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Original Paper

The Outcome of Advanced Soft Tissue Sarcoma Patients with Complete Tumour Regression after either Chemotherapy Alone or Chemotherapy Plus Surgery. The Scandinavian Sarcoma Group Experience

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The intensified induction regimens used and the potential use of high-dose consolidation chemotherapy (CT) in advanced soft tissue sarcomas (STS) has focused interest on the outcome of those patients who can achieve complete remission (CR) by current therapy. The files from four institutions with a special interest in STS were studied. 38 adult patients with advanced STS who were converted disease-free by either CT alone ($n = 14$) or CT followed by surgery ($n = 24$) were found. The median follow-up time was 29 months. The median disease-free survival (DFS) was 18 months and the estimated 2-year DFS 34%. The median disease-specific survival (DSS) was 40 months and the estimated 2-year DSS 78%. For patients who achieved CR by CT alone, and for patients who were converted to CR by surgery, the corresponding DFS figures were 23 months (estimated 2 year DFS 48%) and 10 months (26%) ($P = 0.07$), respectively. The histological response to CT significantly predicted outcome in patients subjected to surgery (DFS P value 0.004, DSS P value 0.02). Patients who achieved CR by surgery shortly after having achieved a clinical partial response (PR with early surgery) did better than those who where converted to CR by surgery after protracted CT following a clinical PR (PR with late surgery) (DFS P value 0.02, DSS P value 0.1). Our results confirm that CT alone can induce prolonged DFS in rare patients with advanced STS. In patients subjected to surgery, a good histological response indicates improved outcome.

Key words: chemotherapy, soft tissue sarcomas

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INTRODUCTION

APPROXIMATELY 25–30% of patients with operable lung metastases from soft tissue sarcoma (STS) can be cured by surgery alone [1, 2]. Whether patients rendered disease-free by chemotherapy (CT) alone can sustain long-term remission is not settled. However, investigators at large cancer treatment centres frequently can recall a few patients apparently cured of advanced soft tissue sarcoma by chemotherapy, although this has not been systematically studied. However, results from randomised studies on adjuvant CT in the primary treatment of STS have not indicated any curative role for CT [3–5], and many consider CT of metastatic STS as mere palliation [6]. In two recent multicentre trials the response rates to CT in advanced sarcomas were 32% and 45%, respectively, and the rates of complete response (CR) were 2% and 10% [7, 8]. Additional patients can be converted to CR with CT followed by surgery or radiotherapy [9], although it is unresolved whether these patients or patients who receive consolidation radiotherapy can experience prolonged disease-free survival (DFS).

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Table 1. Histological types of all 38 treated patients

Malignant fibrous histiocytoma	9
Leiomyosarcoma	8
Synovial sarcoma	6
Extraskeletal Ewing's sarcoma, PNET* or rhabdomyosarcoma	4
Neurofibrosarcoma, malignant schwannoma	2
Liposarcoma	2
Fibrosarcoma	2
Epitheloid sarcoma	1
Haemangiopericytoma	1
Sarcoma, not specified	3

*PNET, peripheral neuroectodermal tumour.

Information on long-term results from these different strategies would be of value when intensified induction regimens and high-dose consolidation therapies are planned. The aim of this study was to examine retrospectively patients who achieved a complete CR with CT alone or with combined therapy in pariticipating Institutes of the Scandinavian Sarcoma Group.

PATIENTS AND METHODS

The files from four institutions actively participating in the Scandinavian Sarcoma Group were searched for patients who had received CT for STS and had either achieved a complete CR by CT alone or by CT combined with surgery. Patients who had been subjected to surgery alone, and patients below 16 years of age were excluded. The total number of patients treated with combination chemotherapy could be determined at three of the participating institutions (Helsinki $n = 53$, 1988–1993; Lund $n = 60$, 1982–1993; Oslo $n = 89$, 1989–1993). Thus, the 38 patients included represented 5–23% of all patients who had received CT for STS at these institutions. The response to the CT was evaluated at the respective institution according to standard criteria [10]. The follow-up was complete in all cases.

