OVERVIEW ARTICLE

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A Systematic Overview of Radiation Therapy Effects in Soft Tissue Sarcomas

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A systematic review of radiation therapy trials in several tumour types was performed by The Swedish Council of Technology Assessment in Health Care (SBU). The procedures for evaluation of the scientific literature are described separately (Acta Oncol 2003; 42: 357–365). This synthesis of the literature on radiation therapy for soft tissue sarcomas (STS) is based on data from five randomized trials. Moreover, data from 6 prospective studies, 25 retrospective studies and 3 other articles were used. In total, 39 scientific articles are included, involving 4 579 patients. The results were compared with those of a similar overview from 1996 which included 3 344 patients. The conclusions reached can be summarized as follows:

- The well-established prognostic factors for tumour-related death from STS—histological grade, tumour size and age—are well documented.
- The importance of superficial versus deep site as well as the anatomic site is also reaffirmed to some extent.
- There is strong evidence that adjuvant radiotherapy improves the local control rate in combination with conservative surgery in the treatment of STS of extremities and trunk in patients with negative, marginal or minimal microscopic positive surgical margins. A local control rate of 90% has been achieved.
- Improvement is obtained with radiotherapy added in the case of intralesional surgery, but the local control rate is somewhat lower. More studies are needed on this issue.
- For STS in other anatomic sites, retroperitoneum, head and neck, breast and uterus, there is only weak indication of a benefit for the local control rate, with the use of adjuvant radiotherapy.
- There is still insufficient data to establish that preoperative radiotherapy is favourable compared to postoperative radiotherapy for local control in patients presenting primarily with large tumours. One small study has shown a possible survival benefit for preoperative radiotherapy.
- There is fairly good evidence to suggest that the preoperative setting results in more wound complications.
- There is no randomized study comparing external beam radiotherapy and brachytherapy. The data suggest that external beam radiotherapy and low dose rate brachytherapy result in comparable local control for high-grade tumours.
- Some patients with low-grade soft tissue sarcomas benefit from external beam radiotherapy in terms of local control.
- Brachytherapy with low dose rate for low-grade tumours seems to be of no benefit, but data are sparse.
- The available data are inconclusive concerning the effect of intraoperative high dose rate radiotherapy for retroperitoneal STS. Further studies are needed.
- Neutron radiotherapy might be beneficial for patients with low- and intermediate-grade tumours considered inoperable and for those operated with intralesional margins. More severe side effects for neutrons have been registered.
- In two small studies investigating hyperfractionation schedules there was no indication of improvements compared to daily fractions of 2 Gy. Further studies should be encouraged.
- One small study using preoperative limb perfusion with TNFα melphalan and ±interferon γ combined with postoperative radiotherapy in the case of marginal or positive surgical margin has shown excellent local control without enhanced morbidity.

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In Sweden there are approximately 300 cases of soft tissue sarcomas (STS) reported per year. STS thus constitute less than 1% of all newly diagnosed malignant diseases. Approximately 50% of the patients with STS will die of their disease. STS represent a heterogeneous group of tumours with wide variations in presentation, histologic appearance and prognosis. Soft tissue sarcomas are labelled and grouped by their cell of origin, although in some types the origin is unknown. Histologic grade, tumour size, and depth (superficial or deep) are well-established prognostic markers for local control and disease-free survival. Besides these parameters, nodal status and distant metastases make

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Table 1

Staging system

Grade (G)					
GX	Grade cannot be assessed				
G1	Well differentiated				
G2	Moderately differentiated				
G3	Poorly differentiated				
G4	Undifferentiated				
Primary tumour (T)					
TX	Primary tumour cannot be assessed				
T0	No evidence of tumour				
T1	Tumour size ≤ 5 cm				
T2	Tumour size > 5 cm				
Regional lymph nodes (N)					
NX	Regional nodes cannot be assessed				
N0	No regional lymph node metastasis				
N1	Regional lymph node metastasis				
Distant metastasis (M)					
MX	Presence of distant metastasis cannot be assessed				
M0	No distant metastasis				
M1	Distant metastasis				
Stage grouping					
Stage I	T1a, 1b, 2a, 2b	N0	M0	G 1–2	G1 Low
Stage II	T1a, 1b, 2a	N0	M0	G 3–4	G 2–3 High
Stage III	T2b	N0	M0	G 3–4	G 2–3 High
Stage IV	Any T	N1	M0	Any G	Any G High or Low
	Any T	N0	M1	Any G	Any G High or Low

Superficial tumour is located exclusively above the superficial fascia without invasion of the fascia; deep tumour is located either exclusively beneath the superficial fascia, or superficial to the fascia with invasion of or through the fascia, or superficial and beneath the fascia. Retroperitoneal, mediastinal and pelvic sarcomas are classified as deep tumour.

up the staging criteria for the current classification of AJCC (6th ed. 2002) and UICC (5th ed. 1997) (see Table 1).

The histologic grade of STS is the most important factor in predicting the probability of metastases and overall survival. Several grading systems are in use to describe the biological activity of STS. Among the factors considered for grading are cellularity, cellular pleomorphism, mitotic frequency and necrosis. The last two parameters are outlined as the most important. More recent studies indicate that also ploidy and proliferation markers can add prognostic information.

STS are distributed throughout the body. About 60% of these tumours are located in the extremities and of these two-thirds occur in the lower limbs. Other common sites are the head and neck region, the trunk and the retroperitoneum. After a complete history and physical examination, CT and MR imaging is used to define the size of the tumour, whether it is deep or superficial to the fascia, and its proximity to surrounding tissues such as neurovascular and bony structures. In order to obtain appropriate management of STS, both concerning diagnostic procedures and surgery including adjuvant treatments, referral of patients to a multidisciplinary sarcoma centre is highly recommended by the Scandinavian Sarcoma Group (SSG) in the following situations:

1) subcutaneous tumours larger than 5 cm
2) deeply localized tumours irrespective of size
3) tumours suspected of malignancy in other ways.

In Sweden, the majority of patients with STS are treated primarily at a multidisciplinary sarcoma centre. This is not the case in many countries. Therefore, treatment strategies in Sweden deviate to some extent, particularly in the use of adjuvant radiotherapy. Conservative surgery aiming at wide excision and good functional outcome is the current standard treatment. In situations where various factors compromise this objective, adjuvant radiotherapy is considered. Preoperative or postoperative external beam radiotherapy (EBRT) as well as brachytherapy (BRT) can be chosen depending on the clinical situation. Even a combination of pre- and postoperative EBRT or a combination of BRT and EBRT is justified in certain situations. Today, comparable local control rates and acceptable complication rates are achieved independently of the method and timing of the radiotherapy, on the assumption that the appropriate dosage and technique are applied for the method used.

SUMMARY OF THE EARLIER REPORT

The synthesis of the literature on radiotherapy in the earlier report of SBU 129/2 was based on 71 scientific articles, including only 4 randomized studies, 5 prospective studies and 26 retrospective studies. Altogether these studies included 3 344 patients. Soft tissue sarcomas of the ex-

tremities can be treated with limb-sparing surgery in more than 90% of cases. For subcutaneous and intramuscular tumours, surgery alone will result in a high local control rate with good functional outcome. In the case of local recurrence, surgery and radiotherapy are the preferred treatment in order to avoid amputation.

