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Surgical resection, intraoperative radiotherapy and immediate plastic reconstruction: A good option for the treatment of distal extremity soft tissue sarcomas

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ABSTRACT

Aim: To show three patients with soft tissue sarcomas of distal extremities conservatively treated after tumor-board discussion, involving margin-free surgery, exclusive intraoperative radiotherapy, and immediate reconstruction.

Background: Current guidelines show clear and robust recommendations regarding the composition of the treatment of sarcomas of extremities. However, little evidence exists regarding the application of these treatments depending on the location of the primary neoplasia. Tumors that affect the distal extremities present different challenges and make multidisciplinary discussions desirable.

Methods/Results: We reported 3 patients who were approached with a conservative intention, after tumor board recomendation. The goals from the treatment performed were aesthetic and functional preservation, while enruring locoregional control. We had wound healing complications in 2 of the cases, requiring additional reconstruction measures. Patients are followed up for 24, 20 and 10 months; local control is 100%, and functional preservation is 100%.

Conclusions: Despite being a small series, it was sufficient to illustrate successful multidisciplinary planning, generating a therapeutic result with improved quality of life for patients who had an initial indication for extremity amputation.

1. Background

Soft tissue sarcomas (STS) are a heterogeneous group of mesenchymal tumors.[1–3] Although they may appear in any location, most cases arise in the extremities.[4–6] In the 1980s and 90 s, several seminal studies validated a conservative multimodality approach, mainly composed by limb sparing surgery followed by radiotherapy (RT), with or without chemotherapy. Similar survival rates were observed when comparing the multimodality conservative management to non-conservative approaches, involving amputation, despite a slight increase in local recurrence rates.[7–12]

Due to anatomic reasons, distal extremity STS may infiltrate tendons, joints, nerves, and bones at early stages. In general, patients with distal tumors were underrepresented in the majority of the studies. Only a randomized study conducted at Memorial Sloan Kettering Cancer Center[12] (with a 20-year update[13]) addressing the efficacy of post-operative external-beam RT versus observation characterized the outcomes of a subset of distal extremity patients (4 and 8% of distal upper, and 30 and 18% of distal lower, respectively), but this variable (distal extremity location) was not analyzed as a predictor of the main study endpoints (toxicity, survival, and limb functionality).

In fact, amputations of distal extremities STS were often indicated due to difficulties in achieving free three-dimensional margins and to perform adequate wide resections and *en bloc* resec-

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tions. In most cases, the reasons that had been used to justify a non-conservative approach to treat patients with distal extremity STS are based on some major points: (1) difficulties in achieving adequate macroscopic surgical and microscopic pathological margins; (2) even with microscopic free margins, marginal resections are clearly associated with a high risk of local recurrence; (3) resections performed for distal extremity STS are generally associated with aesthetic and functional losses and attempts to involve major reconstructions, with a high risk of post-operative complications[14] and losses of flaps/grafts[15] and (4) external-beam RT on distal extremities is worse tolerated by the inherent sensitivity of healthy tissues in these locations, often precluding treatment with enough doses.

Intraoperative RT (IORT) represents an opportunity to deliver the optimal dose, or a fraction of the irradiating treatment dose to the tumor or to the tumoral bed, while the area is being exposed during surgical procedures.[16] This approach yields higher doses than conventional RT treatments while diminishing dose-volume parameters through surrounding organs. Thus, it is a promising technique to compose multimodal treatments involving surgery and radiation. The effectiveness and safety of IORT has been previosuly reported in a range of tumor types and primary sites, such as rectal cancer,[17] retroperitoneal sarcoma,[18,19] pancreatic cancer,[20] early breast cancer,[21] and selected gynaecologic[22] and genitourinary tumors.[23] However, the use of IORT for STS of distal extremities has been discreetly reported, and just a few studies had discribed the use of IORT as an exclusive modality of radiation, once most reports involve external-beam RT either pre- or postoperatively.[24] In addition, the majority of studies describes IORT through the use of either electrom-beam or brachytherapy, which are known to have technical differences between them.

Thus, we sought to report our experience with multimodal treatment in three cases of distal extremity STS, encompassing free surgical margins, IORT and immediate reconstruction.

