

E.O.R.T.C. News

Evaluation of Adjuvant Therapy in Soft Tissue Sarcoma. A Collaborative Multidisciplinary Approach*

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INTRODUCTION

SOFT tissue sarcomas are tumours of mesenchymal origin which may occur in virtually all the connective tissues, and account for about 1% of all malignant tumours in adults. The many histological subclassifications are shown in Table 1. About 50% of these tumours occur in the extremities, the remainder in the head, neck and trunk. Experience has shown that simple excision or enucleation of the primary tumour is followed by local recurrence in 40–80% of cases [1–6] and as two thirds of patients who develop distant metastases do so only concomitantly with or after the appearance of a local recurrence, overall prognosis is closely related to local relapse. The high local recurrence rate is due to the absence of encapsulation of the tumour which spreads along fascial planes and nerve trunks, and possibly also to a multifocal origin. Available data on the influence of the site of a tumour in an extremity on local recurrence is somewhat conflicting [1, 7, 8]. Fibrosarcoma, neurofibrosarcoma and malignant synovioma seem to have the highest local recurrence rate

but the histopathological type seems less important in this respect than the histological grade and the size of the primary lesions [9]. Radical surgery (radical resection or amputation) has been reported to reduce the frequency of local recurrence to 25–30% [4, 10] and to increase survival [11]. However, Suit and Russell have shown that the frequency of local recurrence may be reduced to approximately 15% by the combination of non-radical surgery and post-operative high dose radiation therapy [7, 9, 12]. Nevertheless, distant metastases may occur as a result of local recurrence or may be seeded before the primary tumour is removed.

The 5 and 10 yr survival rates (from the time of diagnosis) may be considerably higher for certain histological types of soft tissue sarcoma, e.g., liposarcoma and fibrosarcoma [13–15] (Table 2) indicating the importance of stratification for histological type in clinical trials. In one series the 5 and 10 yr survival rates for fibrosarcoma were 82 and 73%, respectively [16], whereas others have reported 60 and 43%, respectively [17]. The poor prognosis of leiomyosarcoma has been

Table 1. *Histologic types of soft tissue sarcomas*

1.	Fibrosarcoma
2.	Liposarcoma
3.	Leiomyosarcoma
4.	Rhabdomyosarcoma
5.	Malignant haemangioendothelioma (angiosarcoma)
6.	Malignant lymphangiopericytoma
7.	Malignant lymphangiendothelioma (lymphangiosarcoma)
8.	Malignant synovioma
9.	Malignant Schwannoma (neurofibrosarcoma)
10.	Malignant mesenchymoma
11.	Alveolar soft-parts sarcoma
12.	Malignant granular cell tumour
13.	Chondrosarcoma of soft parts
14.	Osteosarcoma of soft parts
15.	Malignant giant-cell tumour of soft parts
16.	Malignant fibroxanthoma
17.	Clear-cell sarcoma of tendons and aponeuroses

Table 2. *Survival (%) following treatment according to histological type of sarcoma (3 series)*

Histological type	5 yr [4, 16, 48]			10 yr [16, 48]	
Unclassified	43	—	39	—	30
Liposarcoma	47	77	78	64	53
Rhabdomyosarcoma	26	29	10	25	0
Malignant synovioma	40	—	—	—	—
Neurofibrosarcoma	20	—	—	—	—
Fibrosarcoma	44	82	60	73	43

stressed, the mortality being surpassed only by that of rhabdomyosarcoma [16]. Synovial sarcoma [18] and the other rarer types of sarcoma [11, 13, 16, 19] seem to have an intermediate 5 yr survival rate. Within each histological group the haematogenous spread, local recurrence and disease free survival times are determined predominantly by the histological grading. This is derived from many features, including encapsulation, vascularity and necrosis, overall cellularity, cellular pleomorphism and giant cells, but most emphasis is placed on mitotic activity. For instance a mitotic index above 12 in fibrosarcoma has been found to correlate with 100% metastases [20]. For soft tissue sarcoma of the lower extremities, distant metastases were the direct cause of death in 90% of cases.

Although soft tissue sarcomas were initially considered to be radio-resistant tumours, there are a number of reports in the literature of

good regressions [21–23]. Thus, radiation therapy may have, in certain cases, a place in the palliative management of advanced sarcomas.