- Soft tissue sarcomas in the head and neck region and in the retroperitoneum are difficult to remove with adequate margins. Therefore, surgery is often combined with radiotherapy in order to improve the local control rate.
- Preoperative and postoperative radiotherapy give equal antitumour results. However, the preoperative approach reduces the possibility to establish an exact diagnosis and to explore morphological and tumour biological parameters.
- To improve local control for large tumours new fractionation schedules, in particular hyperfractionation, need to be implemented.
- The combination of local intra-arterial chemotherapy and radiotherapy for STS increases the complication rate without any significant improvement in outcome compared to postoperative radiotherapy alone, and is not recommended for clinical routine.
- Intraoperative radiotherapy should be investigated further.

Literature

The articles on which the conclusions in the SBU 129/2 report were based were classified and graded as follows: (number of studies/number of patients)

	1 = High	2 = Moderate	3 = Low	Total
M	–	–	–	–
C	1/117	3/107	–	4/224
P	3/83	2/74	–	5/157
R	25/2 948	1/25	–	26/2 973
L	24	–	–	24
O	12	–	–	12
Total	65/3 148	6/206	–	71/3 344

M = meta-analysis; C = controlled clinical trial; P = prospective trial; R = retrospective study; L = literature review; O = other studies.

ASSESSMENT OF NEW LITERATURE

Search methods and selections

Computerized literature searches were performed in Medline for 1994 to October 2001. A few other articles from this period known for the authors were also included. Recently published and relevant papers were updated in October 2002. Primarily, 110 papers concerning soft tissue sarcoma have been reviewed. Of these, the referees have selected 39 papers presenting 36 patient study groups as the basis for the statements in the present report. The reasons for exclusion of 71 publications were:

Group		
A	4	Reviews
B	5	Short comments
C	5	Basic science investigations
D	22	Paediatric tumours
E	28	Small heterogeneous patient material, short follow-up, and unclear analysis and statistics
F	5	General topics not relevant to the aim of this study
G	2	Specific subgroups (desmoid, dermatofibrosarcoma protuberans)

Prognostic and predictive factors

In the present literature review the majority of the papers represent retrospective studies (27/39) of heterogeneous patient groups and are mostly of limited size. There are few randomized studies. Different inclusion criteria make comparisons difficult. Various techniques are employed for treatment and in most of the studies radiotherapy is only a part of the full treatment. Moreover, the patient study groups are collected over long time periods, usually 10 to 20 years, and have been recruited since 1947 at the earliest. This is a reflection of the characteristics of soft tissue sarcoma. One of the merits of a great proportion of the studies is, however, that independent prognostic and predictive factors have been derived by multivariate analyses.

Histological grade. The malignancy of STS described by grading has been established as important for the outcome. This fact has been confirmed for local control in many of the studies (1–4) and for distant metastasis-free, disease-free and/or overall survival, in a total of 12 studies (1–12). The influence of grade is best documented for extremity STS, but is also seen in studies of STS in other anatomic sites such as the retroperitoneum, head and neck, and breast.

Tumour size. The relationship between tumour size and clinical outcome has long been known. Primary STS have been stratified by size into tumours $\leq$ or >5 cm in the current staging systems. The importance of tumour size, usually with 5 cm as a cut-off, has been verified for either distant metastasis-free, disease-free and/or overall survival in a great number of papers (2–4, 6, 8, 9, 11, 13–15). Tumour size as a prognostic factor for local control is seen for head and neck STS (10).

Tumour site. Tumours that are deep or invade the muscular fascia are described as deep in contrast to superficial, which is a condition considered in the staging systems. The poorer prognosis of extremity STS with deep location compared to superficial has been documented (1).

Anatomic site is a prognostic factor, although not part of the current classification. Patients with extremity STS have a significantly better prognosis for disease-free survival in comparison to patients with STS at the trunk (3) and in the retroperitoneum (7). Extremity-located STS show a higher local control rate than tumours located at other sites. Among extremity tumours, the lower limb is associated with a poorer survival prognosis than the upper limb (2). It has also been stated that distal location on the extremity means a poorer outcome in local control than proximal location (15).

Nodal disease. Lymph nodes are unusual sites of disease for most STS. Nodal disease defines Stage IV disease in the current staging systems. Overall, about 5% of STS will manifest nodal spread. Lymph node metastases portend a poor prognosis. The outcome of positive lymph nodes is only reported in one paper (16).

Histology. The histological subtypes usually identified in extremity STS are liposarcomas, malignant fibrous histiocytoma (MFH), and leiomyosarcomas. In the retroperitoneum, the most common subtypes are leiomyosarcomas and liposarcomas. Age may have an impact on the development of certain histologic subtypes. In young adults, synovial sarcoma is the most common subtype. In older age groups, the most common subtypes are liposarcomas and MFH.

Histology has an impact on outcome. Generally, liposarcomas have higher local control rate than MFH, and synovial sarcomas are somewhere in between (6, 11, 13, 17). The patient populations analysed are small, however, and liposarcoma, for example, is a highly heterogeneous disease, and it has to be emphasized that the outcome is greatly determined by its histologic subtype (14). Data on the effect of radiation on the recently defined gastrointestinal stroma cell tumours have not yet been reported.

Age. Among the papers reviewed, age has been found to be a strong prognostic factor for disease-free and overall survival in STS. Older age, above 50 to 55 years, is associated with a poorer outcome (1, 2, 7, 10, 15).

Surgical margin. Microscopic resection margin has proven prognostic significance for local control and disease-free survival. Positive microscopic margins are in many studies strongly associated with increased risk for local recurrence independent of anatomic site (2, 5, 6, 10, 16–19). In addition, an increased tumour-related death rate is observed after incomplete resections (10, 20). Another aspect of treatment outcome is that local relapse at referral to a sarcoma centre is associated with a poorer local control rate (3, 6, 14).

'Adjuvant' radiotherapy (surgery with negative or marginal margins)

See Overview 1, for a description of the trials, trial results and conclusions.

Radiation therapy plays a major role in the management of STS, mainly in combination with conservative and function-sparing surgery. A recent National Cancer Institute randomized prospective trial has concluded that EBRT improves local control for extremity STS of both low and high grade (21). This study included only patients with negative or minimal microscopic positive resection margins. No increases in persistent negative effects on functional outcome were documented, either in activities of daily life or global quality of life, with adjuvant radiotherapy. There was no advantage of radiotherapy concerning metastatic disease-free survival or overall survival.

In a second randomized study it is shown that adjuvant BRT improves local control for extremity and superficial trunk STS, but only for high-grade tumours (8, 22). Few patients with low-grade tumours were randomized, though. Patients with negative or marginal surgical margins were included in the study. Wound reoperation had to be done more frequently after BRT. Yet, it was concluded that the overall morbidity associated with adjuvant BRT was not significantly higher than that with surgery alone (23). Adjuvant BRT had no impact on disease-free survival.

Several other retrospective studies underscore a benefit of adjuvant radiotherapy for local control for extremity and trunk STS, especially for marginal and positive surgical margins (1, 2, 15, 16). However, selected patients with extremity STS, operated on with wide margins and who have an expected low risk of local recurrence may not require adjuvant radiotherapy after limb-sparing surgery (24, 25).

When using adjuvant radiotherapy a special problem has been recognized for patients where the surgery includes a periosteal stripping. This procedure causes a highly significantly increased risk of bone fractures, predominantly in females, and was enhanced by chemotherapy (26).

For STS in other anatomic sites, e.g. the retroperitoneum, head and neck, breast and uterus, no clear-cut improvement in local control has been demonstrated with adjuvant radiotherapy (10, 18, 19, 27–30). However, in several studies a trend towards an increased local control rate has been observed when radiotherapy is added (10, 19, 29, 30). As for STS of the extremities, prediction of cure of these STS entities is related to tumour grade and the degree of resection.

