Soft tissue sarcomas of the extremities in adults
E Lartigau, A Gerbaulet

1 Introduction

Soft tissue sarcomas (STS) of the extremities are rare tumours (< 1% of adult tumours) and represent 50% of all soft tissue sarcomas. They are seen in all age groups and their aetiology is in general unknown, except in some congenital syndromes. Patients usually present with a painless soft tissue mass. (2,9,35)

A multicentric study carried out by the French Federation of Cancer Centers (7) in 546 patients has proven that the factors most often associated with local recurrence are: pathological grade III, postoperative residual disease, and no adjuvant radiation therapy after surgery.

If the genotype of the tumour is studied, genetic alterations can be detected: these alterations, mostly chromosome translocations, are specific markers for subgroups of soft tissue sarcomas and could constitute a new biological prognostic factor. (11)

Amputation has long been the standard treatment for soft tissue sarcomas giving good local control but with a poor quality of life. To reduce treatment sequelae, different groups in the early 60’s advocated the combination of conservative surgery with pre or post operative radiotherapy. (9,19,26,31,34,35). Successive studies confirmed the good results obtained by a conservative approach and were able to define the prognostic factors for local control (histological grading, tumour size > 5 cm and quality of the surgery) and survival (grade and size). The technique of external beam irradiation was defined according to the treated volumes, fractionation and normal tissue sparing (non circumferencial irradiation).

In parallel, the role of brachytherapy was evaluated for primary and recurrent tumours, in particular in previously irradiated areas. (14,15,17,18,37) In all cases, brachytherapy has been performed as an intraoperative procedure, exclusively for limited and well defined tumours or combined with external beam therapy in large tumours.

In a recent article published by Nag, patient selection for brachytherapy is indicated according to ABS recommendations. (27)

The role of chemotherapy is still controversial (Jones); doxorubicin, ifosfamide and dacarbazine are the most effective drugs. Metastatic recurrences are the commonest cause of failure, particularly for high-grade and bulky tumours. In these situations, therefore, chemotherapy should always be considered. (9,20,35)

2 Anatomical Topography

Any muscle can be the site of STS. More than ¾ of STS are deep seated tumours. The muscles in the extremities are arranged in different compartments as defined by Enneking. (13) Precise knowledge of these compartments is essential as the tumours usually spread within their boundaries. The critical organs for brachytherapy (and radiotherapy) are the skin, the vessels and the nerves.
3 Pathology

Histological diagnosis is difficult and must be based upon a variety of histopathological examinations including immunohistochemistry, and should be confirmed by an experienced pathologist in the field of STS. When reviewed by different pathologists, there can be a discrepancy of up to 25% in subtype. It must be emphasised that the pathological classification and the distribution of tumour subtypes have varied with different time. Nowadays, the most common histologic types are malignant fibrous histiocytoma, liposarcoma, leiomyosarcoma and rhabdomyosarcoma. (35)

Tumour grade is considered for a tumour type the key prognostic factor, based on degree of differentiation, cellular and nuclear pleomorphism, mitotic activity, cellularity, necrosis, and growth pattern. Up to now there has been no complete agreement on a single system. Low grade tumours carry a risk of local recurrence predominantly and high grade tumours a risk of distant recurrence, most frequently in the lung. More than 50% of patients with intermediate and high grade tumours > 5 cm develop distant metastases, compared to 8% in low grade lesions < 5 cm. The incidence of lymph node involvement is low (< 5 - 10%). (7,35)

After surgery, pathological evaluation of surgical margins must contribute to classification of the surgical procedure into four categories. (13) An “intralesional procedure” is accomplished by a biopsy with macroscopic and/or microscopic tumour left in place. A “marginal procedure” removes the tumour from its pseudocapsule (“shellout”) with a high likelihood of residual subclinical disease. In a “wide resection” the tumour is removed within a varying margin of normal tissue within the same compartment. In “radical resection” the entire tumour and the structure of origin are removed en bloc (e.g. “compartmental resection”). The probability of (local) recurrence depends on the type of operation with about 100% after an intralesional procedure, 50 - 80% after a marginal procedure, 30 -60% after wide resection and 10 - 20% after radical resection.

Following the results of a multicentric study, (34) a new classification of surgical resection R for soft tissue sarcomas has been proposed, based on surgical and pathological results:

- R0: resection in sano (within healthy tissue);
- R1: microscopic residual disease;
- R2: residual disease.