2. Case-reports

2.1. Case 1

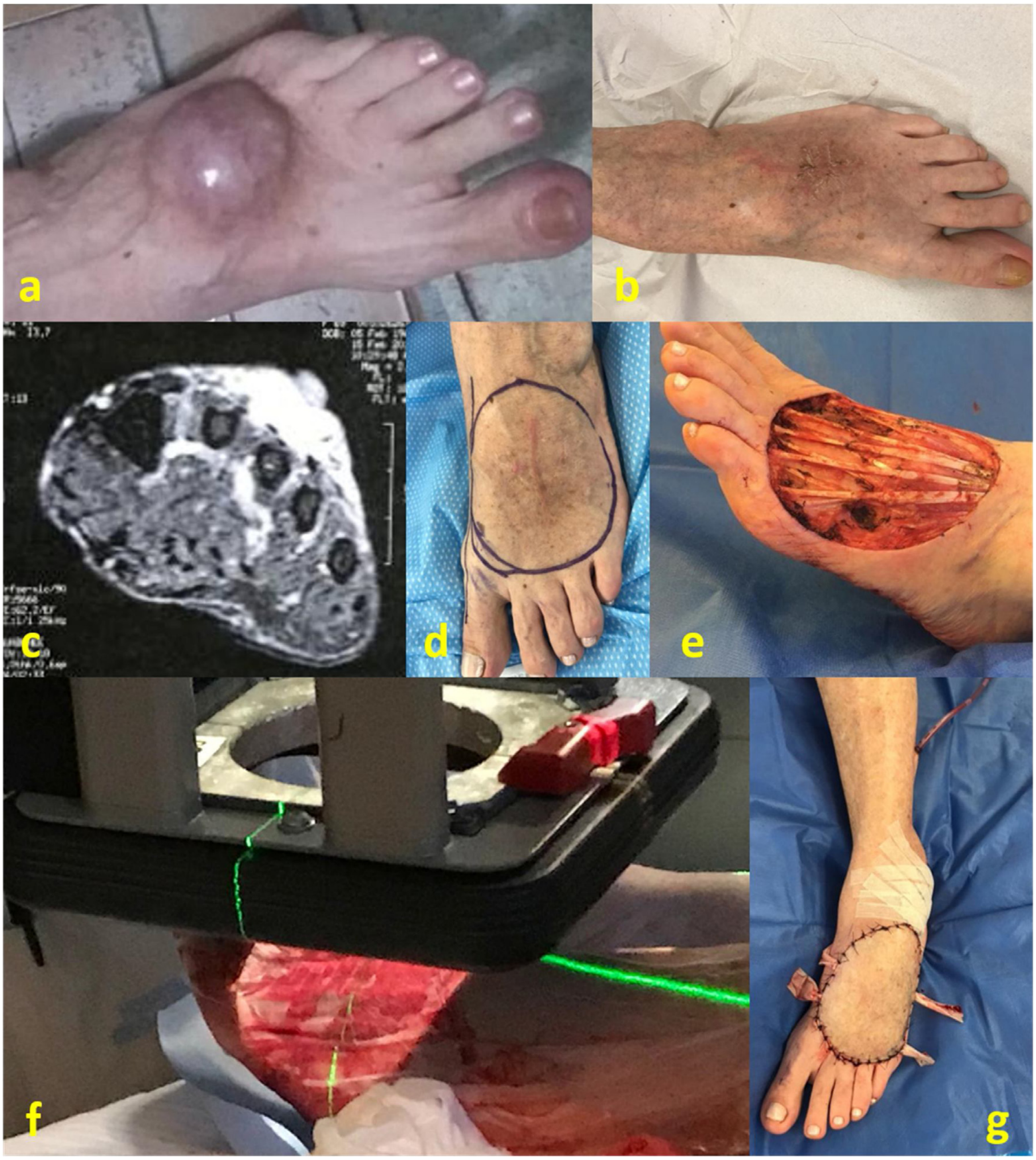
70-year-old woman, who initially presented with a soft-tissue lesion on the dorsum of her left foot with rapid growth. She was submitted, in May 2018, to an excisional biopsy of the lesion, consistent with a high-grade undifferentiated pleomorphic sarcoma. The patient had an indication for the amputation of her left foot and asked for a second opinion. Staging exams showed no evidence of distant metastases. Magnetic resonance imaging of the left foot showed changes in the tumor bed consistent with the previous biopsy. However, on clinical examination, a small subcutaneous lesion adjacent to the surgical scar was appreciable. Her case was discussed on a multidisciplinary tumor board where a central pathology review was requested, as well as the following treatment planning: oncologic surgical procedure with intraoperative analysis of the pathology (frozen section) combined with + IORT and + immediate reconstruction. The report of the central pathology review showed a high-grade pleomorphic undifferentiated sarcoma. In June 2018, the recommended procedures were carried out. The final pathology examination revealed a residual deposit of undifferentiated pleomorphic sarcoma of 1.0 cm, resected with negative margins. Immunohistochemistry showed an AE1/AE3 cytokeratin negative, negative smooth muscle actin, CD68 positive, CD34 negative, EMA negative, Ki-67 80%, S-100 negative, vimentine positive, desmin negative. There was a residual tumor focus of 1.0 cm on the skin. The margins were free. The IORT was performed with a non-dedicated linear accelerator - the patient undergoes the surgery in the operating room, is transferred to the RT room, receives irradiating treatment, then returns to the operating room for the surgery to be completed. This procedure has already been published by our group in the IORT scenario for 152 breast-cancer patients, and we did not have any cases of perioperative infection.[25] We prescribed 18 Gy of dose, and used usual collimators (instead of specific collimators for IORT) with a perpendicular incidence to the tumor bed, and adapted customized cerrobend collimation (coupled to the collimator) to the tumor bed design, preventing the field light (50% isodose) from reaching the skin. The depth was estimated at 1 cm of the surgical bed surface, based on preoperative magnetic resonance imaging (in addition to the 5 mm sterile silicone bolus that had been interposed before the dose delivery). We chose 6 MeV as the electron beam energy for the treatment, at 90% isodose level. As a reconstructive technique, a sural pedicled flap was used. The patient evolved with epidermolysis and partial flap loss, requiring flap debridement, and final closure of the defect with a free graft. The current follow-up of the patient is 24 months, with full functionality of the left foot, without evidence of local or distant disease. She was not given post-operative chemotherapy. Picture 1 illustrates treatment steps.