In recent years, it has been shown that several drugs are effective in advanced soft tissue sarcoma [24–26]. The most potent drugs in adults are adriamycin [27], and DTIC [27–29], but cyclophosphamide [30, 31] probably has some activity (Table 3). Vincristine, which is active in childhood sarcomas, seems to have no activity as a single agent in adult sarcomas [32, 33]. However the efficacy of the combination of adriamycin and DTIC seems to be increased by the addition of vincristine [27, 28]. Both experimental data [34] and clinical studies have shown that adriamycin and DTIC have an additive effect when given together [27, 35]. For this reason these two drugs have been chosen for simultaneous use and are alternated with vincris-

Table 3. Single drug treatment in advanced adult soft tissue sarcoma

Drug	No. of cases	Response rate	References
Vincristine	10	0	33, 34
Cyclophosphamide	14	14	31, 32
Adriamycin	357	27	28, 29
DTIC	61	16	29

tine plus cyclophosphamide in the S2 arm of our protocol for advanced soft tissue sarcoma [36]. The reported overall response rate for combination chemotherapy with adriamycin, DTIC, cyclophosphamide and vincristine is between 50 and 55% with approximately 15% complete remissions [27]. Our own experience with this combination in the S1 arm of our study for advanced sarcomas is different. The 4-drug combination is showing a response rate of 30–35%.

There are several reports documenting the value of adjuvant chemotherapy and immunotherapy in the treatment of malignancies. The use of post-operative adjuvant chemotherapy has improved survival of children with rhabdomyosarcoma [37–40], osteogenic sarcoma [41] and Ewing's sarcoma [17, 42]. There have been few studies of the use of adjuvant therapy in adult soft tissue sarcoma but some preliminary data indicate that the combination of surgery with adjuvant chemotherapy may be beneficial [43]. These authors used a regimen comprising adriamycin and high dose methotrexate with leucovorin rescue. Of the 16 patients given post-operative adjuvant therapy, 11 (68%) had remained disease-free at the time of analysis (mean follow up 9.3 months) whereas only 5 of 22 patients (23%) in the control group without chemotherapy had remained free of metastases. However, this series includes both skeletal and soft tissue sarcomas and no indication is given of the number of cases in each histological group.

Sordillo [44] has used an adjuvant regimen comprising vincristine, high dose methotrexate, adriamycin, DTIC, actinomycin D and chlorambucil (ALOMAD) in 73 patients following surgery for soft tissue sarcoma. Twenty-four of 27 having adequate surgery for a primary or locally recurrent tumour remained disease-free 3–34 months (median 15 months) from surgery. These are very preliminary results and there were no controls. A randomised study conducted by

Rosenberg [45] compares amputation with limb sparing surgery and post-operative radiotherapy in adult soft tissue sarcoma. However, both groups received adjuvant chemotherapy with adriamycin, cyclophosphamide and high dose methotrexate with or without immunotherapy. The value of chemotherapy was assessed by comparison with historical control group of 66 patients treated at the NCI by radical surgery alone. There had been two local recurrences and three patients had developed distant metastases of 49 evaluable patients followed for 5–30 months (median 16 months). Actuarial analysis showed improved disease-free interval and survival for the patients receiving adjuvant chemotherapy compared with historical controls.

This paucity of information has prompted the E.O.R.T.C. and WHO to initiate a trial of adjuvant chemotherapy in adult soft tissue sarcoma. In view of the observations made in advanced sarcoma, preference has been given to the combination of adriamycin, DTIC, vincristine and cyclophosphamide as the adjuvant chemotherapy in the present protocol. In the treated group these drugs are given for eight monthly cycles following surgery, while the control group receives no chemotherapy.

Surgery, radiotherapy and pathology subcommittees have outlined guidelines for treatment of each modality. If the guidelines are not followed cases will be excluded from the trial.

OBJECTIVES OF THE TRIAL

The objective of this E.O.R.T.C. trial is to study the role of chemotherapy as an adjunct to surgery in the management of soft tissue sarcoma of the extremities and of the head and neck region. The disease-free interval and survival of patients receiving eight cycles of chemotherapy will be compared with a control group receiving no chemotherapy.

Selection of patients

1. *Conditions for patients' eligibility.* (a) All patients must have histological proven soft tissue sarcoma (Table 1). (b) The aim of surgery should have been total removal of the primary tumour. Tumours in the axillae, groins, scapular regions and buttocks will be considered as pertaining to the trunk. (c) There should be no metastases, neither distant nor in regional lymph nodes. Macroscopic residual disease excludes the patient from the trial, but the patient is still eligible if microscopic disease is demonstrated after presumed total excision. (d) The patients must have adequate bone marrow reserve (for details see protocol). (e) Chemotherapy should commence within 13 weeks following primary surgery, i.e., the first definite operation. A second operation may be required if, in the surgeon's opinion, the primary excision has not been adequate, but should be performed in the 13 week period following primary surgery, as should any post-operative chemotherapy. (f) Patients with locally recurrent disease, without distant metastases, are eligible for the trial. Removal of local residual tumour which should be followed by a course of radiotherapy must have been carried out less than 13 weeks prior to the start of chemotherapy.

