Soft tissue sarcomas (STS) are rare malignancies which can be further subdivided into several histological subtypes, each with their own clinical presentation and behavior, biology, genetics, response to treatment etc. The state-of-the-art approach to patients with such rare tumors can be found in the ESMO Clinical Practice Guidelines\(^1\) and the website of the National Comprehensive Cancer Network. In brief, surgery is the cornerstone managing primary non-metastatic STS patients. Where the disease affects the extremities STS (ESTS), this approach has been proven to be as safe as amputations with respect to local control and overall survival provided (neo-) adjuvant radiotherapy (RT) is applied, when indicated.

A discussion on the indications and techniques for RT in ESTS has recently been published.\(^2\) In summary, pre- and postoperative RT regimens provide comparable local control (80–90%) and survival although they differ in their toxicity profile. Preoperative RT results in an increased likelihood of wound complications, with a factor of 2 as compared to limb conserving surgery without prior RT [3; 17% versus 35%]. On the other hand, after prolonged follow up, postoperative RT results in worse functional outcomes (i.e. fibrosis, edema, joint stiffness, etc.) also roughly with a factor of 2.\(^4\) However serious, the wound healing problems are usually temporary, but the late complications are permanent and often progressive. The difference between the two regimens can be explained by 2 radiotherapeutic aspects: dose and volume. With neo-adjuvant RT only the sarcoma (with certainty margins for both microscopical extensions and daily setup variations at the linear accelerator) is conventionally irradiated in 1.8—2 Gy once-daily fractions to a total dose of 50 Gy in 5 weeks. Definitive surgery then takes place 4—6 weeks later, taking into account all changes induced by the RT. However, the most frequent observation during preoperative RT up to the day of surgery, is a stabilization of growth. Few cases show a slight increase in size and only myxoid liposarcomas (MLS) will shrink markedly.\(^5\)

As such, in cases of primary inoperable disease, preoperative RT will not render the tumor operable. Le Grange and colleagues\(^7\) have investigated a group of 68 patients with borderline resectability features with a median size of 12.5 cm predominantly located in extremities, treated by 25 × 2 Gy preoperative RT. By RECIST, on post-radiotherapy imaging, there was stable disease in 89%, partial response in 7% and progressive disease in 4%. For the entire group, however, the resection status was R0 in 93%, and R1 in 7%. After a 2 year follow-up benefit (increase in local control) of preoperative RT, which is only intended to “devitalize” tumor cells.

Postoperative RT is usually divided into two phases. The first 50 Gy in 5 weeks is applied to the entire surgical bed (again with certainty margins) directly followed by another 10—16 Gy on the area where the original sarcoma was located.\(^3\)

Consulting the Memorial Sloan Kettering Cancer Center nomogram\(^6\) and their online accessible prediction tool, even the most unfavorable patient (age >50 years, high grade sarcoma resected with close or positive margins of an unfavorable histological subtype) faces a 5 year local control probability of 53% without (neo-) adjuvant RT. When RT is administered, the local control probability goes up to at least 80% and some series even ≥90%.\(^3\)

Overall 30—40% operable ESTS patients will benefit from (neo-) adjuvant RT, 10—20% will develop a local recurrence despite RT and 50% will not require RT after adequate surgery alone. This may not seem much, but it is exactly the same clinical benefit gained by adjuvant RT in the breast conserving therapy for invasive breast cancers with a population incidence of at least 20 times that of STS. It is precisely this window of opportunity that 3 articles published on EJSO are exploring.\(^7\)\(^9\)\(^10\)

**Paradigm A: preoperative RT in ESTS is especially designed for primary operable cases and, as a rule, it will not render an inoperable case operable**

Le Grange and colleagues\(^7\) have investigated a group of 68 patients with borderline resectability features with a median size of 12.5 cm predominantly located in extremities, treated by 25 × 2 Gy preoperative RT. By RECIST, on post-radiotherapy imaging, there was stable disease in 89%, partial response in 7% and progressive disease in 4%. For the entire group, however, the resection status was R0 in 93%, and R1 in 7%. After a 2 year follow-up
the local relapse free survival was 87.5%; only a few tumors increased in volume and there was no definite relationship between the increase in volume and poor surgical outcomes or inferior local control.

This patients group was dominated by the MLS subtype (32%), known for its radiation sensitivity. This study confirms this feature in figure 1 showing volume reductions up to 84.7% of initial size for MLS. Even when a MLS does not shrink, necrosis and hyalinization in the resection specimens can be appreciated (case #11, table 4). The authors correctly suggest to refrain from using RECIST in this setting.

The study by Levy and colleagues reports on 64 ESTS patients. They show how, even in a (negatively) selected patients population (i.e. locally advanced disease, elderly patients and/or failures after neoadjuvant chemotherapy and/or isolated limb perfusions) favorable results can be obtained with good local control and low toxicity (both early and late). Early toxicities were usually mild (grade I–II). Wound healing problems were only seen in 20% cases which compares favorably to the 35% described in O’Sullivan’s NCIC SR-2 trial. Late toxicities, mild in severity and low in incidence, were predominantly seen in those cases where a postoperative boost was applied. However, a median follow-up of 3.5 years may have been somewhat short for this conclusion. The 3-year actuarial local control rate approximates 98% (2% failures).