2.2. Case 2

57-year-old man who sought medical attention due to a lesion on the dorsum of his right foot, initially evaluated as a “lipoma”. He noticed an increase in the lesion and had difficulty putting on his shoes. He again sought care in September 2018, and imaging tests and a tru cut biopsy were requested. Magnetic resonance imaging showed a 5.9 × 2.0 × 5.0 cm lesion with no cleavage planes with halux extensor muscles and tendons. Biopsy showed low grade myxoid sarcoma. The patient initially had an indication for amputation of the right foot, and sought our service for a second opinion. Staging exams had shown no evidence of distant disease. Pathology review revealed grade II mixofibrosarcoma. His case was discussed at a multidisciplinary tumor board where oncologic surgery was proposed, with intraoperative analysis of the pathology (frozen section) combined with + IORT and + immediate reconstruction. In November 2018, the recommended procedures were carried out. The final examination of the pathology revealed a grade II mixofibrosarcoma. Immunohistochemistry showed a smooth muscle actin negative, caldesmon positive, CD10 positive, CD34 negative, desmine negative, Ki-67 20%, S-100 negative, vimentin positive. The margins were free. The IORT was carried out with the same specifications as the procedure performed in case 1. We prescribed an 18 Gy dose with a 6 MeV electron beam +5 mm sterile bolus at 90% isodose level, systematically with the same technique as described in case 1. As a reconstructive technique, microsurgical anterolateral cutaneous free flap was used. The patient evolved favorably. The current follow-up of the patient is 20 months, with full functionality of the right foot, with no evidence of local or distant disease. No systemic treatment was prescribed. Picture 2 shows the treatment steps.

2.3. Case 3

62-year-old man who sought medical care reporting a lump at the infero-lateral aspect of his left leg for 1 year, becoming more evident, reddish and elevated after local trauma 2 months previously. In August 2019, an excisional biopsy was performed, which revealed a 1.7 cm grade-III mixofibrosarcoma with positive margins, confirmed at a centralized pathology review (S-100 negative, smooth muscle actin negative, Ki-67 70%, CD34 positive, CD68 positive). He sought care at our institution where sataging images showed no signs of distal metastasis. Local magnetic resonance



Picture 1. a) initial presentation; b) post-excision biopsy; c) Axial-STIR view of magnetic resonance imaging on the centre of scar; d) surgical plannings; e) after surgical margin-widening; f) electrom-beam positionning; g) after immediate reconstruction.

imaging suggested no signs of residual disease. The therapeutic proposal was discussed at a tumor board session, and the patient was submitted to a marginal resection with intraoperative margin control (frozen section) followed by IORT (18 Gy was prescribed with an electron beam of 6 MeV +5 mm sterile bolus, at 90% isodose level, systematically following the same technique as described in case 1) and immediate reconstruction with a skin-free graft in October 2019. The final examination of the pathology confirmed a residual high-grade myxofibrosarcoma affecting the skin, dermis, subcutaneous tissue and soft tissues (fascia). The patient evolved with partial graft loss, and is currently (10 months) in the final phase of wound closure by second intention. In spite of this, patient's left leg is fully functional. No systemic treatment was recommended. There is no evidence of local or distant disease. Picture 3 shows the steps of treatment.