2. *Conditions for patient exclusion.* (a) Patients who have had any pre-operative radiotherapy and/or chemotherapy. (b) Patients with macroscopic residual disease. (c) Patients under the age of 15 and above the age of 70. (d) Patients with serious post-operative complications who are not fit to start chemotherapy within 13 weeks of operation. For further details see protocol.

GUIDELINES FROM THE SURGICAL SUBCOMMITTEE

In order to unify the group of patients entering this trial, the surgical treatment should be standardised as much as possible. The following points should serve as guidelines for surgical treatment when amputation is not indicated.

Biopsy

1. If it seems likely on clinical assessment that a space occupying lesion is a soft tissue sarcoma, no attempt should be made to remove it immediately unless adequate excision with a margin of 2 cm of macroscopically healthy tissue can be performed. In all other

cases, the biopsy should be sited with the definitive procedure in mind so that the biopsy wound area need never subsequently be entered and can be excised in continuity with the specimen. Directions concerning the tissue to be removed will be found in the pathology section.

2. In view of the danger of local spread of the tumour, infiltration anaesthesia should never be used. Contamination of the pleural or peritoneal spaces should always be avoided. Trephine biopsy may only be used when open biopsy is not feasible. As a rule, however, the pathologists will require a generous biopsy including part of the tissue surrounding the tumour. When using a trephine (drill, biopsy needle, etc.) care should be taken never to pass through the tumour into normal tissue as impaction and local recurrence can easily occur.

3. When arteriography under general anaesthesia is indicated to ascertain whether there is involvement of major arteries or other important structures, it may be rewarding to perform the biopsy at the end of this procedure. When the tumour is localised in one of the extremities, the catheter should not be introduced from any site in the same limb. On rare occasions a frozen section may provide sufficient information to perform the definite excision immediately.

Definite procedure

1. The incision should always extend several cm beyond the palpable margins of the tumour. If the tumour is located in or adjacent to a muscle this muscle should be completely removed.

2. Vital structures that need to be preserved should be identified 2-5 cm from the border of the tumour. They can be followed towards the tumour area to ascertain whether an excision may be performed or amputation is unavoidable.

3. If it appears feasible to dissect vital structures away from the tumour without leaving macroscopic tumour behind, dissection may be carried out provided radio-opaque markers are left along the borders of the area where the dissection came nearer to the tumour than the desired 2 cm. If, however, macroscopic tumour tissue has to be left behind, the patient should not be entered into the trial.

4. When the tumour lies near to a bone, the periosteum with a layer of underlying cortex should be removed in the danger area.

Care of wound area

After removing the specimen the wound may be washed with some cytotoxic fluid to reduce the chance of implantation of tumour cells mobilised during the excision. Washing with a liberal amount of Dakin's fluid for 5 min is suggested. Effective drainage with a suction device is desirable, especially when post-operative radiotherapy is indicated. The drain site should be placed in such a way that it will be covered by the radiotherapy portals. Pressure bandages should be avoided wherever possible as these may interfere with wound healing. The period between excision and irradiation must be as short as possible and wound complications tend to delay radiotherapy.

GUIDELINES FROM THE RADIOTHERAPY SUBCOMMITTEE

Indications for radiotherapy

Radiotherapy has been shown to be helpful in preventing local recurrence when microscopic residual disease is present after surgery. To do this, high doses of radiation are required and the late effects, particularly fibrosis, may be severe.

When adequate surgery has been performed and there is no residual disease, macroscopic or microscopic, radiotherapy is not indicated. Radiotherapy is indicated in the following situations:

1. when there is microscopic residual disease after surgery;
2. when there is less than a one cm margin of normal tissue around the tumour specimen;
3. when a second operation has been performed, either for a local recurrence or an inadequate first operation. If the second operation has been an amputation, X-ray treatment should not be given and if X-ray treatment followed the primary operation, radiotherapy should not be repeated. Some radiotherapists will feel that all post-operative cases should receive radiotherapy. It has been decided, however, that if the above guidelines are not followed, cases will be excluded from the trial.

Radiation dosage

Soft tissue sarcomas vary widely in size, site and their proximity to critical organs and radiotherapy techniques and dosages will vary depending upon these various factors.

Where the dose need not be modified by the proximity of a critical tissue, the minimum dosage should be 5000 rad in 4 weeks (5 fractions/week), or the biological equivalent of this dose as calculated from the TDF tables of Orton [46]. The decision as to the areas to be included in the radiotherapy fields is made easier by the placement of radio-opaque clips on the margin of the tumour bed at surgery.