4 Work Up

The following procedures should be performed systematically: general history (familial cases); physical examination; plain X-ray of the site involved; magnetic resonance imaging (and CT or US) for evaluation of tumour local extension (pre and/or post operative situation); (Fig 27.1 – see overleaf) chest X-ray/CT. Angiography is rarely performed nowadays; electro-myography may be useful if there is nerve involvement.

Biopsy should be performed by a surgeon experienced in soft tissue sarcoma surgery. As STS are often diagnosed after removal of a “benign” soft tissue mass by a general surgeon, this surgical procedure must be carefully documented and evaluated according to the classification by Enneking (13) and Stöckle. (34)

In recurrent disease, a comprehensive knowledge of the first diagnosis and treatment is essential including imaging, pathologic specimen, surgery, and maybe radiotherapy.
5 Indications

At the time of presentation of a patient with a STS to the multidisciplinary team (surgeon, radiation oncologist, medical oncologist, radiologist, pathologist), two clinical situations are commonly seen: (9,15,27)

- A malignant tumour is suspected and has not been removed: after radiological evaluation (MRI), an incisional biopsy is performed to obtain sufficient material for a precise diagnosis. This biopsy must be performed with great care and must not compromise future conservative surgery (orientation of the scar). Based on the essential characteristics such as tumour size and site, stage, local invasion and pathological findings, local and general treatment strategies will be chosen. (3,26)
- The tumour has already been removed: the pathological slides are reviewed for confirmation; the surgical procedure is classified according to Enneking (13) and Stöckle (36); a systematic post operative MRI is performed. If residual disease is seen or suspected, the patient will undergo operation. According to the initial tumour characteristics and to the findings from re-operation, local and general treatment strategies will be chosen. (1,26,27,33,36)

Brachytherapy is indicated if there is a (significant) risk of local recurrence after surgery. It is an integrated part of the multidisciplinary treatment of STS and can only be considered as an intra-operative procedure. It is used as a tumour bed boost after surgery, either on its own or in combination with external beam radiotherapy (pre or post operatively) delivered to a larger volume. For intermediate and high grade tumours, and for local recurrences in non irradiated and irradiated areas, the risk of recurrence is significant. Brachytherapy should therefore be integrated into the general treatment strategy and can be combined with external beam radiotherapy in selected cases. For low grade tumours, radiotherapy (mostly external) will be given only for large tumours (> 5 cm) if resection is inadequate. (7,16)
The ABS gives recommendations for the use of brachytherapy in different situations: (27)

- When the tumour is completely resected (Gr2 – Gr3): surgery followed by brachytherapy alone;
- When the CTV cannot be adequately implanted, and the surgical margins are positive: surgery followed by brachytherapy and EBRT.
- Other situations, different kinds of brachytherapy may be indicated and are described.

6 Indications, Contra-indications

Target volume is defined from preoperative imaging and/or intra operative evaluation. As brachytherapy for STS is always an intra- or peri-operative procedure, target volume will be defined in collaboration with the surgeon and the tumour bed implanted according to the following rules.

The GTV is based on imaging (MRI) and the pre-operative description, as the CTV is considered to be the GTV plus a 2 - 5 cm margin. (17) A 5 - 10 cm margin around the tumour bed is used for external beam therapy, a margin substantially wider than that used for the implant. However, margins are now considered to be based more on anatomical muscular compartments than on cm margins. This concept has been comprehensively reviewed in a recent publication. (24)

7 Technique

Interstitial implants are performed at the time of surgery. After determining the CTV according to the surgical and pathological findings, as well as the preoperative imaging (MRI), the plastic tubes are implanted. The CTV is delineated by radiopaque markers and will be encompassed by different plastic tubes.

The plastic tubes should be implanted parallel and equidistant, transverse (IGR method) (10,17) or parallel (MSKCC method) to the surgical incision. Depending on the pathological and surgical findings (quality of the resection) (13,34), a single plane is sufficient in most cases of resection in sano R0 and microscopical residual disease R1; for macroscopic residual disease R2, a double plane is necessary.

The surgical bed must be as large as possible, (Fig 27.2A, Fig 27.2B) so as to allow a well-adapted tumour removal and plastic-tube implantation while respecting a conservative approach. Guide needles are implanted through the skin at least 2 cm away from the surgical incision (Fig 27.2C). The needles may be straight or curved to fit the CTV. The guide needle are then replaced by plastic tubes (Fig 27.2D, 2E).

To reduce the radiation dose to critical organs (nerves, vessels, bones, etc.), some perioperative surgical procedures are indicated, e.g. a spacer or layer of muscles can be inserted (maintaining normal blood supply) between the afterloading system and the structure to be avoided.