Although postoperative RT is preferred world widely, this multidisciplinary team believes that there are pros and cons for both pre- and post-operative RT in ESTS. Arguments such as wound complications after preoperative RT should be balanced against a better functional outcome at prolonged follow-up.

They argue that there are several reasons to be discussed upfront, one of them being the histological subtype MLS (in 13% of cases). They offered their patients a median preoperative dose of 50 Gy (range, 36–50 Gy). Ten patients received less than 50 Gy. According to MRI results (available in 44 cases), 25% had progressive disease, 57% stable disease, 5% partial response, and 16% complete response according to RECIST 1.1.

These two studies clearly demonstrate how the risk of progressive disease during preoperative RT in borderline resectable STS patients is very low; surgeons should thus not be reluctant to refer such cases to their radiation oncologist for preoperative irradiation. A local control probability of 87.5–98% at 2–3 years can be expected and it compares favorably to other published series. These observations are even more likely to be true in the case of MLS histology. These studies add 4 dimensions to the above described paradigm: 1. It is unlikely that preoperative RT in borderline resectable ESTS cases will render the patient inoperable; 2. the clinical benefit of RT is of the same magnitude as in primary operable cases with an anticipated local control of 87.5–98%; 3. in dedicated teams, the risk of wound complications may be lower than previously published and 4. don’t use RECIST to decide whether preoperative RT in STS has any clinical benefit.

Paradigm B: 2 Gy fractions to a total dose of 50 Gy in 5 weeks is the “golden standard” in preoperative RT for STS

The study by Kasela-Paterczyk and colleagues on preoperative hypofractionated RT in STS is intriguing for several reasons. First, the Polish schedule, as a copy from the experience in rectal cancer, is totally new in STS management. Secondly, the investigators deviated extensively from paradigm B. Their rationale is based, however, on reasonable radiobiological principles. It should be noted that, although there is vast experience with 50 Gy in 5 weeks, it does not come forth from randomization between different preoperative dose levels and as such, it is no more than just “common practice”. It may well be that the so called alpha-beta ratios for sarcoma cells (a measure for sensitivity to fractionation in RT) are in the range found for both breast and prostate cancer. Especially in breast cancer (moderate) hypofractionation showed to be equally effective in providing local control without compromising cosmesis nor late fibrosis (references in the full paper). Thirdly, surgery was performed after 3–7 days rather than after 4–6 weeks.

In general, the probability of achieving local control depends on the quality of surgery, the size of the sarcoma, its grade, the disease status (primary or recurrent) and the addition of RT. This study population is dominated by 64.6% grade III cases, 42.1% patients with tumors larger than 10 cm, 38.6% non-primary disease status, and 78.7% R0 resections. Although the perceived local control rate of 80.5% may seem somewhat at the lower level of the 80–90% range, considered from this perspective it is comparable to other series (table 4). Also, the toxicity profile (both early and late) compares favorably to prior published series.

The regimen is convenient: within 14 days the patient is irradiated, operated and discharged from hospital compared to 2.5–3 months in the reference schedule. In areas of the world with limited radiation resources and/or long travel distances this treatment plan may be a very good alternative. The regimen also provides socio-economic advantages, with less radiation fractions, less travel costs and a shorter period off-work.

The take-home message from this prospective phase II study, is that it is time to reconsider fractionation schedules and total doses in STS on a scientific basis. In the study by Levy, in ten patients it was already decided to apply less than 50 Gy. Although the experience on breast cancer is a good example any research on STS is much more difficult due to the rarity of the disease. Nevertheless, there are already two good efforts. The first is the Polish regimen and the second is the prospective phase II “DOREMY” study reducing the dose to 18 × 2 Gy in the MLS subset.
(Trial Identifier NCT02106312). The latter is designed with Bayesian statistics. Perhaps these sophisticated calculations may prove to be of help in studying rare diseases.

Where does this leave us for the future? What do surgeons expect from radiation-oncologists? Studies on modern RT techniques like intensity modulated RT and image guided RT\textsuperscript{11} are showing reduced wound complications without jeopardizing local control. Regimens with other-than 2 Gy fractions (like the Polish regimen) and other-than 50 Gy total doses (like in MLS) should be further explored. Finally, the interaction of conventional chemotherapy and/or targeted agents concurrent with preoperative RT is far from being fully exploited. In all these kinds of investigations, side studies and translational research are mandatory: they will teach us how to individualize the preoperative RT management of STS. Radiation-oncologists would expect their surgeons to fully appreciate the robust and safe nature of preoperative RT and to discuss these patients referrals before surgery. This is a mandatory step to allow our two professions conducting all the research that is needed to fulfill our social obligation of Personalized Medicine.

Acknowledgment

The author acknowledges his colleagues radiation-oncologists, medical oncologists and surgeons from the STS working group, for carefully reading the manuscript.

Conflicts of interest statement

None.

References


R.L.M. Haas*
Department of Radiotherapy, The Netherlands Cancer Institute, Amsterdam, The Netherlands
*Department of Radiotherapy, The Netherlands Cancer Institute, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands. Tel.: +31 20 512 2135; fax: +31 20 669 1101. E-mail address: r.haas@nk.nl