Table 2. Characteristics of the 38 treated patients

Site of primary	
Extremity	19
Trunk or head and neck	6
Retroperitoneum or viscera	13
Malignancy grade	
High	34
Low	3
Undefined	1
Disease status at start of chemotherapy	
Primary with metastases	6
Local recurrence with metastases	1
Primary tumour or local recurrence without metastases	6
Metastatic disease only	25
Site of metastases	
Lung only	13
Liver only	4
Soft tissues only	3
Multiple sites	12
Previous adjuvant chemotherapy	0
Previous surgery for metastases	8
Time from primary treatment to start of chemotherapy	
Median	17 months
Range	0–110 months
Number of lesions at start of chemotherapy	
Median	3
Range	1–60
Size of the primary/locally recurrent tumour	
Median	8 cm
Range	1.5–12 cm
Size of the metastases	
Median	2.3 cm
Range	0.8–22 cm

There was no uniform treatment protocol for advanced soft tissue sarcomas during the study time. In three of the participating hospitals, chemotherapy was reserved for patients with inoperable, advanced STS, and patients not eligible for resection of lung metastases. In case of operable lung metastases, surgical resection was preferred. One centre (Oslo) also used chemotherapy before planned surgery.

The characteristics of the patients and the histologic types of the tumours are presented in Tables 1 and 2. The mean age of the patients was 45 years (range 16–70). The CT consisted of the VIG regimen [11, 12] in 17 patients, the VIG regimen supplemented with doxorubicin in 4 patients, and the IVADIC regimen [13] in 12 patients (Table 3). 5 patients had received various other CT regimens, all including doxorubicin.

The response to CT was determined histologically in patients subjected to surgery. Tumours with no or little identifiable necrosis (grade 1 histological response) or tumours with areas of necrosis, with other areas containing viable tumour (grade 2) indicated a poor response. In a good response, there were no (grade 4) or only scattered foci (grade 3) of histologically viable or possibly viable tumour cells present. This classification is based on the previous experience by several groups in the treatment of skeletal sarcomas and more recent reports in the STS literature [14–18].

Patients subjected to surgery were classified further, since patients operated on during clinical partial response (PR) represent either chemosensitive or -resistant disease at the time of surgery. Those patients operated on shortly after achieving a clinical PR (i.e. the patients received a maximum of one CT course after the first date of clinical PR, and before surgery, $n = 11$) were grouped together (early surgery). Patients who were operated on due to failure to achieve a clinical CR (i.e. received more than one CT course after a clinical PR, before surgery, $n = 7$) were defined as having been subjected to late surgery. The median time from a clinical PR to surgery was 0.6 months in patients with early surgery versus 4.1 months in patients with late surgery. All patients with a good histological response had been subjected to early surgery. 3 patients operated on in PR had localised tumour only, all were subjected to early surgery.

Disease-specific survival (DSS) was calculated from the start of chemotherapy, and DFS from the data of CR (in patients made disease-free by surgery, the date of surgery). Factors possibly determining DFS (all recurrences and recurrences within previous sites of disease evaluated separately) and DSS were tested univariately with the Kaplan–Meier method and the significance of detected differences was estimated with the log rank test or the Cox proportional hazard model. Variables studied were: age, tumour grade, disease-free interval from primary therapy, combined local and metastatic disease versus only local or metastatic dis-

Table 3. The VIG and IVADIC chemotherapy regimens

VIG		
Etoposide	600 mg/m^2	72-h continuous infusion
Ifosfamide	1.5 g/m^2/day	Days 1–3 (2-h infusion)
Mesna	0.3 g/m^2 × 3/day	Days 1–3
G-CSF		
Cycle repeated every 21 days	5 μg/kg/day	Days 4–15
IVADIC		
Ifosfamide	1 g/m^2/day	Days 1–5 (2-h infusion)
Vincristine	1.5 mg/m^2 (max. 2 mg)	Day 1
Doxorubicin	50 mg/m^2	Day 1 (5-min infusion)
Dacarbazine	250 mg/m^2/day	Days 1–5 (30-min infusion)
Mesna		
Cycle repeated every 21 days	0.2 g/m^2 × 3/day	Days 1–5

ease, site of metastases (lung only or other), number of lesions (continuous variable), and size of largest lesion (continuous variable). Treatment-related factors studied were CT regimen (VIG ± doxorubicin, IVADIC, or other), clinical CR with CT alone or CT followed by surgery, consolidation radiotherapy, clinical response to CT and histological response in patients who received surgery, and finally, early versus late surgery in patients subjected to surgery in clinical PR.

RESULTS

14 patients (37%) reached a CR by CT alone. These patients received a median of 9.5 (range 7–10) CT cycles. The response was verified by computed tomography in 13 patients, and by clinical examination and plain X-ray in one patient. 4 of these patients were also surgically explored—in 3 patients tumour(s) were excised, but this comprised of necrotic tissue without viable tumour cells; in one patient, operated on for cosmetic reasons, no suspect tissue could be detected.