Many other studies that include miscellaneous anatomic sites are reported and emphasize various aspects of the sarcoma treatment, but do not add any clear evidence relating to the benefits of adjuvant radiotherapy (3, 5, 9, 11, 13, 14, 26).

The literature shows that:

– Adjuvant radiotherapy in addition to function-sparing surgery improves local control for soft tissue sarcomas in the extremities and trunk. There is no advantage of radiotherapy concerning disease-free survival.

Overview 1

Soft tissue sarcoma. 'Adjuvant' radiotherapy (surgery with negative or marginal margins)

Author Year (Ref. no.) Design	Aim/study question	Patient population	Results	Conclusion/comments
Yang 1998 (21) C	Value of postoperative RT A: Surgery alone B: Surgery + RT 45 Gy + 18 Gy Surgery: all pts had negative or minimal microscopic positive margins	1983–1991 Site: extremity Low grade / High grade A: 24 pts / 44 pts B: 26 pts / 47 pts Postoperative CHT concomitantly with RT was given to high grade pts	Median follow-up 10 y Act. LC% OS% at 10 y High grade A 78 74 B 100 75 p = 0.003 ns Low grade A 65* NR B 95 NR p = 0.016 ns No sign. difference in global QoL.	RT is highly effective in preventing local recurrence. Stratification for grade, site and margin. The study is too small to show any impact on survival. C2 *The figures are estimated from Kaplan–Meyer curves.
Pisters 1996 (8) C Pisters 1994 (22) C Alektiar 2000 (23) C	Value of postoperative BRT A: Surgery B: Surgery + BRT 42–45 Gy Surgery: all pts had negative or marginal margins	1982–1992 Site: extremity, trunk Low grade / High grade A: 23 pts / 56 pts B: 22 pts / 63 pts CHT was given postop. to 68 pts with tumour ≥ 5 cm	Median follow-up 76 m Act. LC% at 5 y Low grade / High grade / All pts A 78 / 66 / 69 B 73 / 89 / 82 ns / p = 0.0025 / p = 0.04 No difference in DFS (all pts). Prognostic factors for distant metastases: tumour size ≥ 5 cm, high grade. (multivariate analysis) Wound compl. % Wound reop.% A 14 0 B 24 10 ns p = 0.006	Adjuvant BRT after complete resection improves LC in high-grade STS; no impact on DFS. Adjuvant BRT of no benefit in low-grade STS. No increase in wound complic. if BRT was started after the first 5 postop. days. Width of excised skin > 4 cm prognostic factor for wound complication. Overall morbidity not sign. higher in gr B. Stratification for grade, size, site, deep or superficial, primary or recurrent sarcoma. The study is too small to show any impact on survival. C2
Peiper 1995 (16) R	Value of postoperative EBRT A: Surgery B: Surgery + RT 50–85 Gy	1972–1993 Site: extremity, trunk Low and high grade A: 91 pts B: 49 pts	Act. LC% A 72 B 94 Prognostic factors for LC: surgical margin, RT* and N+. *Only in univariate analysis	Postoperative RT is indicated if marginal or positive surgical margins. Prognostic factors, evaluated in multivariate analysis. R3
Alektiar 2000 (15) R	Value of postoperative RT (positive surgical margins) A: Surgery B: Surgery + EBRT and/or BRT EBRT 60–70 Gy BRT 45 Gy BRT + EBRT: 15–20 Gy + 45–50 Gy	1982–1997 Site: extremity High grade 110 pts A 19 pts B EBRT 33 pts BRT 34 pts EBRT+BRT 24 pts	Median follow-up 41 m Act. LC% DFS% OS% at 5 y A 56 44 52 B 74 45 53 p = 0.01 ns ns Prognostic factors (multivariate analysis): Proximal location, RT for LC, tumour size > 5 cm for DFS, tumour size > 5 cm, age for OS	Adjuvant radiotherapy improves local control rate for extremity STS with positive margins, but there is a need for further improvement. Few pts in group A. LC is independent of radiotherapy method. Chemotherapy to 27 pts, no benefit. R2
Vraa 1998 (2) R	Identification of prognostic factors A: Surgery B: Surgery + RT 50 Gy	1979–1993 Site: extremity, trunk Low and high grade A 266 ps B preop 16 pts postop 34 pts	Median follow-up 71 m Prognostic factors Act. LC / OS Grade / Grade Surgical margin / Tumour size (> 5 cm) Radiotherapy / Age Type of surgery / Location Compartment / Compartment No sign. difference in LC% (80 vs. 88) or OS% (73 vs. 80) between gr A vs. gr B.	Consecutive pts, children included, 35 pts ≤ 20 years of age. RT if marginal resection. Prognostic model is developed for survival. Chemotherapy to 13 pts, not evaluated. R2

Overview 1 (*Continued*)

Author Year (Ref. no.) Design	Aim/study question	Patient population	Results	Conclusion/comments
Keus 1994 (1) R	Retrospective analysis of treatment results A: Surgery B: Surgery (marginal)+RT 40 Gy+20 Gy C: Surgery (intralesional)+RT 40 Gy+20 Gy	1977–1983 Site: extremity Low and high grade A 26 pts B 64 pts C 53 pts	Median follow-up 114 m Act. LC% OS% at 5 y A 81 65 B 92 73 C 74 60 All pts 83 69 Prognostic factors (multivariate analysis): LC: Grade, Treat. group OS: Grade, Deep location, Age	Limb preservation in 90% of pts with good functional result. Severe fibrosis in 16%, fractures in 6%. Chemotherapy to 9 pts, not evaluated. R2
Catton 1994 (18) R	Value of postoperative RT A: Complete excision+RT B: Incomplete excision+RT RT: ≥ 35 Gy 21 pts < 35 Gy 15 pts No RT 9 pts	1975–1988 Site: retroperitoneum Low and high grade A: 45 pts B: 57 pts	Median follow-up 6.3 y Act. LC% DMF% OS% at 5 y All pts 28 76 36 A 50 88 55 B 14 60 15 p < 0.0002 p = 0.02 p < 0.0001	RT of no advantage if complete excision. RT > 35 Gy resulted in prolonged median time to local relapse in pts with positive surgical margin, p = 0.06 and reduced in field relapse rate, p = 0.02. Univariate analysis. Adjuvant chemotherapy to 16 pts, no benefit. R3
van Doorn 1994 (19) R	Value of postoperative RT A: Complete excision+RT B: Incomplete excision+RT RT: 40–62 Gy	1973–1990 Site: retroperitoneum Low and high grade A: 30 pts (22 with positiv margins) B: 4 pts 19 pts did not receive RT	Median follow-up 38 m Act. LC% OS% at 5 y A 63 35 B – – RT a sign. factor for LC, p < 0.01	Complete excision and postop. RT improves outcome. R3
Le 1997 (10) R	Retrospective analysis of treatment results A: Surgery B: Surgery+RT C: RT alone (non-resectable tumour) RT-dose variable, median 54 Gy	1961–1993 Site: head and neck Low and high grade 65 pts A: 14 pts B: 40 pts C: 11 pts	Median follow-up 64 m Act. LC% at 5 y All pts 66 T1 92 A 59 T2 40 p = 0.004 B 77 g 1–2 80 C 0 g 3 48 p = 0.01 OS and DFS at 5 y for all pts were 56% and 60%, respectively. Prognostic factors (multivariate analysis): tumour size > 5 cm and grade for LC, age, grade, surg. margin, extent of resection for DFS	A trend towards improved LC with surgery+RT for high-risk pts. Gross disease needs > 65 Gy if RT alone is given. Chemotherapy to 14 pts, no benefit. R2
Barrow 1999 (27) R	Role of postoperative RT A: Surgery B: Surgery+RT RT variable	1947–1990 Site: breast Low and high grade A: 42 pts B: 17 pts	Median follow-up 40 m Act. LC% All pts; LC% Post. mastectomy; LC% Post. segm. resection A 62 66 86 B 71 ns 87 ns 100 ns All pts 64 36 64 LC 40% with positive margins and no RT. Prognostic factors (multivariate analysis): tumour size, surgical margin	No significant benefit of RT, probably because of limited patient numbers. Axillary dissection should be avoided. Cystosarcoma phylloides excluded. Chemotherapy to 13 pts, no benefit. R3
Mc Gowan 2000 (28) R	Value of postoperative RT A: Surgery B: Surgery+RT 36–60 Gy	1958–1990 Site: breast Low and high grade A: 52 pts B: 26 pts	Act. LC% DFS% All pts 75 57 Gr 1–2 – 84 Gr 3–4 – 55 p < 0.0001 pos margin 33 neg margin 80 RT dose > 48 Gy sign. prognostic factor for DFS, p = 0.03 (univariate analysis)	RT to 50 Gy+boost ≥ 10 Gy to the tumour bed is recommended in case of negative surgical margin after conservative surgery. Axillary lymph node dissection is not indicated. Cystosarcoma phylloides in 32 pts included. Univariate analysis. R3