Nevertheless, direct contact between sources and critical organs is not an absolute contraindication; as always doses and irradiated volume must be taken into account, as ever. The positioning of the plastic tubes is adapted to the dimensions of the CTV. Parallel and equidistant, the different plastic tubes are spaced 10 to 20 mm, according to the depth of the tissue to be treated. To achieve good parallelism and equidistance between the plastic tubes, they can be partially fixed by surgical sutures inside the directly-visible tumour bed and at skin level (entrance and exit points), by way of surgical sutures using a pre-perforated catheter to which the plastic tubes are inserted (Fig 27.3A). (17)
Fig 27.2 Recurrence of a soft-tissue sarcoma of the shoulder: perioperative interstitial implant:

Fig 27.2A Drawing of the skin limit of the surgical resection including the whole scar

Fig 27.2B Tumour resection

Fig 27.2C Implantation of the metallic needles

Fig 27.2D Replacement of the needles by parallel plastic tubes

Fig 27.2E Closing of the surgical bed; preperforated catheters maintain the equidistance of the plastic tubes
8 Dosimetry

Dosimetry is based on two radiographs taken after intraoperative implantation of the tubes. The radioactive length is determined according to the width of the target, taking into account the definitive pathological report. In any case the skin is spared at the entrance and exit points of the tube, by not loading the proximal and distal part of each tube within the skin for a distance of at least 5 - 10 mm each (see Fig). The spacing between the lines is adapted to the thickness of the tumour to be treated, e.g. in a single plane implant if the tumour thickness is 1 cm, the distance between two lines must be 2 cm, if the implant is performed at the middle of the tumour thickness (see figure). The minimal target dose then corresponds to 85% of the mean central dose (Fig 27.3B and 27.3C). The maximum distance between two lines should not exceed 2.5 cm; if the distance is larger, the overdosage volume becomes unacceptable because of the risk of complications (e.g. necrosis). For thicker tumours, the number of planes and by definition of lines is higher, so the dosimetry and dose distribution are adapted taking into account the same rules for details see “generalities”, physics). Specific care must be taken with regard to nerves and vessels.

To document residual tumour volume, CT and/or MRI scans are performed before surgery and after intraoperative implantation with the afterloading system in place. The position of the applicators in relation to the target volume can then be precisely assessed. The dose distribution is adapted to the length and thickness of the target. Dose to and volume of critical structures are noted accurately (e.g. nerves, vessels, bone).
The tubes are loaded with Ir192 on day 2-4 in the IGR technique (15,17) and on day 6 - 8 in the MSKCC technique. (18,19)

9 **Dose, Dose Rate, Fractionation**

If LDR brachytherapy is used alone a total dose of 60 - 75 Gy at a dose rate of 40 - 60 cGy/hour is delivered depending on the surgical and pathologic results. (15,17,37) If LDR brachytherapy is combined with external beam therapy the dose of brachytherapy is dependant on the dose of external beam therapy. The overall total dose varies from 70 - 80 Gy with a brachytherapy dose of 25 - 35 Gy. When the dose of brachytherapy is more than 65 Gy (brachytherapy alone), or more than 30 Gy (in combination treatments), the volume receiving more than 65/30 Gy is reduced. (15,17). The loading should be adjusted to focus this boost volume on the area at highest risk of local recurrence. This optimisation of dose distribution can also be easily applied using the stepping source technology.

For HDR brachytherapy the recommendations from the ABS: for intraoperative HDR brachytherapy the doses range from 10 to 15 Gy (prescribed at a 0.5 cm depth of this brachytherapy is used as a boost to EBRT).

10 **Monitoring**

In perioperative brachytherapy specific care must be taken in relation to the early side effects of to the surgical procedure and brachytherapy and their interaction.

Typical surgical complications are haemorrhage, infection, haematoma and wound dehiscence. In these cases, it is essential to check with the geometry of the implant compared to the initial plan by X rays, and if there is displacement to recalculate the dosimetry.

Systematic prophylactic antibiotics are not mandatory but are used if there are local or general symptoms.

11 **Results**

Most treatments have been with low dose rate but there is some experience with high or pulsed dose rates.

