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Soft tissue sarcomas of the extremity and superficial trunk: do we need radiotherapy?

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INTRODUCTION

Soft tissue sarcomas (STS) are a heterogeneous group of mesenchymal malignancies with a propensity for local recurrence (LR) and metastasis. Surgical resection remains the cornerstone of management. Adjuvant radiotherapy (RT) reduces LR and current guidelines recommend RT for the majority of intermediate-to-high-grade tumours.[1-3] The indications for RT, however, vary between centres.[4,5]

RT is associated with short- and long-term concerns including wound complications, pathological fractures, fibrosis, stiffness, lymphoedema and radiation-induced malignancy.[6-8] The value of RT is diminished if surgery achieves an optimal margin.[5] Many authors have shown that small, low-grade STS are adequately treated by surgery alone.[4,9-12] Recent studies have extended this to selected high-grade STS.[13,14]

With advancements in surgical management, a greater proportion of patients may be cured by surgery alone, thus avoiding the morbidity and costs associated with RT. We began treating STS in 2004, and in 2005, established a management protocol involving wide margin resection without routine RT regardless of size, grade or location of tumour. RT is reserved for patients with positive margins who are not amenable to further complete surgical clearance. This approach differs significantly from current evidence-based guidelines for historic reasons; the senior author (MC) began this protocol prior to widespread adoption of these guidelines.

We report the oncological outcomes of a complete cohort of STS patients treated without routine RT and review the factors associated with local recurrence-free survival (LRFS).

METHODS

This study is a single-institution review of patients from a prospective database (Bone and Soft Tissue Tumour Database, Tan Tock Seng Hospital, reference no. TTSH/2019-00039). Ethics approval was granted by our institution review board (NHG-DSRB reference: 2017/00739). The study period was from August 2004 to April 2019. All patients had at least one year from surgery to the start of the study. We included all primary STS of extremity or superficial trunk, including those that had undergone prior unplanned excision. Patients for whom primary oncological surgery was performed outside of our unit and those who had undergone palliative surgeries were excluded.

Patients underwent clinical assessment and imaging with contrast-enhanced magnetic resonance (MR) imaging. Histological diagnosis was confirmed on core needle or incisional biopsy, except in patients with prior unplanned excision. Staging was performed with computed tomography (CT) of the thorax, with CT abdomen/pelvis or PET-CT performed for selected high-risk cases.

Resections were performed by two fellowship-trained orthopaedic oncology surgeons. Surgery was planned on the basis of the MR imaging, aiming for en bloc resection with a 2.5–5-cm margin of normal tissue or an intact fascial plane. The biopsy tract was included in the resection. In cases of prior unplanned excision, the resection aimed to remove all tumour and surgically contaminated tissue, as indicated by MR imaging.

The resection specimen was examined by a musculoskeletal pathologist. Margins were classified as negative (R0), or microscopically (R1) or macroscopically positive (R2). Positive margins were treated with further resection where possible; complete re-excision of the entire field was preferred to a limited excision of the involved margin. Where further excision was not possible, amputation or salvage RT was recommended by the treating surgeon in

conjunction with the multidisciplinary tumour board. Patients with high-risk disease were referred for adjuvant chemotherapy.

For well-differentiated liposarcoma/atypical lipomatous tumour (WDLS/ALT), wide resection was performed where possible; however, planned positive margins were considered adequate and not treated with further surgery or RT because of the relatively innocuous nature of the disease. None of the WDLS underwent simple enucleation.

Tumour grading was according to the French Federation of Comprehensive Cancer Centres (FNCLCC) criteria, whereas staging was according to the American Joint Committee on Cancer (AJCC), 7th edition. Patients were followed-up for eight years with clinical examination and advanced imaging.

The primary endpoint was LR. Secondary endpoints were metastasis and death. Time to event was calculated from the date of surgery.

LRFS, metastasis-free survival (MFS) and overall survival (OS) were estimated by the Kaplan-Meier method. Subgroup analysis was performed by log-rank analysis. Statistical analyses were performed using SPSS version 25 (IBM, Armonk, NY, USA). A p-value < 0.05 was considered statistically significant.

