Randomized Controlled Trials in Soft Tissue Sarcoma: We Are Getting There!

Andrea J. MacNeill, MD, MSc[a], Abha Gupta, MD, MSc[b,c], Carol J. Swallow, MD, PhD[d,e,*]

KEYWORDS

• Randomized controlled trial • Soft tissue sarcoma • Extremity sarcoma
• Retroperitoneal sarcoma • Preoperative radiotherapy • Chemotherapy

KEY POINTS

- The rarity and heterogeneity of soft tissue sarcoma (STS) pose challenges to the design and conduct of randomized controlled trials (RCTs).
- The only level 1 evidence to guide the surgical management of STS is a small RCT that established the equivalence of limb salvage to amputation for extremity STS.
- Improved local control of extremity STS with radiotherapy (RT) has been demonstrated in 2 landmark RCTs, and the relative advantages of preoperative versus postoperative RT are documented in the NCIC SR2 trial. Level 1 evidence regarding the use of RT in retroperitoneal sarcoma is as yet pending, from the European Organization for Research and Treatment of Cancer–led STRASS trial.
- With the exception of specific histologic subtypes, there is a lack of evidence to support routine neoadjuvant/adjuvant chemotherapy as a standard of care for most adult STS. However, multiple agents have been shown to prolong survival in the metastatic setting.
- Large collaborations in pediatric oncology have generated robust level 1 evidence for the management of pediatric STS.

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[a] Division of Surgical Oncology, Department of Surgery, Diamond Health Care Centre, BC Cancer Agency, University of British Columbia, 5199-2775 Laurel Street, Vancouver, British Columbia V5Z 1M9, Canada; [b] Department of Hematology/Oncology, The Hospital for Sick Children, 555 University Avenue, Toronto, Ontario M5G 1X8, Canada; [c] Department of Medical Oncology, Princess Margaret Cancer Centre, 610 University Avenue, Toronto, Ontario M5G 2M9, Canada; [d] Department of Surgical Oncology, Mount Sinai Hospital/Princess Margaret Cancer Centre, 600 University Avenue, Suite 1225, Toronto, Ontario M5G 1X5, Canada; [e] Department of Surgery, University of Toronto, Stweart Building, 149 College Street, Toronto, Ontario M5T 1P5, Canada
* Corresponding author. Mount Sinai Hospital, 600 University Avenue, Suite 1225, Toronto, Ontario M5G 1X5, Canada.
E-mail address: Carol.Swallow@sinaihealthsystem.ca

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INTRODUCTION

Soft tissue sarcoma (STS) is a family of rare malignant neoplasms with an incidence of 4 to 5 per 100,000. As these are of predominantly mesenchymal origin, they can occur in any anatomic location. This anatomic diversity has important implications for treatment, in particular with respect to operative considerations, such that extremity/trunk and retroperitoneal/intra-abdominal STS are in many ways distinct entities.

More than 70 histologic subtypes of STS are now recognized with widely variable biology and sensitivity to systemic treatments. Increasingly, the discovery of characteristic underlying molecular alterations is facilitating targeted treatment of individual subtypes. For these reasons, it is imperative to conceptualize STS as a family of disparate malignancies requiring treatment strategies tailored to individual patients and disease. The rarity and heterogeneity of STS pose a considerable challenge to the design, conduct, and interpretation of randomized controlled trials (RCTs). The STS literature is, therefore, limited in high-level evidence and in the general applicability of many of the existing RCTs.

Surgery remains the mainstay of curative-intent treatment of STS. The ability to achieve complete excision is the primary determinant of survival and overt local recurrence for most histologies.[1–3] Radiotherapy (RT) is often used to allow preservation of critical structures and to decrease local recurrence, but a survival benefit has not been shown.[4,5] Chemotherapy has an important role in the primary treatment of specific chemosensitive subtypes of STS, including nonpleomorphic rhabdomyosarcoma (RMS) and Ewing sarcoma (ES), but in other subtypes its use is generally reserved for treatment of advanced or metastatic disease. The level 1 evidence available for each of these treatment modalities is discussed below.

SURGERY

Seminal work on the surgical approach to extremity STS was published in 1982 by Rosenberg and his colleagues[6] at the National Institutes of Health (NIH). A total of 43 patients were randomized to either amputation (N = 16) or limb salvage with adjuvant external beam RT (N = 27). All patients received postoperative systemic chemotherapy. There was no significant difference in overall survival (OS) between the two groups, and local control in the limb salvage group was 85%. These results instigated a paradigm shift toward limb preservation that has long remained the standard of care.

The optimal extent of surgery for retroperitoneal sarcoma (RPS) has not been evaluated in a similarly rigorous fashion. The anatomic constraints of the retroperitoneum render microscopic margin negative resection difficult. In contradistinction to extremity/trunk STS, local failure remains a predominant pattern of RPS recurrence, leading to disease-specific mortality that continues to accrue even 20 years postoperatively.[7] Based on retrospective data from multiple institutions, particularly in Europe, there has been an evolution in recent years toward more liberal en bloc resection of adherent but grossly uninvolved organs in an attempt to improve local control in RPS.[8,9] However, this approach has not been compared with more conservative resection using true prospective data collection, even in an observational manner; it is difficult to imagine how a meaningful RCT could be conducted.

RADIATION

Extremity Soft Tissue Sarcoma

As in the limb-sparing approach supported by the landmark work of Rosenberg and colleagues,[6] RT has for several decades been used to facilitate function-preserving surgery by allowing close/microscopically positive margins along critical neurovascular