Overview 1 (*Continued*)

Author Year (Ref. no.) Design	Aim/study question	Patient population	Results	Conclusion/comments
Ferrer 1999 (29) R	Value of postoperative RT A: Surgery B: Surgery+EBRT± BRT EBRT: 45–50 Gy BRT: 15–20 Gy	1979–1995 Tumour site: uterus Low and high grade A: 49 pts B: 54 pts	Median follow-up 49 m Act. LC% DFS% OS% at 5y A 36 33 37 B 76 53 73 All pts 57.4 48.7 56 $p < 0.0001$ $p < 0.0001$ $p < 0.0001$ Prognostic factors (multivariate analysis): EBRT and stage for LC, OS and DFS	Postop. EBRT radiotherapy has impact on LC, OS and DFS. Chemotherapy to 33 pts, no benefit. R2
Hoffmann 1996 (30) R	Role of postoperative RT A: Surgery B: Surgery+RT 45–60 Gy	1958–1994 uterine sarcoma Low and high grade A: 22 pts B: 32 pts	Act. OS% at 5y A 34 B 75 $p = 0.0002$ Prognostic factors for OS (multivariate analysis): stage and histologic subtype	Postop. RT between 50 and 60 Gy is recommended. Assessment of LC unclear CHT to 8 pts with metastatic disease. R3
Cakir 1995 (5) R	Analysis of treatment results Surgery+RT 45–50 Gy+10 Gy+10 Gy	1978–1990 Tumour site: Extremity 35 pts Trunk 32 pts Head and neck 8 pts Low and high grade	Median follow-up 49 m Act. LC% OS% at 5 y 67 50.5 Prognostic factors (multivariate analysis): incomplete resection for LC and OS, high grade for OS	Low local control rate in spite of adequate radiotherapy dose. No dose response for RT. Chemotherapy to 19 pts, no benefit. R2
Wolfson 1998 (9) R	Dose response, postoperative radiotherapy RT dose range 26–72 Gy, median 63 Gy	1984–1992 Site: extremity Low and high grade 41 pts	Median follow-up 65 m Act. DFS% OS% at 5 y 70 71 Prognostic factors: tumour size and RT dose assessed as continuous variables in multivariate analysis: DFS OS Tumour size RT dose Grade Tumour size	A radiation dose-response relation exists for OS, but not for DFS. Chemotherapy to about 50% of the pts with no benefit. R3
Dinges 1994 (3) R	Value of radiotherapy pre- or postoperative RT pre- or postoperative 40–50 Gy+10–20 Gy	1974–1990 All sites Low and high grade A < 50 Gy 16 pts B 50–65 Gy 63 pts C > 65 Gy 23 pts	Median follow-up 49 m Act. LC% at 5 y A 65 B 83 C 100 Prognostic factors (multivariate analysis): LC DFS DMF Grade Grade Grade Local Local relapse relapse Tumour site RT dose Tumour size > 5 cm	Combined surgery and RT is an effective modality for STS. No difference between pre- or postop. RT. Compl. rate, grade 3 16%. Chemotherapy to 14 pts, no benefit. R2
Mundt 1995 (11) R	Evaluation of RT field margin, RT dose, in vitro radiosensitivity RT pre- or postoperative or both pre- and postoperative	1978–1991 Site: extremity Low and high grade RT field margin: A < 5 cm 12 pts B ≥ 5 cm 38 pts Postop. RT dose: C < 60 Gy D 60–64 Gy E ≥ 64 Gy F Liposarc. 20 pts G Synovial sarc. 13 pts H MFH 22 pts I Others 9 pts	Median follow-up 43 m Act. LC% at 5 y A 30 B 93 $p < 0.001$ C 0 D 74 E 87 ns F 83 G 76 H 68 I 67 Prognostic factors (multivariate analysis): LC DFS Field margin Grade Histology Tumour size	Field margin should be > 5 cm for postop. RT. No sign. difference in LC between RT margin 5–10 cm vs. > 10 cm. With negative margin less than 60 Gy is needed. In vitro radiosensitivity did not predict local failure. Chemotherapy to 20 pts, no benefit. R2
Lin 1998 (26) R	Effect of periosteal stripping EBRT or BRT or both Mean RT dose 52.5 Gy (15–116 Gy)	1982–1997 Site: thigh Low and high grade 205 pts	Median follow-up 38 m Act. Risk of fracture at 5 y After stripping 29 No stripping 0 Prognostic factors after stripping (multivariate analysis): female, chemotherapy	Periosteal stripping and radiotherapy result in high risk of bone fractures. Chemotherapy to 78 pts. R2

Overview 1 (*Continued*)

Author Year (Ref. no.) Design	Aim/study question	Patient population	Results	Conclusion/comments
Mullen 1994 (13) R	Retrospective evaluation of treatment results Surgery+RT given pre- or postoperatively	1969–1992 Extremity 68 pts Trunk 11 pts Head and neck 6 pts Age ≤ 20 20 pts Age > 20 65 pts	Median follow-up 8.4 y Act. LC% OS% DMF% at 5 y All pts 86 76 61 80 63 52 at 10 y Prognostic factor: tumour size, age > 20 y OS and DMF. Sex for OS	Conservative surgery and RT gives satisfactory LC. LC did not correlate with RT dose, tumour size or tumour location. Chemotherapy to 35 pts of no benefit. R2
Zagars 1996 (14) R	Retrospective evaluation of treatment results Preoperative RT 50 Gy+surgery or surgery+postoperative RT 50 Gy+10–15 Gy	1964–1992 Liposarcoma, all sites Low and high grade 112 pts A Well-diff. 15 pts B Myxoid. 71 pts C Pleomorf. 26 pts	Median follow-up 9 y LC% DMF% OS% at 10 y All pts 87 77 69 Well-diff – 100 87 Myxoid – 78 76 Pleomor. 63 59 39 Prognostic factors (multivariate analysis): histology for LC, OS and DMF, tumour size > 5 cm for OS and DMF	Consecutive pts. The outcome is greatly determined by histologic subtype. LC (10 y) well-diff. and myxoid > 90%. Chemotherapy to 19 pts with no benefit. R2

Abbreviations: BRT = brachytherapy; CHT = chemotherapy; DFS = disease-free survival; DMF = distant metastasis free; EBRT = external beam radiotherapy; LC = local control; mets. = metastases; m = month(s); MFH = malignant fibrous histocytoma; NR = not reported; ns = not significant = OS = overall survival; pts = patient(s); QoL = quality of life; reop. = reoperation; RT = radiotherapy; STS = soft tissue sarcoma; y = year(s).