RESULTS

After application of inclusion and exclusion criteria, 106 patients were available for review. The population characteristics are summarised in Table I.

Table I. Population characteristics (n = 106).

Characteristic	No. (%)
Gender	
Female	46 (43.4)
Male	60 (56.6)
Mean age* (yr)	58 (18–95)
Tumour size (cm)	

≤ 5	32 (30.2)
> 5	74 (69.8)
Site	
Upper limb	45 (42.5)
Lower limb	51 (48.1)
Superficial trunk	10 (9.4)
Depth	
Superficial	46 (43.4)
Deep	60 (56.6)
FNCLCC grade	
1	36 (34.0)
2	26 (24.5)
3	39 (36.8)
Unknown/ungraded	5 (4.7)
AJCC7 stage	
IA/B	38 (35.8)
IIA/B	42 (39.6)
III	19 (17.9)
IV	6 (5.7)
Unknown	1 (0.9)
Histotype	
WDLS/ALT	20 (18.9)
Undifferentiated pleomorphic	15 (14.2)
Myxofibrosarcoma	13 (12.3)
Other liposarcoma	11 (10.4)
Synovial sarcoma	8 (7.5)
Dermatofibrosarcoma	8 (7.5)
Leiomyosarcoma	8 (7.5)
MPNST	4 (3.8)
Other sarcoma	19 (17.9)
Prior unplanned excision	
Yes	26 (24.5)
No	80 (75.5)
Surgery type (extremity, n = 96)	
Limb salvage	86 (89.6)
Amputation	10 (10.4)
Surgical margin	
R0	90 (84.9)
R1	15 (14.2)
R2	1 (0.9)
Radiotherapy	
None	99 (93.8)

Preoperative	0 (0)
Postoperative	7 (6.6)
Chemotherapy	
Yes	6 (5.7)
No	100 (94.3)

**Data presented as mean (range). AJCC7: American Joint Committee on Cancer staging system 7th edition; FNCLCC: French Federation of Comprehensive Cancer Centres; MPNST: malignant peripheral nerve sheath tumour; WDLS/ALT: well-differentiated liposarcoma/atypical lipomatous tumour*

Of the 106 patients, 96 (90.6%) underwent wide resection 10 (9.4%) underwent amputation. 15 (14.2%) patients had positive margins; of these, seven WDLS/ALT did not undergo further treatment. Of the remaining eight patients, two underwent complete field re-resection alone, one underwent limited re-resection and postoperative RT, two had RT alone, two underwent amputation, and one refused amputation and was lost to follow-up.

7 (6.6%) patients received postoperative RT: two were treated in 2004 prior to our protocol change and received RT despite negative margins, two with negative margins were referred for RT by other clinicians against the advice of the treating surgeon and three had RT after positive margin resections.

The median follow-up period was 5.4 years (range 1 month–12.7 years). Patients with short follow-up (< 1 year) included those who defaulted follow-up or returned to their home country after treatment. They were censored as per Kaplan-Meier method and did not skew the statistical analysis.

Four patients had LR at a mean of 13 (range 5–27) months. At one, five and eight years, the rate of LRFS was 99.0%, 96.1% and 96.1%, respectively (Fig. 1a). 18 patients had metastases. The median time to metastases was 2.9 (range 0.5–8.0) years. At one, five and eight years, the MFS was 98.6%, 94.5% and 89.0%, respectively (Fig. 1b). 20 patients died; the OS at one, five and eight years was 96.2%, 89.6% and 87.7%, respectively (Fig. 1c).

A subgroup analysis of LRFS was performed according to potential prognostic factors. LRFS was associated with FNCLCC grade (p = 0.02) and AJCC stage (p = 0.006) (Figs. 1d & 1e). No LR was noted in grade 1 or 2 sarcomas. No difference was found among the patients in terms of tumour depth (p = 0.15), size (p = 0.72), margin status (p = 0.39), or previous unplanned excision (p = 0.20).

