap	
Failures after neoadjuvant chemotherapy	
In conservative approach when R1 resection is certain	
Lower radiation doses and smaller volumes needed	Better tailoring of the radiation dose according to surgical margin status
When dose and field size issues are the most important criteria: -tumours close to joints or neurovascular structures -upper limb close to brachial plexus - need of complex surgical reconstruction as vascular by-pass or nerve graft	
Radiosensitive soft tissue sarcoma subtype such as myxoid liposarcoma	
Better definition of the target volume thanks to preoperative MRI	
Better long-term functional and late toxicity outcome	
Better anticipation of planned surgery: avoiding whoops surgery	
<i>“Prerequisite” for preoperative radiotherapy</i>	
Discussion of all cases in a sarcoma multidisciplinary board	
Preoperative diagnosis of sarcoma	
Preoperative imaging (MRI) for radiotherapy volume delineation	
Daily image-guided radiotherapy available (adaptative radiotherapy)	
Multidisciplinary surgical team including plastic, and sarcoma surgeons	