- The overall morbidity associated with adjuvant radiotherapy is not significantly higher than that with surgery alone for extremity and trunk STS.
- Adjuvant radiotherapy to STS in the retroperitoneum, head and neck, breast and uterus shows a trend towards improved local control rate, and is worth considering if negative margins are compromised.

Different timing of radiotherapy: pre-, intra- or postoperative. Radiotherapy with neutrons

See Overview 2 , for a description of the trials, trial results and conclusions.

EBRT, BRT and IORT. The goal of radiotherapy given in combination with surgery is the optimization of local control with the best functional outcome for the patients. A variety of radiotherapeutic approaches have been used in the adjuvant local management of soft tissue sarcoma. These include EBRT, BRT at a low dose rate and intraoperative radiotherapy (IORT) at a high dose rate. Various combinations of these methods are also used. With any technique, it is essential to avoid joint spaces if possible, and not to irradiate the full limb circumference (31).

Brachytherapy is an irradiation technique that is performed with intraoperative placement of catheters directly on the surgical bed. Loading with ^{192}Ir or ^{125}I takes place 5 days after surgery. The experience so far is with low dose rate, about 10 Gy/day. BRT has been used as monotherapy or as a boost to EBRT with satisfactory local outcome (8, 22). The shorter overall treatment time with BRT monotherapy is a logistic advantage compared to EBRT. Low-dose BRT allows safe delivery of a high dose to the tumour bed, and normal tissues are relatively spared to a greater extent than with EBRT (32). There are scarcely any reports of high-dose BRT for STS.

The treatment approach (EBRT or BRT) used to deliver adjuvant radiotherapy depends on the institution, expertise of the physician and the clinical situation. Today, similar local control rates, close to 90% after complete tumour resection for non-retroperitoneal STS, and acceptable complications, are possible to achieve independently of the method of radiotherapy. One exception is low-grade STS, for which treatment with BRT seems to be of no benefit for local control (8, 22).

Experience of IORT is still limited (7, 12). Most clinical data on IORT are based on electron beams. Recently, radioactive devices and mobile linear accelerators have been introduced to facilitate IORT in different operating rooms. This will improve the logistics for IORT and probably result in a larger utilization of this modality. It is hoped that randomized studies can be performed in the near future.

A favourable local control rate with IORT has previously been observed for retroperitoneal STS in a small, randomized NCI trial (33) and in a recently published non-randomized study also comprising only a few patients (12). Gastrointestinal obstruction is a common complication and peripheral neuropathy is the dose-limiting factor (7, 12). In a larger, non-randomized study, including extremity, trunk and retroperitoneal STS, IORT was seen to improve disease-free survival, but not local control of retroperitoneal tumours (7). The reason for this discrepancy is not known.

Overview 2

Soft tissue sarcoma. Different timing of radiotherapy: pre-, intra- or postoperative. Radiotherapy with neutrons

Author Year (Ref. no.) Design	Aim/study question	Patient population	Results	Conclusion/comments
Lehnert 2000 (7) P	Intraoperative radiotherapy (IORT) A: Surgery B: Surgery + IORT 10–18 Gy ± EBRT 40 Gy	1988–1999 Extremity 131 pts Trunk 58 pts Retroperitoneum 62 pts Low and high grade A: 159 pts B: 92 pts	Act. Extr. Trunk Retrop. LC% at 5 y A 68 80 100 B 83 100 60 ns ns p = 0.06 Infectious complications more frequent with IORT Prognostic factors (multivariate analysis): age, grade, retroperitoneal site, IORT for DFS	IORT improved DFS. Prognostic factors derived for 204 pts with complete resection. RT a confounding factor not described. P2
Alektiar 2000 (12) P	Intraoperative radiotherapy (IORT) Surgery + IORT 12–15 Gy ± EBRT 45–50 Gy 25 pts got EBRT	1992–1996 Site: retroperitoneum low and high grade primary or relapse treatment A Prim. treatm. 12 pts B Relapse 20 pts C Low grade 12 pts D High grade 20 pts	Median follow-up 33 m Act. LC% OS% All pts 62 45 A 74 75 B 54 ns 30 ns C 66 75 D 58 ns 33 ns 82% of all pts were DMF at 5 y. 100% of low-grade pts vs. 70% of high-grade pts were DMF at 5 y, p = 0.05.	IORT resulted in favourable LC with acceptable morbidity. Peripheral neuropathy is the dose-limiting factor for IORT and occurred in 6%. Chemotherapy to 4 pts. P3
Schönekaes 1999 (35) Prott 1999 (36) R	Radiotherapy with photons vs. neutrons or mixed A: RT with photons B: RT with neutrons or mixed	1965–1994 All sites Low and high grade 161 pts	Act. LC% OS% at 5 y A 44.8 43.1 B 51.8 42.5 RT-related complications 4% in group A vs. 11% in group B.	Low- and intermediate-grade tumours with positive margin benefit from neutron RT. Unclear statistics. R3
O'Sullivan 2002 (39)	Pre- vs. postoperative RT – wound complication A: Preop. RT 50 Gy B: Postop. RT 66 Gy	1994–1997 Site: extremity A: 94 pts B: 96 pts	Median follow-up 3.3 y Act. Wound compl.% OS% A 35 p = 0.048 B 17 p = 0.01 Prognostic factors (multivariate analysis): tumour size, site	More wound complications with preoperative RT. Stratification for tumour size ≤ 10 cm vs. > 10 cm. C2
Cheng 1996 (38) R	Pre- and postoperative radiotherapy A: Preop RT B: Postop RT RT dose mean 63 Gy	1979–1993 Site: extremity Low and high grade A: 48 pts B: 64 pts	Act. LC% RFS% OS% at 5 y A 83 56 75 B 91 67 79 ns ns ns Surgical complications: 31% in group A vs. 8% in group B p = 0.0014 Prognostic factors (multivariate analysis): stage, wound complication for OS	Postop. RT is recommended; preop. RT reserved for situations where adequate surgery is compromised. RT dose poorly described. R2
Pollack 1998 (6) R	Pre- vs. postoperative radiotherapy as primary treatment or at relapse I. Primary treatment A: Preop. RT 50 Gy + surgery B: Surgery + postop. RT 64 Gy II. Relapse treatment A: Preop. RT 50 Gy + relapse surgery B: Relapse surgery + postop. RT 64 Gy C: Postop. RT 64 Gy alone Preop. RT 128 pts Postop. RT 165 pts RT alone 160 pts	1965–1992 MFH, synovial sarcoma, liposarcoma (retroperitoneal sarcoma excluded) intermediate and high-grade 453 pts	Median follow-up 97 m Act. LC% at 5y I. A 88 B 74 p = 0.027 II. A 73 B 88 A vs. B p = 0.065 C 80 B vs. C p = 0.019 LC% (5 y) for liposarcoma 88, synovial sarcoma 86, MFH 77, p = 0.04 Prognostic factors (multivariate analysis): LC DFS Histology, prim. treatment Grade Tumour size (> 5 cm) Local relapse Tumour site Negative margin	Preop. sign. better in primary treatment. Postop. better in case of re-excision. 50 Gy alone is inadequate after gross total excision at an outside centre. Wound compl. preop. 25%, postop. 6% (p < 0.001). Late effects equal for preop. Vs. postop. vs. EBRT alone. Moderate to severe complications 7% at 15 y. Chemotherapy to 139 pts of no benefit. R2

Abbreviations: DFS = disease-free survival; DMF = distant metastasis free; EBRT = external beam radiotherapy; IORT = intraoperative radiotherapy; LC = local control; m = month(s); ns = not significant = OS = overall survival; pts = patient(s); RT = radiotherapy; y = year(s).