3. Discussion

We presented three cases of patients with soft tissue sarcomas of distal extremities where the association of marginal surgical resection, IORT and immediate plastic reconstruction allowed to complet the whole treatment in one go, with aesthetic and functional preservation and locoregional control during the period of follow-up achieved until now. In our view, considering the difficulties of obtaining adequate surgical margins, the risks associated with pre- and post-operative radiotherapy techniques and the need for elaborate plastic reconstructions, makes this strategy a reasonable option for the treatment of distal extremity high grade STS.

Radiation therapy plays an important role in the local control of extremities STS. Limb-sparing surgery with postoperative

Picture 2. a) axial-T1 post-contrast MRI view; b) surgical borders' delineation; c) after surgical procedure; d) electrom-beam positionning; e) after immediate reconstruction.

external-beam RT[7,12] or interstitial brachytherapy[11] resulted in similar disease-free survival and overall survival rates when compared to amputation. The main reason for this parity is the relatively high likelihood of salvage second local treatment (new conservative approach, or amputation) in patients who have local-recurrence after an initial conservative treatment. Several issues may affect

Picture 3. a) Presentation after excisional biopsy; b) after marginal surgical resection; c) wet gas placement + occlusive dressing; d) Radiation beam set-up; e) after graft interposition.

oncologic effectiveness, such as tumor size, margin status, extension of resection, tumor location, patient age, tumor grade and receipt of RT, among others.[26,27]

Toxicity rates following postoperative RT for STS – such as cellulitis, neuritis, fibrosis, pathologic fractures, wound complications, radiation dermatitis, edema – are frequent, occurring in 10 to 40% of the cases.[28,29] The number, severity, duration, and timing of complications are directly related to some variables, such as patient's comorbidities, type of RT,[30,31] receipt of systemic treatments, among others. In an attempt to reduce toxicity, a seminal study from Canadian researchers[32] randomized 200 patients to preoperative RT (50 Gy in 5 weeks) versus postoperative RT (66 Gy in 33 fractions). After a median follow-up of 3.3 years, they found 35% and 17% of wound compliations, respectively. However, fibrosis and edema were both higher in the second arm. As their local control rates were of no difference, the findings of this study are used to support preoperative treatments in some circumstances.

Due to the assumption that toxic effects may be related to the intensity of the RT dose, some attempts to de-escalate the dose, and to decrease the gross treatment area, in addition to the use of combined treatment methods have been studied. Among them, IORT appears to be an interesting option because the treatment is delivered in a single dose, in a lower target-volume than in other modalities of RT, and because of the possibility of physically moving away adjacent organs at risk that would not tolerate tumoricidal radiation. In addition, this technique involves logistical and other potentially beneficial issues - the patients receive surgery and RT in the same time, enabling them to return to their life more quickly, and also allowing the use of immediate plastic reconstruction features that will not suffer the effects of postoperative RT.

The main indication for IORT in the scenario of extremity STS is the composition of IORT with external-beam treatments (either pre- or postoperative RT).[33,34,35,39] Delivery methods include electrom-beam, and brachytherapy – flexible applicators or catheters. Pooled results from some small studies[36,37,38,39] show a tendency towards lower toxicity rates when IORT was incorporated, due to the decrease in the dose used with external-beam RT.[40] Even in cases treated with preoperative RT (whose doses were not purposely decreased), the use of IORT seemed to be advantageous in terms of toxicity,[41] but there is no level I evidence to support this hypothesis. Nonetheless, there is scarce evidence that only IORT is used in the management of STS.[39]

Patients with STS affecting distal extremities (wrist, hand, ankle, foot) are underrepresented in the main studies that dictate the main treatment guidelines. There are some assumptions why recommendations generally followed to treat a thigh tumor, for example, cannot actually be applied in such distal locations:

1) There is little m̈arginf̈or healthy structures to obtain an ideal and conservative oncological surgery while maintaining functionality of the extremity.[42] Amputation or disarticulation rates in these regions are quite higher probably due to this fact.
2) External-beam RT at these regions might be more difficult to tolerate (compared to the proximal parts of the limbs). Patients have more pain, and treatment interruptions are more frequent.
3) Brachytherapy is not recommended in regions very close to tendons, nerves or bones, without m̈inimalm̈uscle tissue or fat. Complications will become very high.
4) Preoperative RT, even if done in its entirety, may lead to high surgical wound complication rates and higher than the average of the main studies.
5) Reconstructive methods are more likely to complicate in these regions, especially when using free grafts in previously irradiated areas.