GUIDELINES FROM THE PATHOLOGY SUBCOMMITTEE

1. The pathologist must be provided with sufficient material for diagnosis. If primary treatment takes place outside the participating centre, a representative section of untreated tumour tissue should be available.
2. The sections will be studied by at least two pathologists of the panel. If there is disagreement, the sections will be sent to other members of the panel. In order to achieve a consensus of opinion, meetings of the members of the panel will be held at regular intervals. The Pathological Institute of the State University of Utrecht acts as co-ordinating centre for the pathology of this trial. All members of the pathology panel will be informed about the cases received by the co-ordinating centre.
3. Each member is entitled to study all cases entered into the trial, if he so wishes. The sections or tissue fragments should be sent to the co-ordinating centre accompanied by relevant information which should be entered on to a special pathology form distributed by the pathology subcommittee.
4. As a basis for diagnosis the WHO classification (Table 1) is used. The members of the panel will try to formulate a grading system.
5. Cases of fibromatosis and so-called well differentiated liposarcomas are excluded.
6. The surgical specimen should be accompanied by a diagram and clearly marked to enable the pathologist to orientate the tissue in the body. Points of special interest should be marked separately.
7. In the pathology report from the local pathologist the relationship between the tumour tissue and the dissection plane should be clearly stated, preferably illustrated by a diagram or photograph.
8. It would be helpful to receive a copy of the angiogram.
9. If biopsies are performed when the patient

goes off study or an autopsy is performed, the subcommittee would be keen to study this material as well.

DESIGN OF THE TRIAL

1. Randomisation of the patients will take place within 13 weeks following definite surgery for the primary tumour or local recurrence.
2. Eligible patients will be randomised either to the chemotherapy group receiving the S1 schedule (see below) for eight cycles, or to the control group receiving no chemotherapy.
3. Stratification at the time of randomisation will be according to:
 - (a) the site of the primary tumour:
 - (i) trunk [including tumours in the groins, buttocks, axillae and scapular regions but excluding intrathoracic and intra-abdominal tumours (see e.)] and head and neck;
 - (ii) limbs.
 - (b) radiotherapy or no radiotherapy. In addition retrospective stratification at the time of statistical analysis will recognise the following groups:
 - (c) patients for whom the interval between primary operation and initiation of chemotherapy is:
 - (i) less than 8 weeks;
 - (ii) 8–13 weeks.
 - (d) patients who have further removal of a local recurrence occurring more than 13 weeks after the primary operation. The operation for local recurrence should have been performed less than 13 weeks prior to initiation of chemotherapy.
 - (e) patients with intrathoracic or intra-abdominal tumours (including visceral organs and retroperitoneal tumours).
 - (f) patients with uterine sarcomas.

THERAPEUTIC REGIMEN

Treatment group 1: S1 (8 cycles).

Treatment group 2: Control (no further treatment).

S1: adriamycin 50 mg/m², day 1, i.v., cyclophosphamide 500 mg/m², day 1, i.v., vincristine 1.5 mg/m² (top dose 2 mg), day 1, i.v., DTIC 400 mg/m², days 1–3 i.v.

This scheme is repeated on days 29, 57 etc. There will be no dose adjustments for age.

1. *Initiation of chemotherapy*

Chemotherapy should be started as soon as possible, although one may have to wait until radiotherapy (if indicated) has been terminated. However, chemotherapy should not be postponed for more than 13 weeks after surgery.

2. *Duration of chemotherapy*

In treatment group 1, the S1 treatment will be given for 8 cycles and then all treatment will be discontinued.

3. *Treatment after going off study*

Patients developing local recurrence or metastases will go off study. Patients relapsing in treatment group 1 can be entered into a Phase II study. Patients going off treatment in Group 2 should receive the S1 regimen so that survival of patients in the two arms can be compared.

Details of dose modifications for drugs, pre- and post-treatment investigations, registration and randomisation of patients, together with statistical considerations are given in the protocol and follow general E.O.R.T.C. policy.

CONCLUSIONS

Soft tissue sarcomas are a rare group of tumours with widely ranging natural histories. Adequate surgery is often mutilating and may still be followed by widespread dissemination. Adjuvant chemotherapy has the aims of destroying any seeding metastases or microscopic residual tumour when the tumour burden is at its lowest, but has its own hazard and toxicity. It is important to determine whether chemotherapy is preventing or merely delaying the appearance of metastases as has been suggested for osteosarcoma [47] and whether survival could be similar if chemotherapy is given at the time of overt relapse. These questions can only be answered by a large randomised trial, with a concurrent control group of patients, examining the value of chemotherapy following adequate surgery. The current E.O.R.T.C./WHO trial was set up with these questions in mind and approximately 200 eligible patients will be required to provide a reliable answer.

ADMINISTRATIVE RESPONSIBILITIES

This study is a joint study of institutions working in the E.O.R.T.C. Soft Tissue and Bone Sarcoma Co-operative Group and institutions working in the WHO Melanoma Group:

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Statistical Service

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