Neutron radiotherapy. A substantial number of patients with STS have been treated with neutrons, but yet there no randomized trial has been performed. In the most recent reports it has been suggested that neutron EBRT alone or as boost to photon EBRT might be superior for patients with low- and intermediate-grade STS, operated on with intralesional margins or considered not resectable. In the case of negative or marginal margins, similar local control rates are achieved with photon and neutron EBRT. However, the rate of late complications is usually higher with neutron radiotherapy (34–36).

Preoperative versus postoperative radiotherapy. For a high proportion of patients with STS, a combination of surgery and radiotherapy is the most appropriate treatment. The rationale behind the choice of preoperative radiotherapy rather than postoperative radiotherapy, or vice versa, has been debated extensively (37). Several advantages are advertised for preoperative radiotherapy. It has been established that the field size, the number of joints included, and dose can be reduced compared to the postoperative alternative. In this way, an improvement in functional outcome may be achieved. With preoperative radiotherapy there is a potential towards eliminating contamination of the surroundings by tumour cells during surgery, and resectability may be improved with tumour shrinkage. On the negative side, preoperative radiotherapy is associated with a higher wound complication rate (6, 38, 39). Moreover, the preoperative setting demolishes exact histopathological diagnosis and molecular assessments of the surgical specimen.

Postoperative radiotherapy is more widely used than preoperative. One reason is that many patients have their tumours surgically removed in local hospitals, and thereafter are referred to a sarcoma centre. There are several advantages of postoperative radiotherapy. Surgery can be performed without delay. This approach provides a more accurate assessment of histology and grade than an incisional biopsy. This fact is especially important for forecasting the risk for distant metastases and indications for adjuvant chemotherapy. Adjuvant postoperative radiotherapy makes it possible to adjust the technique and dose to the tumour extent as demonstrated during surgery or pathological investigation. Finally, primary surgery means that adjuvant radiotherapy can be omitted in some patients with wide surgical margins.

Recently, a fairly small, randomized trial was published comparing pre- and postoperative adjuvant radiotherapy with wound complication as the primary endpoint (39). Significantly more wound problems were seen after preoperative radiotherapy. Overall survival was slightly better after preoperative compared with that after postoperative radiotherapy. In retrospective studies both approaches show similar effectiveness, and there is still no consensus on the optimal sequencing of radiation and surgery. The current suggestion is to use preoperative radiotherapy for large tumours and tumours where adequate surgery is compromised (37, 38, 40). In a large retrospective study, preoperative EBRT and primary surgery at the M.D. Anderson Cancer Centre showed a significant improvement in local control compared with primary surgery and postoperative EBRT. It has to be said, however, that postoperative radiotherapy was given to the patients not primarily treated at the large centre. On the other hand, there is a trend towards lower local control with preoperative radiation if re-excision of the tumour is performed. If re-excision is judged to be necessary, postoperative EBRT is recommended. Furthermore, it is has been observed that patients have a higher local control rate with the re-excision approach than patients without re-excision treated with EBRT alone to 50 Gy after gross total excision at an outside centre (6).

In support of Herman Suit et al.'s previous work (40), most investigators today use preoperative radiotherapy to achieve local control for patients presenting primarily with gross disease tumours larger than 5 cm in diameter. In particular, consideration for the preoperative setting is motivated when the ability to achieve a wide surgical margin is difficult without causing significant morbidity. For instance, if there is involvement of the neurovascular bundle or extensive tumour growth near the joint spaces, the possible reduction of tumour size may decrease the extent of surgical resection required.

Radiotherapy field margin. The field margin needed to include potential microscopic disease is poorly defined and practices tend to vary. The recommended margin depends on the grade, size and anatomic location of the tumour. In a retrospective failure analysis of extremity STS, a dramatically inferior local control rate is achieved when the field margin surrounding the tumour bed/scar is < 5 cm for postoperative radiotherapy (11). The exact margin is dictated by particular anatomical constraints. Bone, interosseous membranes and fascial plans are barriers to tumour growth and the margins employed are principally in the craniocaudal direction.

In contrast to the wide field margin recommended for EBRT, for BRT in extremity and trunk STS, a margin of only 2 to 3 cm around the surgical bed is applied. This approach results in about a 90% local control rate for high-grade tumours (8). One explanation for this difference in margins may be that pretreatment biopsies and the surgical technique may have a considerable impact on the degree of dissemination of tumour cells, and thereby dictate the field margin needed. Further studies are needed to examine this issue.

Radiotherapy dosage. The doses prescribed for adjuvant radiotherapy are based upon local failure analyses. However, there is a paucity of dose-response data (3, 9, 11, 28). In general, the preoperative EBRT dose used in most

centres is 50 Gy in 2 Gy fractions (2, 6, 38). Depending on the pathological findings, a postoperative boost of 10 to 15 Gy is given. The wound complication rate after a preoperative dose of 50 Gy is significant (6, 38, 39) and it would therefore be worthwhile to investigate the optimal dosage for this setting. The complications might also be related to the principles that are used for surgery and radiotherapy.

In using postoperative EBRT, the radiation volume, encompassing the entire surgical bed with a margin including the biopsy and surgical scars and drain site, has received mostly 50 Gy (range 40–50 Gy). A boost dose of at least 10 Gy is considered for the highest risk areas. For gross residual tumour or intralesional margin the dose is escalated to 65–70 Gy (1–3, 5, 6, 10, 15, 21). For extremity STS there is a trend towards dose response with an increased local control rate above 60 Gy. But, a dose escalation is compromised by more pronounced late complications. Less than 60 Gy is needed if the surgical margin is negative (11).

When low dose rate BRT is used as monotherapy, 40 to 45 Gy over 4 to 6 days is applied. When BRT is used as a boost in combination with preoperative or postoperative EBRT, a dose between 15 and 20 Gy is delivered (8, 15, 22).

Intraoperative high dose rate IORT is delivered in a single dose of 10 to 18 Gy, usually in addition to EBRT of 40 to 50 Gy (7, 12).

The literature shows that:

- Similar local control rates are achieved with external beam radiotherapy and low dose rate brachytherapy for high-grade soft tissue sarcoma. For low-grade tumours, brachytherapy seems to be of no benefit.
- There are still no convincing results showing any advantages for intraoperative radiotherapy.
- There is no clear evidence for the use of neutron radiotherapy.
- The circumstances at referral, untouched tumour or surgery at a local hospital, often determine if pre- or postoperative adjuvant radiotherapy is chosen. Primarily referred tumours larger than 5 cm should be considered for the preoperative setting. Significantly more wound complications are seen with preoperative compared with postoperative radiotherapy.
- The field margin should be at least 5 cm in the use of EBRT and at least 2 cm in the use of BRT in the postoperative settings. The exact margin is dictated by particular anatomical constraints. Appropriate margins for the preoperative settings have not been established.
- There is a paucity of dose-response data for adjuvant radiotherapy. The optimal dosage in the preoperative setting has not been established. An adequate dose in the postoperative setting depends on the surgical margin.