Thus, patients with STS in distal extremities might benefit from conservative approaches that include surgery with m̈inimallyf̈ree margins - and confirmed by frozen biopsy - followed by IORT and immediate reconstruction. These patients should be followed more often than they used to be, seeking to detect an early recurrence and be treated properly, without having a major impact on the natural history of their disease.

In all three cases, the surgeries were performed in the main operating room and patients were transferred to the RT room, received irradiating treatment and then returned to the operating room for the plastic reconstruction to be performed. This procedure has already been published by our group in the IORT scenario for breast cancer,[23] where we did not have any cases of perioperative infection. Also in our experience (both in cases of breast cancer and in our 3 patients from this study), our group observed that the transit of the patient between the 2 rooms generated an average increase of 30 min in the surgery, when compared with our patients who were not submitted to IORT. Therefore, the investment in a dedicated linear accelerator for IORT has become less justifiable in our institution. Nevertheless, the use of this strategy (IORT without the need for a dedicated linear accelerator) can be replicated in a greater number of institutions, provided that due care is taken in sterilization, and that there is assistance from the hospital infection control team.

In our STS patients, we decided to prescribe doses of 18 Gy, based on the linear-quadratic model of bioequivalence.[43] Eighteen-gray delivered in single-dose would be equivalent to a conventional fractionation treatment with doses of 50 Gy in terms of tumor control – assuming alpha-beta ratio of 10 Gy, the biologically equivalent dose (BED) is 50.4Gy_{10}, and dose equivalent to 2 Gy (EQD2) is 42 Gy. In terms of toxicity this ecquivalence would reach 75 Gy – taking alpha-beta ratio of 3 Gy, the BED is 126 Gy_3, and EQD2 is 75.6 Gy. It is important to note that dose equivalence models use concepts based on radiobiology, but uncertainties may be taken into account regarding the prediction of effectiveness and / or toxicity when higher doses per fraction are used.[44]

These uncertainties could support an increased risk of late toxicity when using isolated IORT (compared to IORT + EBRT), but in fact there is not much evidence to draw clear conclusions in this regard. This was one of the reasons why we chose the 18 Gy dose level. Undoubtedly, our study differs from other publications. For instance, in a Japanese series, Matsumine et al.[38] treated 5 patients with STS of distal extremities in a tumor bed necessarily containing tendons. The doses varied between 25 and 50 Gy with electron beams. No severe toxicities were observed in the follow-up of these patients. On the other hand, in a series involving 53 patients treated exclusively with IORT (that is, without associated pre- or postoperative external-beam RT), the authors[45] used doses ranging from 7.5–12.5 Gy. Local control rates were acceptable, and toxicity rates were not reported.

In fact, the actual tolerance of the extremity structures to radiation is unclear because of some uncertainties, such as the lower oxygen perfusion of the body's extremities, the alteration of the cellular microenvironment in a post-surgical stress/trauma condition, and the influence of interposition of plastic reconstruction immediately after the administration of the irradiating dose. Some animal[46,47] and pre-clinical models indicate that the tolerance of some normal tissues to high doses of radiation: nerves up to 30 Gy, muscles can tolerate before fibrosis up to single doses of up to 50 Gy,[48] and tendoms and bones usually receive single-doses of up to 30 Gy without several necroses.[38] However, clinical evidence indicates otherwise. For instance, the risk of neuropathy will increase when the IORT dose exceeds 15 Gy.[49]

Neuropathy in fact will be the most impairing-toxicity due to its potential to generate pain and, therefore, lead to a decrease in the quality of life. Nonetheless, we believe that the risk of neuropathy should be taken into account when we speak of a p̈eripheraln̈erve (instead of a ẗrunkn̈erve, e.g., sciatic nerve). These aspects were discussed with the multidisciplinary team, as well as the patients before they underwent the treatment. In other words, we balanced the use of IORT as monotherapy - a minimally adequate dose for cancer control while yielding the risk of neuropathy in the preserved limb.