11.1 **Results of surgery**

The results of surgery are dependent on tumour and patient related factors. In addition, different types of surgery carry a characteristic risk of local recurrence: intrallesional procedure 100%, marginal procedure 50 - 80%, wide excision 30 - 60%, radical excision 10 - 20% (Enneking et al. 1981?). These results underline the fact that a high local control rate can only be achieved by performing a radical procedure which will be associated with significant morbidity. (2,9,13,16,26,35)

11.2 **Results of external beam therapy combined with surgery**

Conservative limb sparing treatment including nonradical surgery and adjuvant radiotherapy for localised extremity sarcomas has been shown to be as effective as radical surgery alone in a prospective randomised NCI trial comparing amputation vs a limb-sparing operation followed by
adjuvant radiotherapy. There was no statistically significant difference between the two groups in terms of survival. (30)

According to the long term experience from some major groups with preoperative and/or postoperative radiotherapy in combination with limb conserving surgery, has demonstrated long term local control > 80 % has been demonstrated. (9,25,35,36)

Two groups of patients were compared at the NCI in a phase III trial. All patients presented a grade 1 soft tissue sarcoma. After gross total resection the first group received postoperative irradiation, and the second group no further treatment. The local recurrence rate at 5 years was 0% and 30% for the first and second group, respectively. (26)

In an overview of other publications including a total of 812 patients treated with surgery followed by radiation therapy, Calais reported a local-recurrence rate of 13% to 45% and a 5-year survival rate of 54% to 67%. (3)

11.3 Results of brachytherapy (Tables 27.1 and 27.2)

11.3.1 Local control and survival

The MSKCC was the first to publish large series on exclusive or combined brachytherapy using Iridium-192 afterloading catheters. (19) A prospective randomised trial (18) was performed between 1982 and 1987 in 126 patients with STS of the extremity or superficial trunk. They all underwent a complete, limb-sparing resection of the tumour and were randomised to receive an adjuvant implant or no further treatment. Some patients received adjuvant chemotherapy. Brachytherapy consisted of low dose rate treatment with catheters covering the tumour bed + 2 cm margin. The total dose was 45 Gy over 4 - 6 days. Local control at 5 years was significantly improved with BRT (82% vs. 67%, p=0.049) but only for patients with high grade lesions, without any difference in either the incidence of distant metastasis or survival. The disease specific survival at 5 years was 80% in both arms. Only 29 patients had a low grade tumour and they had no improvement in local control (overall 20 - 30% local failure rate).

Table 27.1 Results of perioperative LDR brachytherapy: comparison between first-line (F) and salvage (S) brachytherapy

<table>
<thead>
<tr>
<th>Author</th>
<th>Pts N.</th>
<th>Treatment</th>
<th>Brachy</th>
<th>Survival %</th>
<th>Local control %</th>
<th>Complications %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delannes (10) *</td>
<td>85</td>
<td>A 31, B 54</td>
<td>F 62, S 38</td>
<td>AS: F 75, S 62</td>
<td>F96, S 68</td>
<td>15</td>
</tr>
<tr>
<td>Gerbaulet (15) *</td>
<td>50</td>
<td>A 48, B 2</td>
<td>F 15, S 35</td>
<td>OS 68</td>
<td>F 96, S 64</td>
<td>25</td>
</tr>
<tr>
<td>Habrand (17) *</td>
<td>48</td>
<td>A 44, B 4</td>
<td>F 22, S 26</td>
<td>OS, F 62, S 57</td>
<td>68, 81 **</td>
<td>20</td>
</tr>
</tbody>
</table>

Legends:
A: Surgery + brachytherapy
B: Surgery + Brachytherapy + EBRT
* Some patients are included in both Delannes (10) and Thomas (37) series; the same applies to Gerbaulet (15) and Habrand (17)
** Locally controlled after salvage treatment

Another interesting study, of 45 patients with soft-tissue sarcoma presenting with neurovascular involvement, was published be Zelefsky. (39) These patients were treated at the Memorial Sloan Kettering Cancer Center by surgical resection and brachytherapy. Sixty-four per cent of the patients had high-grade tumours; 11% had microscopic and 58% macroscopic residual disease. The local control inside the implanted volume was 79%, with 84% limb preservation. These results
demonstrate that neurovascular involvement does not constitute a contraindication for combined treatment (surgery + brachytherapy).