Miscellaneous experimental studies (hyperfractionation (HRT), hyperfractionated accelerated fractionation (HART), radiosensitizer, hyperthermia)

See Overview 3 for a description of the trials, trial results and conclusions.

Radiosensitivity. The clinical radioresponsiveness of soft tissue sarcomas is generally slow and this has been interpreted as associated with radioresistance. When human soft tissue sarcoma cell lines are studied in vitro the inherent radiosensitivity, e.g. determined as the surviving fraction at 2 Gy, appears to be comparable to that of epithelial cancer cell lines, e.g. from breast cancer and head and neck cancer. Therefore, the appearance of radioresistance may be a reflection of other tumour characteristics for STS, i.e. a large tumour clonogen number is to be expected within the typically large STS. There might also be a great proportion of quiescent and hypoxic clonogens, and these cells are relatively more radioresistant than cycling and oxic tumour cells. Finally, it is known that STS has a low cell loss, which also contributes to a slow radiotherapy response.

In a study of in vitro radiosensitivity parameters established from a subset of patients with STS prior to treatment, no correlation was observed between local control and radiosensitivity. The study is too small for definite conclusions, but indicates that the inherent tumour cell radiosensitivity of STS is not particularly low and is not a major determinant of local failure (11).

Radiosensitizers. One interesting randomized study has been conducted concerning the effect of razoxane in the treatment of STS (41). Razoxane is a radiosensitizer that blocks dividing cells in the G2 phase of the cell cycle, which is the phase that is most sensitive to irradiation. Razoxane per os beginning 5 days before radiotherapy and then given concomitantly was compared with radiotherapy alone. In the adjuvant postoperative setting, no difference was observed in local control or survival. In the treatment of gross disease, however, a significant improvement in local control was seen. The acute toxicity was more pronounced with razoxane, but the frequency of long-term complications was the same. The findings are consistent with razoxane as being a true radiosensitizer.

Unconventional fractionation. Alternative fractionation schedules have been investigated in order to improve local control. Hypofractionation, i.e. larger dose fractions than 2 Gy, are often associated with more pronounced late effects. Hyperfractionation, which means dose fractions lower than 2 Gy, has been evaluated in a couple of non-randomized studies (4, 42). The use of 2×1.2 Gy/day, totalling 72 Gy, to patients with marginal or intralesional surgical margins of intermediate- and high-grade tumours has been found to be feasible. The use of hyperfractionated accelerated fractionation with 2×1.5 Gy/day, totalling 45 Gy, to extremity STS has also been proven feasible. In these two studies, hyperfractionation did not seem to be superior to

Overview 3

Soft tissue sarcoma. Miscellaneous experimental studies (hyperfractionation (HRT), hyperfractionated accelerated fractionation (HART), radiosensitizer, hyperthermia)

Author Year (Ref. no.) Design	Aim/study question	Patient population	Results	Conclusion/comments
Jacob 1999 (42) P	Value of hyperfractionation RT 1.2 Gy/fr/2 fr/d, 72 Gy pre- or postoperatively	1990–1995 Site: extremity 29 pts, others 8 pts Intermediate and high grade Preop. RT 8 pts Postop. RT 29 pts Curative treatm. 30 pts Palliative treatm. 7 pts	Median follow-up 44 m Act. RFS% 76 DFS% at 5 y 86	Hyperfractionation 2 × 1.2 Gy/day, total dose 72 Gy is feasible, and results in similar LC and complications as conventional fractionation. RT to pts with marginal or intralesional margin only. Salvage surgery for local recurrence if possible. P3
Le Péchoux 1999 (4) R	Hyperfract. accel.radiotherapy, (HART) A: RT conventional 2 Gy/fr, 1 fr/d, 50 Gy + 5–10 Gy B: HART 1.5 Gy/fr, 2 fr/d, 45 Gy	1984–1993 Site: extremity Low and high grade A: 45 pts B: 17 pts	Median follow-up 72 m Act. LC% DFS% OS% at 3 y A 84 44 70 B 64 47 82 ns ns ns Prognostic factors (multivariate analysis): LC DFS OS Surg. margin Grade Surg. margin Size Tumour size ≥ 5 cm	No difference between HART and conventional RT. Only 17 pts in group B. R3
Rhomberg 1996 (41) C	Value of razoxane (radiosensitizer) I. A: Surgery + RT 40–50 Gy + 10–20 Gy B: Surgery + RT as A + razoxane II. Gross tumour A: RT 40–50 Gy + 10–20 Gy B: RT as A + razoxane RT for retroperitoneal tumour: 40–50 Gy	1978–1988 All sites Low and high grade I: A 26 pts B 22 pts II: A 40 pts B 42 pts	Median follow-up 7 y Act. LC% OS% at 7 y I. A 81 76 B 73 ns 60 ns II. A 30.5 B 64 $p < 0.05$ No sign. difference in late side effects.	Razoxane is of benefit for LC in inoperable, residual or recurrent soft tissue sarcoma. Chemotherapy to 31 pts, not evaluated. C2
Prosnitz 1999 (17) P	Radiotherapy with hyperthermia Preop. RT 50 Gy + hyperthermia	1984–1996 Site: extremity, others intermediate and high-grade 97 pts	Follow-up 12–115 m Act. LC% DFS% OS% at 10 y All pts – 50 47 Extremity 94 Others 63 $p = 0.074$ Prognostic factors (multivariate analysis): tumour size, histology, surgical margin for LC and OS	Preop. EBRT + hyperthermia provided excellent LC for high-grade extremity STS. No benefit for OS and DFS. Fairly high risk of burns. Chemotherapy to 7 pts, not evaluated. P2
Scully 1994 (20) R	Value of hyperthermia Preop. RT 50 Gy + hyperthermia	1984–1990 Deep-site High-grade 44 pts	Minimum follow-up 2 y Act. LC% DFS% OS%at 3 y 97.5 58 72 Prognostic factors (multivariate analysis): surgical margin for OS and DFS.	Excellent LC for RT and hyperthermia. Short follow-up. R3
Olieman 1998 (43) P	Postoperative hypertherm. perfusion (HILP) A: HILP B: HILP + postop. RT (to marginal and pos. margins) HILP: Hyperthermia + TNFα + IFN-γ + melphalan RT: 50 Gy + 10–20 Gy	1991–1995 Site: extremity low and high grade A: 19 pts B: 15 pts	Median follow-up 34 m Act. LC% at 5 y A 74 B 100 $p < 0.05$	Adjuvant RT and HILP for locally advanced extremity STS is feasible and may increase LC without increasing morbidity. P3

Overview 3 (*Continued*)

Author Year (Ref. no.) Design	Aim/study question	Patient population	Results			Conclusion/comments
Temple 1997 (44) P	Radiotherapy + chemotherapy preoperatively Preop. RT 30 Gy/10 fr + doxorubicin 90 mg over 3 d, i.v. or i.a.	1984–1994 Intermediate and high grade Extremity 35 pts Trunk 3 pts Head and neck 2 pts	Median follow-up 5 y Act.	LC% 97	OS% at 5 y 79	Excellent LC with low postoperative morbidity. Paediatric tumours included. P3

Abbreviations: DFS = disease-free survival; EBRT = external beam radiotherapy; fr = fraction(s); LC = local control; m = month(s); ns = not significant = OS = overall survival; pts = patient(s); RFS = relapse-free survival; RT = radiotherapy; STS = soft tissue sarcoma; y = year(s).

conventional fractionation, either in terms of local control or disease-free survival. Moreover, the long-term side effects were the same as those after standard postoperative EBRT.