DISCUSSION

Wide surgical resection remains the cornerstone of STS care. In 1976, Simon and Enneking reported 2% LR for patients with adequate resection but 100% recurrence with inadequate surgery; adequate surgery, however, was deemed an amputation for over 50% of patients.[15] Over the following decades, limb-sparing surgery (LSS) and RT became the standard of care. The efficacy of RT was established in the 1980s and 1990s by two randomised control trials showing improved LRFS with RT and surgery compared to surgery alone.[16,17]

STS management has continued to advance from the pre-MR imaging era,[18] with MR imaging-based surgical planning, improved understanding of margins[19] and recognition of factors affecting LR, including infiltrative tumour growth[20] and prior surgical contamination.[21] Reconstructive techniques for bone and soft tissues have increased patient eligibility for LSS without requiring compromise of margins.

While RT reduces overall LR, many authors have demonstrated that small, superficial and low-grade STS are adequately treated with surgery alone.[4,9,10,12] Recently, Alektiar et al showed no additional benefit of RT in small, high-grade STS with negative margins (AJCC IIB).[13] Fiore et al reported that RT could be safely omitted in clinician-selected high-grade STS.[14] The benefit of RT appears to be inversely related to the ability of surgery to remove all local malignancy. As surgical care improves, we believe that the role of RT will also continue to evolve.

This study demonstrates that high LRFS is possible (96.1% at eight years) with minimal use of RT (6.6%). A comparative summary of recent studies (2010–2020) is shown in Table II. Our RT utilisation rate is the lowest in the current literature, with LRFS comparable to that reported by Novais et al[22] and King et al,[23] although both reports excluded high-risk populations for LR (prior unplanned excision and positive margins, respectively).

Our protocol is surgically aggressive and requires strict adherence to surgical margins. We do not advocate using RT to reduce required margins or to permit planned positive margins. This approach is reflected in a low rate of positive margins (8/86 for non-WDLS). In practice, strict adherence to wide margins translates to increased surgical complexity or a higher rate of amputation. Our rate of primary limb salvage was 90%, which was comparable to modern reports (Table II). We consider this LSS rate to be a reasonable balance between function and oncological control.

Tumour stage and grade were associated with LR (Figs. 1d & 1e). The benefit of RT is likely to be greater in high-stage or high-grade tumours. In agreement with Fiore et al, we believe that further research is required in the modern surgical context to determine which high-grade STS require RT.[14] Positive margins were not associated with LR ($p = 0.39$). This may be attributable to type 2 statistical error or aggressive treatment of positive margins minimising the effect on LRFS.

This study was not without limitations. As the study was a two surgeon, single-centre cohort without a comparison RT arm, the outcomes are specific to our surgical practice. The limited cohort size precluded subgroup analysis. Functional outcomes were not included; however, we hope to review this as part of future research.

In conclusion, high rates of LRFS and limb salvage are possible without routine RT. We suggest that the role of RT is evolving and that current guidelines should be interpreted in the context of local expertise. Decisions regarding the omission of RT against established

guidelines should be made in the context of an experienced multidisciplinary team and on-going clinical audit to ensure acceptable levels of oncologic control.