Table 27.2: LDR / HDR intra- or perioperative brachytherapy combined with ERBT: local control and complications

<table>
<thead>
<tr>
<th>Author</th>
<th>Pts N.</th>
<th>Brachytherapy</th>
<th>Local control %</th>
<th>Complications %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alekhteyar (1)</td>
<td>18</td>
<td>LDR-HDR</td>
<td>90</td>
<td>38</td>
</tr>
<tr>
<td>Chaudhary (4)</td>
<td>118</td>
<td>LDR</td>
<td>96</td>
<td>10</td>
</tr>
<tr>
<td>Chuba (5)</td>
<td>32</td>
<td>HDR</td>
<td>82</td>
<td>48</td>
</tr>
<tr>
<td>Cionini (6)</td>
<td>33</td>
<td>LDR</td>
<td>91</td>
<td>6</td>
</tr>
<tr>
<td>Crownover (8)</td>
<td>10</td>
<td>HDR</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>Donath (12)</td>
<td>19</td>
<td>HDR</td>
<td>70</td>
<td>16</td>
</tr>
<tr>
<td>Donath (14)</td>
<td>25</td>
<td>LDR</td>
<td>80</td>
<td>36</td>
</tr>
<tr>
<td>Germaine (1)</td>
<td>16</td>
<td>HDR</td>
<td>50</td>
<td>6</td>
</tr>
<tr>
<td>Germaine (14)</td>
<td>25</td>
<td>Iodine</td>
<td>93</td>
<td>20</td>
</tr>
<tr>
<td>Germaine (28)</td>
<td>68</td>
<td>LDR</td>
<td>91</td>
<td>22</td>
</tr>
<tr>
<td>Germaine (29)</td>
<td>25</td>
<td>HDR</td>
<td>84</td>
<td>24</td>
</tr>
<tr>
<td>Rosenblatt (31)</td>
<td>11</td>
<td>LDR</td>
<td>100</td>
<td>15</td>
</tr>
<tr>
<td>Schray (32)</td>
<td>63</td>
<td>LDR</td>
<td>96</td>
<td>10</td>
</tr>
<tr>
<td>Thomas (37)</td>
<td>57</td>
<td>LDR</td>
<td>89</td>
<td>28</td>
</tr>
<tr>
<td>Yoshida (38)</td>
<td>13</td>
<td>HDR</td>
<td>72</td>
<td>8</td>
</tr>
</tbody>
</table>

The local control rates for a total of 318 patients (LDR) and 103 patients (HDR) appear comparable. The comparison in terms of complications is not available, because the mean follow-up is longer for the LDR group (about 3 years) than it is for the HDR group (about 2 years).

Brachytherapy can be used as a boost performed by an intra- or peri-operative procedure to a limited volume (gross tumour), combined with external irradiation to larger (prophylactic) volumes. (5,6,32) In general, the implant delivers 15 - 20 Gy and external beam 45 - 50 Gy. A 5 - 10 cm margin around the tumour bed is used for external beam, a margin substantially wider than that used for the implant. In most the series local failure occurs in about 10%. Brachytherapy is useful if there are positive post-operative margins. (1)

In the Institut Gustave Roussy experience (17), 48 patients with sarcoma were treated initially or after local recurrence by exclusive brachytherapy (median dose: 60 Gy). The local tumour control was 80%. There was a 30% incidence of marginal failures, half of them cured, and a high incidence of necrosis (35%), occurring in previously-irradiated areas in over 60% of cases. (15,17)

When brachytherapy is performed in patients with recurrent sarcomas in a previously irradiated area, local control is about 60% but with a G2 - 3 complication rate of approximately 40%. (15,17)

These different results are results are summarised in the n° … to be compared with other brachytherapy series.

11.3.2 Side effects

Acute effects of combined surgery and radiation therapy for STS are wound dehiscence and skin breakdown (Fig 27.4, 5). (21) which depend on the interval between surgery and loading of the
plastic tubes. In the initial experience of MSKCC (19), conducted between 1982 and 1985, moderate and major wound complications for patients undergoing surgery alone were compared with those treated with surgery plus brachytherapy. Forty four percent of brachytherapy patients had wound complications, compared with 14% for surgery alone (p=.006). Implants loaded within the first five postoperative days were associated with a significantly higher incidence of wound breakdown compared with later loading. The explanation given was related to fibroblast proliferation. From 1985, loading was delayed until at least post-operative day five. (18,19) With this scheme the moderate and major wound complication rate in the brachytherapy group was 14% vs. 10% in the surgery alone patients.

Fig 27.4: Typical necrosis: groin        Fig 27.5: Typical necrosis: foot

In conclusion, brachytherapy can play a useful role in the treatment of soft tissue sarcomas of the. Local control is improved and a more conservative approach is possible. Precise knowledge of the target volume is crucial, based on CT scan or MRI. It is also necessary to perform a perioperative implant must be performed with the help of the surgeon and pathologist. As far as brachytherapy dose-rates are concerned, LDR can used alone, or in combination with EBRT; HDR is mostly performed in combination with EBRT.

Tumour size, histopathological subtype and grade determine the risk of metastases and remain crucial therapeutic issues.

12 References