In all, 28 patients (74%) were subjected to surgery after initial CT. The clinical and the histological tumour response of those 27 patients from whom a suspect lesion was removed are presented in Table 4. The 24 patients (63%) subjected to surgery who did not achieve a clinical CR preoperatively received a total of 7.5 cycles of CT (median, range 3–11). Only patients with a clinical PR before surgery received CT postoperatively (median 2 cycles, range 0–6).

After the patients were rendered disease-free, 8 patients received radiotherapy to the sites of prior metastatic ($n = 4$) or local ($n = 4$) disease.

The median follow-up of patients alive was 29 months from the start of CT (range 13–76), and of patients without recurrence 25 months (range 4–82) from the date of CR.

Table 4. The histological response to chemotherapy by pre-operative clinical response (poor = areas with viable tumour, good = no or few, very small areas of possibly viable tumour cells)

Clinical response	Histological response Poor	Good	Total no. of patients
Complete response		3 (100%)	3
Partial response	12 (67%)	6 (33%)	18
Stable disease	2 (100%)		2
Progressive disease	4 (100%)		4
Total no. of patients	18	9	27

The estimated 2-year (and median) DSS and DFS rates were 78% (40 months) and 34% (18 months), respectively. During the follow-up period, the disease recurred in 25/38 patients (66%), after a median of 8 months from the time of CR. In 17 patients, the disease recurrence was either solely [9], or partly [8] in previous disease locations. 19 patients (50%) died, one from intercurrent disease while in continuous remission after a follow-up of 91 months. 13 patients (34%) were in continuous CR. At the start of therapy, 9 of these patients had metastatic disease, and 4 had locally advanced disease only. Those 4 patients with small round cell tumours (extraskeletal Ewing's sarcoma, PNET (peripheral neuroectodermal tumour) or rhabdomyosarcoma) all relapsed.

For patients who achieved CR by CT alone, and for patients who were converted to CR by surgery, the median DFS (and estimated 2-year DFS) were 23 months (48%) and 10 months (26%) ($P = 0.07$), respectively (Figure 1). In patients subjected to surgery, the histological response predicted outcome (P values for DFS 0.004 and for DSS 0.02) (Figure 2).

In those 18 patients operated in PR, the median DFS and DSS were 19 and 41 months, respectively, in patients subjected to early surgery, and 5 and 22 months, respectively, in patients subjected to late surgery ($P = 0.02$ and 0.1,

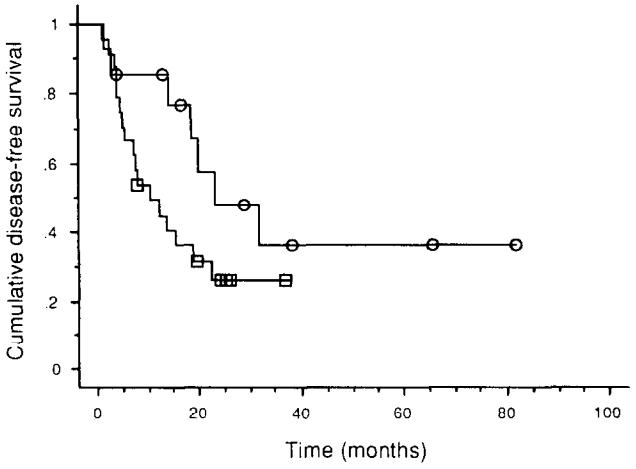

Figure 1. Cumulative disease-free survival in patients who achieved clinical CR by chemotherapy ($n = 14$) (○), and patients who were rendered disease-free by surgery after PR, SD or PD to initial chemotherapy ($n = 24$) (□).

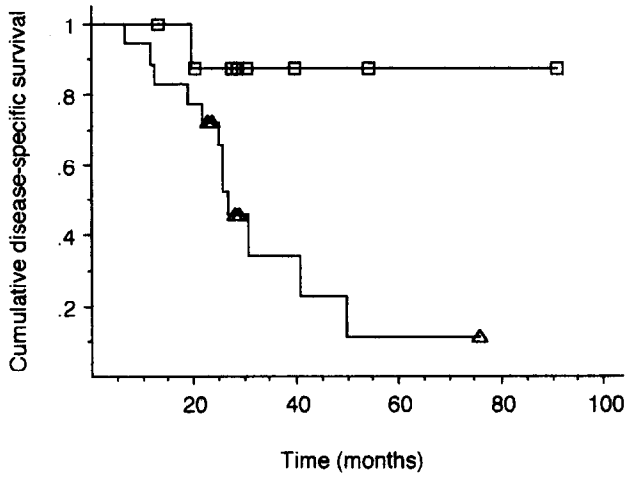

Figure 2. Cumulative disease-specific survival in patients who, after initial chemotherapy, were subjected to surgery, according to histological chemotherapy response (□ = good response, △ = poor response).

respectively). Early surgery also predicted improved DFS within sites of previous disease only ($P = 0.004$).