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FIGURE

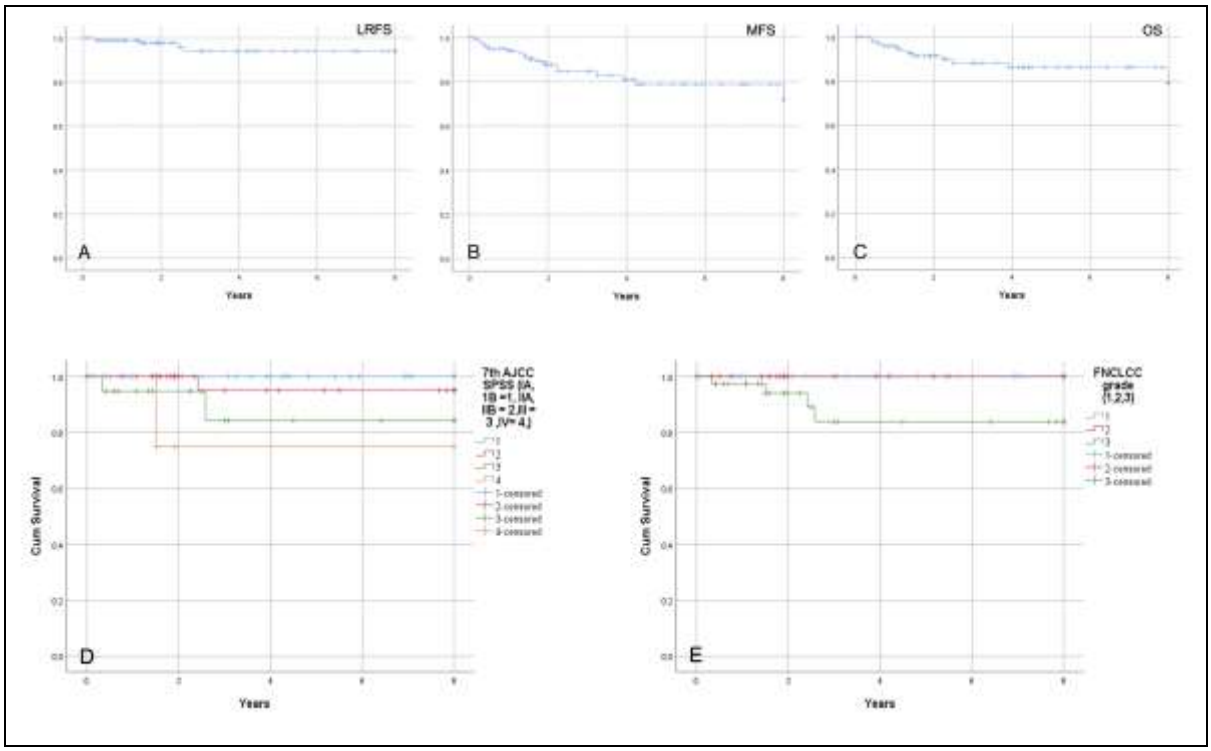

Fig. 1 Kaplan-Meier survival curves show (a) local recurrence-free survival (LRFS) (99.0%, 96.1% and 96.1% at one, five and eight years, respectively); (b) metastasis-free survival (94.2%, 84.6% and 82.7% at one, five and eight years, respectively); and (c) overall survival (96.1%, 89.4% and 87.5% at one, five and eight years, respectively). Kaplan-Meier survival curves show LRFS according to (d) FNCLCC grade (p = 0.02) and (e) AJCC classification (p = 0.006). AJCC: American Joint Committee on Cancer staging system; FNCLCC: French Federation of Comprehensive Cancer Centres

Table II. Recent studies (2010–2020) on adult non-retroperitoneal soft tissue sarcoma.

Study	Study period	No. of patients	Inclusion/exclusion criteria	Radiotherapy (%)	Positive margin rate (%)	Primary limb salvage (%)	Five-year LRFS (%)
Novais 2010[22]	1995–2008	248	Inclusion: Extremity STS, G2–3, deep tumours Exclusion: Prior surgery at another institution	70	2	95	95.9
Gronchi 2010[18]	1987–1992 1993–1997 1998–2002 2003–2007	250 194 274 376	Inclusion: Extremity STS Exclusion: Palliative intent, WDLS, DFSP, desmoid	32 43 51 60	14 16 9 11	92 98 99 99	89.6 75.3 86.9 90.2
King 2012[23]	2001–2007	117	Inclusion: Primary STS. Limb salvage patients. Negative margins Exclusion: Positive margins WDLS, Prior surgery	26% PoRT 62% PrRT	NA	NA	96.6
Fiore 2018[14]	2000–2012	390	Inclusion: High-risk sarcoma (> 5 cm, deep, G2–3). Limb salvage only	82%	21% (RT + S) 30% (S)	NA	83.9% RT + S 81.2% S
Present study	2004–2019	106	Inclusion: Primary trunk and extremity STS Exclusion: palliative resections	7% PoRT	15	90	96.1

DFSP: dermatofibrosarcoma protuberans; LRFS: local recurrence-free survival; NA: not applicable; PoRT: postoperative radiotherapy; PrRT: preoperative radiotherapy; RT: radiotherapy; S: surgery; STS: soft tissue sarcoma; WDLS: well-differentiated liposarcoma