In our 3 cases, we had favorable outcomes in terms of healing and completion of immediate reconstruction in case 2. Cases 1, and 3 required the 2nd surgical procedure (case 1) or wound closure by second intention (case 3). It is not possible to correlate wound healing issues or complications in immediate reconstruction with IORT because we did not have a control group for comparisons. One of the possible causes (or contribution) of wound healing issues could be an eventual irradiation of the skin at the edge of the tumor bed; however, we were careful not to allow more than 50% of the dose to reach this region, through the individualized collimation we placed in each case. Moreover, after IORT delivery, a small margin of the skin was additionally removed before reconstruction procedures. In addition, the choice of graft instead of a flap (microsurgical or pedicled) may have contributed to this outcome. Some studies suggest that the use of systemic therapies, the combination of preoperative RT with IORT, vascular involvement, or the choice of grafts may prolong the healing period.[50–53] The radiation damage will include DNA mutation in the surgical bed, leading to double-strand breaks, and free-radical production at cell microenvironment. The inflammation pathways by generation of cytokines, transendothelial migration of leukocytes, mast cells, and neutrophil signaling activation will undoubtedly make graft adherence difficult, especially in hypovascularized regions, in addition to microvascular damage. Therefore, perhaps the choice of flaps – with äctivev̈ascularization – hypothetically generates better chances for reconstruction to be integrated.

Our experience is small, but the purpose of these reports was to illustrate the conservative therapeutic planning carried out by a multidisciplinary team, involving various therapeutic modalities.

So far, patients' follow-up is short – 24, 20, and 10 months – but encourages us to continue deciding in a multidisciplinary discussion on the best approaches for patients affected by STS of distal extremities. One last detail to mention is the fact that - like our case series on IORT in breast cancer - no patient had a peri-hospital infection. It gives us confidence in performing these procedures. This strategy can be replicated in other RT centers, as long as the recommendations for cleaning and sterilizing surgical and hospital environments are respected.

4. Conclusions

Even though our patients need further follow-up to consolidate the effectiveness and safety of this strategy, we might infer from a small experience of 3 cases that the multidisciplinary proposal for conservative surgery with free margins, IORT and immediate reconstruction in patients suffering from STS from distal extremities allowed for limb-preserving approaches. Strategies like this should be encouraged and become the subject of robust studies.

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Conflict of interest statement