The only additional factor studied that predicted poor outcome was combined disease (the combination of local disease and metastases as opposed to either metastases only or local disease only) (DSS = 0.002, DFS within previous sites only $P < 0.0001$).

The outcome of the patients as related to therapeutic strategy is presented in Table 5. It should be noted that two non-responding patients are in continuous remission after a follow-up of 23 and 29 months, respectively. The exclusion of 6 patients with local tumour only (four locally recurrent tumours) did not alter the results (data not shown).

DISCUSSION

Our results indicate that a proportion of patients with advanced STS can be rendered disease-free by CT alone for a prolonged time. This fraction of patients appears to be of the same magnitude as after resection of lung metastases in patients with STS [1, 2]. However, patients rendered disease-free by surgery alone represent a highly selected population [19].

Although many recommend surgery after CT in advanced STS, survival results after multimodality treatment of advanced STS are sparse [9, 20, 21]. In our study, the DFS was longer in patients rendered CR by CT alone compared to those treated with CT followed by surgery. Furthermore, local consolidation therapy (surgery or radiotherapy) did not influence the failure rate at sites of previous disease either. However, the small number of patients, precludes any conclusion regarding the value of consolidation radiotherapy. Some of those patients rendered disease-free by surgery after CT could perhaps have been treated with surgery alone. The majority of our patients were initially inoperable. Moreover, the influence of the histological response to CT on outcome also suggests a benefit of CT in these patients.

The classically defined clinical response did not predict the long-term outcome, emphasising the imprecise nature of current definitions of clinical response to CT [10]. In particular, the heterogeneity of the group of partial responders should be emphasised. In a previous study on surgery of advanced STS following CT, which included only patients in PR or with stable disease, the clinical response was not found to predict outcome either [21]. In accordance with this finding, the clinical response correlated well with the histological response in complete responders, in patients with stable disease and progressive disease, but not in those with a PR. We were, however, able to demonstrate a significant impact of the histological response on outcome. The prognostic significance of histopathological response to CT has previously been reported for locally advanced STS, but not for advanced STS patients [16, 17]. While clinical response failed to predict outcome, the classification of the patients by chemosensitivity did identify two prognostic subgroups. This classification has not previously been tested. The rationale to subgroup PRs is that patients who receive surgery very soon after achieving a PR potentially might

Table 5. The number of patients rendered disease-free by different treatment modalities, the number of patients in continuous remission and the number of subsequently relapsed patients who relapsed only within previous disease location

		No. of patients	No. of patients in continuous remission (disease-free survival in months of the individual patients)	No. of patients who relapsed within previous sites only
CR by chemotherapy alone*	All patients	14	7	3
	No local therapy for consolidation	9	4 (13+, 19+, 42+, 70+)	3
	Consolidation surgery	2	2 (20+, 91+)	0
	Consolidation radiotherapy	2	1 (37+)	0
	Consolidation surgery and radiotherapy	1		0
Surgery after initial chemotherapy†	All patients	24	6	6
	No consolidation radiotherapy	19	4	5
	Pre-operatively in clinical PR	13	2 (13+, 27+)	
	Pre-operatively in clinical NC	2	1 (29+)	
	Pre-operatively in clinical PD	4	1 (23+)	
	Consolidation radiotherapy	5	2	1
	Pre-operatively in clinical PR	5	2 (31+, 40+)	
Total		38	13	9

*Clinical and radiological complete response. †Without a clinical and radiological complete response before surgery.

have achieved a CR on further CT and are thus still chemosensitive. In contrast, patients who have achieved a PR and are subjected to surgery only after protracted CT are generally operated on because of a lack of further response, i.e. the tumours are chemoresistant. The clinical implication of our results would be to favour early surgery if surgery is applied.

Cure after CT for advanced solid tumours is rare. In breast cancer, the rate of complete responders after CT for advanced disease was 8% in a recent extensive review [22]. However, even in selected series, less than 20% of these are alive at 5 years [23]. Our results on STS and previously published results suggest a different biology for STS [1, 2, 24]. The proportion of patients in continuous CR is higher, and some patients with metastatic disease can be cured by surgery. However, a significant number of the patients still relapse.

The latter observation raises the question of consolidation therapy in advanced STS. In addition to local consolidation therapy, some groups have advocated high-dose consolidation CT [25, 26]. Although the issue remains unresolved, by using previously described prognostic factors for CT response in advanced STS [27], and those described by us in patients rendered disease-free, selected patients could be offered dose-intensive CT with curative intent.

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