Hyperthermia. Hyperthermia and radiotherapy have been applied to high-grade including deep-located STS in a preoperative setting (17, 20). Excellent local control rates were documented, especially for extremity tumours. As a complication, a fairly high risk of burns was noticed.

Limb perfusion. Isolated limb perfusion with tumour necrosis factor (TNFα), melphalan and interferon γ has been studied. The results suggest increased resectability and acceptable complications. This regime, used with postoperative radiotherapy in the case of marginal or positive surgical margin showed outstanding local control without enhanced morbidity in a moderately sized study (43). Excellent local control and low postoperative morbidity have also been achieved with preoperative EBRT in combination with adriamycin given intra-arterially or intravenously (44).

The literature shows that:

- Radiosensitizers may improve local control in the use of radiotherapy for inoperable STS, but seem not to be of any benefit in the adjuvant setting.
- Hyperfractionation is feasible in the adjuvant setting, but no clear-cut advantage to conventional fractionation has been demonstrated yet.
- Hyperthermia and radiotherapy applied preoperatively to extremity tumours result in excellent local control rates, but with a fairly high risk of burns.
- So far, limited data on preoperative limb perfusion combined with postoperative radiotherapy shows promising results.

Radiotherapy in patients with HIV-associated Kaposi's sarcoma

See Overview 4 for a description of the trials, trial results and conclusions.

Kaposi's sarcoma affects up to 20% of patients with AIDS. The main manifestation is the skin, but other common sites are oral cavity, genitals, eyelid and conjunctiva. It is recommended that 30 Gy be given in 2 Gy fractions to cutaneous lesions. A lower response rate is documented with 20 Gy. For palliative purposes, 20 Gy for the eyelids and conjunctiva, and 15 Gy for oral lesions are sufficient (45, 46). In a randomized study it is established that a single dose of 8 Gy is appropriate treatment for Kaposi's sarcoma in patients with a limited life expectancy (47).

The literature shows:

- Cutaneous lesions of Kaposi's sarcoma should be treated with 30 Gy in 2 Gy fractions for curative purposes. For palliative treatments and particular anatomic sites, doses can be reduced to 15 to 20 Gy. Single doses of 8 Gy are appropriate for patients with a short life expectancy.

LITERATURE

The articles on which the conclusions in this report were based were classified and graded as follows (number of studies/number of patients):

	1 = High	2 = Moderate	3 = Low	Total
C	–	5/682	–	5/682
P	–	2/348	4/143	6/491
R	–	14/2 588	11/818	25/3 406
L	–	–	3/–	3/–
O	–	–	–	–
Total	–	21/3 618	18/961	39/4 579

C = controlled clinical trial; P = prospective study; R = retrospective study; L = literature review; O = other article.

CONCLUSIONS AND COMMENTS

Because STS are rare tumours, referral of patients with STS to multidisciplinary sarcoma centres should be seriously considered.

- The well-established prognostic factors for tumour-related death from STS—histological grade, tumour

Overview 4

Soft tissue sarcoma. Radiotherapy in patients with HIV-associated Kaposi's sarcoma

Author Year (Ref. no.) Design	Aim/study question	Patient population	Results				Conclusion/comments
Saran 1995 (45) R	RT 20 Gy	1991–1993 Site: skin, oral cavity 43 pts	CR% 34	PR% 55	NR% 11		A lower response rate is achieved with 20 Gy compared to the standard dose of 30 Gy. R3
Kirova 1998 (46) R	RT 10–30 Gy	1986–1996 Site: skin, oral cavity, genitals, eyelid, and conjunctiva 6 777 lesions 643 pts		CR%	PR%	NR%	Doses of 15 Gy for oral lesions, 20 Gy for eyelids, conjunctiva and genitals are sufficient for palliative purposes; 30 Gy is recommended for cutaneous lesions. Large study. R2
			Skin	66	26	8	
			Oral cavity	18	82	–	
			Conjunc., eyelid and genitals	18	82	–	
			For skin a RT dose of 30 Gy is superior to an RT dose of 20 Gy, p = 0.04				
Harrison 1998 (47) C	A: RT 16 Gy, 4 fr B: RT 8 Gy, 1 fr	1990–1994 596 cutaneous lesions 57 pts		CR%	PR%	NR%	A single dose of 8 Gy is an appropriate treatment for pts with limited life expectancy. C2
			A	49	15	4	
			B	53	13	9	

Abbreviations: CR = complete remission; fr = fraction(s); NR = no response; ns = not significant; OS = overall survival; PR = partial remission; pts = patient(s); RT = radiotherapy.

size and age—are well documented in the studies presented in Overviews I to III.

- The importance of superficial versus deep site as well as the anatomic site is also reaffirmed to some extent ((1) R2).
- There is strong evidence that adjuvant radiotherapy improves the local control rate in combination with conservative surgery in the treatment of STS of the extremities and trunk in patients with negative, marginal or minimal microscopic positive surgical margins. A local control rate of 90% can be reached ((21) C2, (22) C2, (8) C2, (23) C2).
- Improvement is obtained with radiotherapy in addition to intralesional surgery, but the local control rate is somewhat lower. More studies are needed on this issue ((16) R3, (15) R2, (2) R2, (1) R2).
- For STS in other anatomic sites, retroperitoneum, head and neck, breast and uterus, there is only a weak indication of a benefit for the local control rate using adjuvant radiotherapy ((19) R3, (10) R2, (29) R2, (30) R3).
- There is still insufficient data to establish that preoperative radiotherapy is favourable compared to postoperative radiotherapy for local control in patients presenting primarily with large tumours ((6) R2). One small study has shown a possible survival benefit for preoperative radiotherapy ((39) C2).
- There is fairly good evidence to suggest that the preoperative setting can cause more wound complications ((39) C2, (38) R3, (6) R2).
- There are no randomized studies comparing EBRT and BRT. The data suggest that external beam radiotherapy and low dose rate brachytherapy result in comparable local control for high-grade tumours ((21) C2, (22) C2, (8) C2).
- Some patients with low-grade soft tissue sarcomas benefit from external beam radiotherapy in terms of local control ((21) C2).
- Brachytherapy with low dose rate for low-grade tumours seems to be of no benefit, but the data are very sparse ((22) C2, (8) C2).
- The available data are inconclusive concerning the effect of intraoperative high dose rate radiotherapy in retroperitoneal STS ((12) P3, (7) P2). Further studies are needed.
- Neutron radiotherapy might be beneficial for patients with low- and intermediate-grade tumours considered inoperable and for those operated on with intralesional margins ((34) L3, (35) R3, (36) R3). More severe side effects for neutrons are registered ((34) L3).
- In two small studies investigating hyperfractionation schedules there was no indication of any improvements compared to daily fractions of 2 Gy ((42) P3, (4) R3). Further studies should be encouraged.
- One small study using preoperative limb perfusion with TNFα melphalan and $\pm$interferon γ combined with postoperative radiotherapy in the case of marginal or positive surgical margins has shown excellent local control without enhanced morbidity ((43) P3).

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