None

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;68:394–424.
2. Stiller CA, Trama A, Serraino D, et al. Descriptive epidemiology of sarcomas in Europe: report from the RARECARE project. *Eur J Cancer*. 2013;49:684–695.
3. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin*. 2020;70:7.
4. Alektiar KM, Brennan MF, Singer S. Influence of site on the therapeutic ratio of adjuvant radiotherapy in soft-tissue sarcoma of the extremity. *Int J Radiat Oncol Biol Phys*. 2005;63:202–208.
5. Berner K, Bruland ØS. Prognostic impact of proximal versus distal localization in extremity long bone osteosarcomas. *Anticancer Res*. 2019;39:2459–2466.
6. Ottaviani G, Jaffe N. The epidemiology of osteosarcoma. *Cancer Treat Res*. 2009;152:3–13.
7. Rosenberg SA, Tepper J, Glatstein E, et al. The treatment of soft-tissue sarcomas of the extremities: Prospective randomized evaluations of limb-sparing surgery plus radiation therapy compared with amputation and the role of adjuvant chemotherapy. *Ann Surg*. 1982;196:305.
8. Rosenberg SA, Tepper J, Glatstein E, et al. Prospective randomized evaluation of adjuvant chemotherapy in adults with soft tissue sarcomas of the extremities. *Cancer*. 1983;52:424–434.
9. Williard WC, Hajdu SI, Casper ES, Brennan MF. Comparison of amputation with limb-sparing operations for adult soft tissue sarcoma of the extremity. *Ann Surg*. 1992;215:269–275.
10. LeVay J, O'Sullivan B, Catton C, et al. Outcome and prognostic factors in soft tissue sarcoma in the adult. *Int J Radiat Oncol Biol Phys*. 1993;27:1091–1099.
11. Pisters PW, Harrison LB, Leung DH, Woodruff JM, Casper ES, Brennan MF. Long-term results of a prospective randomized trial of adjuvant brachytherapy in soft tissue sarcoma. *J Clin Oncol*. 1996;14:859.
12. Yang JC, Chang AE, Baker AR, et al. Randomized prospective study of the benefit of adjuvant radiation therapy in the treatment of soft tissue sarcomas of the extremity. *J Clin Oncol*. 1998;16:197.
13. Beane JD, Yang JC, White D, Steinberg SM, Rosenberg SA, Rudloff U. Efficacy of adjuvant radiation therapy in the treatment of Soft tissue sarcoma of the extremity: 20-year follow-up of a randomized prospective trial. *Ann Surg Oncol*. 2014;21:2484–2489.
14. Blacam C, Colakoglu S, Ogunleye AA, et al. Risk factors associated with complications in lower extremity reconstruction with the distally-based sural flap: A systematic review and pooled analysis. *Br J Plast Surg*. 2014;67:607–616.
15. Ring A, Kirchhoff P, Goertz O, Behr B, Daigeler A, Lehnhardt M, Harati K. Reconstruction of soft-tissue defects at the foot and ankle after oncological resection. *Front Surg*. 2016;3:15–24.
16. Pilar A, Gupta M, Laskar SG, Laskar S. Intraoperative radiotherapy: Review of techniques and results. *Ecancer*. 2017;11:750, http://dx.doi.org/10.3332/ecancer.2017.750.
17. Mirnezami R, Chang GJ, Das P, et al. Intraoperative radiotherapy in colorectal cancer: Systematic review and meta-analysis of techniques, long-term outcomes, and complications. *Surg Oncol*. 2013;22:22–35.
18. Sindelar WF, Kinsella TJ, Chen PW, et al. Intraoperative radiotherapy in retroperitoneal sarcomas. Final results of a prospective, randomized, clinical trial. *Arch Surg*. 1993;128:402–410.
19. Roeder F, Alldinger I, Uhl M, et al. Intraoperative Electron radiation therapy in retroperitoneal sarcoma. *Int J Radiat Oncol Biol Phys*. 2018;100(2):516–527.
20. Willett CG, Del Castillo CF, Shih HA, et al. Long-term results of intraoperative electron beam irradiation (IOERT) for patients with unresectable pancreatic cancer. *Ann Surg*. 2005;241:295–299.
21. Veronesi U, Orecchia R, Maisonneuve P, et al. Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): A randomised controlled equivalence trial. *Lancet Oncol*. 2013;14:1269–1277.
22. Haddock MG, Petersen IA, Webb MJ, et al. IORT for locally advanced gynecological malignancies. *Front Radiat Ther Oncol*. 1997;31:256–259.
23. Hallemeier CL, Karnes RJ, Pisansky TM, et al. Multimodality therapy including surgical resection and intraoperative electron radiotherapy for recurrent or advanced primary carcinoma of the urinary bladder or ureter. *Am J Clin Oncol*. 2013;36:596–600.
24. Roeder F, Lehner B, Saleh-Ebrahimi L, et al. Intraoperative electron radiation therapy combined with external beam radiation therapy and limb sparing surgery in extremity soft tissue sarcoma: A retrospective single center analysis of 183 cases. *Radiother Oncol*. 2016;119(1):22–29.
25. Hanna SA, de Barros ACSD, de Andrade FEM, et al. Intraoperative radiation therapy in early breast cancer using a linear accelerator outside of the operative suite: An ïmage-guidedäpproach. *Int J Radiat Oncol Biol Phys*. 2014;89(5):1015–1023.
26. Rydholm A, Gustafson P, Rooser B, et al. Limb-sparing Surgery without radiotherapy based on anatomic location of soft tissue sarcoma. *J Clin Oncol*. 1991;9:1757–1765.
27. Markhede G, Angervall L, Stener B. A multivariate analysis of the prognosis after surgical treatment of malignant soft-tissue tumors. *Cancer*. 1982;49:1721–1733.
28. Andrews SF, Anderson PR, Eisenberg BL, Hanlon AL, Pollack A. Soft tissue sarcomas treated with postoperative external beam radiotherapy with and without low-dose-rate brachytherapy. *Int J Radiat Oncol Biol Phys*. 2004;59:475–480.
29. Davis AM, O'Sullivan B, Turcotte R, et al. Late radiation morbidity following randomization to preoperative versus postoperative radiotherapy in extremity soft tissue sarcoma. *Radiother Oncol*. 2005;75:48–53.
30. El-Bared N, Wong P, Wang D. Soft tissue sarcoma and radiation therapy advances, impact on toxicity. *Curr Treat Options Oncol*. 2015;16:19.
31. Emory CL, Montgomery CO, Potter BK, Keisch ME, Conway SA. Early complications of high-dose-rate brachytherapy in Soft tissue sarcoma. A comparison with traditional external-beam radiotherapy. *Clin Orthop Relat Res*. 2012;470:751–758.
32. O'Sullivan B, Davis AM, Turcotte R, et al. Preoperative versus postoperative radiotherapy in soft-tissue sarcoma of the limbs: A randomised trial. *Lancet*. 2002;359(9325):2235–2241.
33. Nag S, Shasha D, Janjan N, et al., American Brachytherapy Society. The American Brachytherapy Society recommendations for brachytherapy of soft tissue sarcomas. *Int J Radiat Oncol Biol Phys*. 2001;49:1033–1043.
34. Holloway CL, Delaney TF, Alektiar KM, et al. American Brachytherapy Society (ABS) consensus statement for sarcoma brachytherapy. *Brachytherapy*. 2013;12:179–190.
35. Naghavi AO, Fernandez DC, Mesko N, et al. American Brachytherapy Society consensus statement for soft tissue sarcoma brachytherapy. *Brachytherapy*. 2017;16:466–489.
36. Rachbauer F, Sztankay A, Kreczy A, et al. High-Dose-Rate Intraoperative Brachytherapy (IOHDR) Using Flab Technique in the Treatment of Soft Tissue Sarcomas. *Strahlenther Onkol*. 2003;179:480–485.
37. Tinkle C, Weinberg V, Braunstein S, et al. Intraoperative radiotherapy in the management of locally recurrent extremity Soft tissue sarcoma. *Sarcoma*. 2015. ID 913565, 8 pages.
38. Matsumine A, Tsujii M, Nakamura T, et al. Minimally invasive surgery using intraoperative electron-beam radiotherapy for the treatment of soft tissue sarcoma of the extremities with tendon involvement. *World Jour Surg Oncol*. 2016;14:214–221.
39. Roeder F, Krempien R. Intraoperative radiation therapy (IORT) in soft-tissue sarcoma. *Radiat Oncol*. 2017;12:20–33.
40. Roeder F, De Paoli A, Alldinger I, et al. IORT after gross total resection combined with EBRT in extremity soft tissue sarcoma: A pooled analysis [abstract]. *Radiother Oncol*. 2015;115(suppl 1):251.
41. Call JA, Stafford SL, Petersen IA, Haddock MG. Use of intraoperative radiotherapy for upper-extremity soft-tissue sarcomas. *Am J Clin Oncol*. 2014;37(1):81–85.
42. Talbot SG, Mehrara BJ, Disa JJ, et al. Soft tissue coverage of the hand following sarcoma resection. *Plast Reconstr Surg*. 2008;121:534–543.
43. Brenner DJ. The linear-quadratic model is an appropriate methodology for determining isoeffective doses at large doses per fraction. *Semin Radiat Oncol*. 2008;18:234–239.
44. Kirkpatrick JP, Soltys SG, Lo SS, Beal K, Shrieve DC, Brown PD. The radiosurgery fractionation quandary: single fraction or hypofractionation? *Neuro Oncol*. 2017;19(suppl2):ii38–ii49.
45. Alvarez A, Calvo FA, Gonzales C, et al. IORT in soft tissue sarcomas involving extremities: Toxicities and long-term functional results [abstract]. *Revisiones en cancer*. 2008;22:55.

46. Vujaskovic Z, Gillette SM, Powers BE, et al. Intraoperative Radiation (IORT) injury to sciatic nerve in a large animal model. *Radiother Oncol*. 1994;30:133–139.
47. Kinsella TJ, Sindelar WF, DeLuca AM, et al. Tolerance of peripheral nerve to intraoperative radiotherapy (IORT): Clinical and experimental studies. *Int J Radiat Oncol Biol Phys*. 1985;11(9):1579–1585.
48. Powers BE, Gillette EL, Gillette SLM, LeCouteur RA, Withrow SJ. Muscle Injury following experimental intraoperative irradiation. *Int J Radiat Oncol Biol Phys*. 1991;20:463–471.
49. Shaw EG, Gunderson LL, Martin JK, Beart RW, Nagorney DM, Podratz KC. Peripheral nerve and ureteral tolerance to intraoperative radiation therapy: Clinical and dose-response analysis. *Radiother Oncol*. 1990;18(3): 247–255.
50. Schwartz A, Rebecca A, Smith A, et al. Risk factors for significant wound complications following wide resection of extremity Soft tissue sarcomas. *Clin Orthop Relat Res*. 2013;471:3612–3617.
51. Barwick WJ, Goldberg JA, Scully SP, Harrelson JM. Vascularized tissue transfer for closure of irradiated wounds after soft tissue sarcoma resection. *Ann Surg*. 1992;216:591–595.
52. Davis AM, O'Sullivan B, Turcotte R, et al. Late radiation morbidity following randomization to preoperative versus postoperative radiotherapy in extremity soft tissue sarcoma. *Radiother Oncol*. 2005;75:48–53.
53. Enneking WF, Dunham W, Gebhardt MC, Malawar M, Pritchard DJ. A system for the functional evaluation of reconstructive procedures after surgical treatment of tumors of the musculoskeletal system. *Clin Orthop Relat Res*. 1993;286:241–246.