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Local Recurrences of Soft Tissue Sarcomas in Adults: a Retrospective Analysis of Prognostic Factors in 102 Cases After Surgery and Radiation Therapy

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Between 1974 and 1990, 102 adult patients (age 18–86 years) with the diagnosis of a soft tissue sarcoma (STS) were treated with photons and/or electrons in combination with surgery. The total doses in the initial treatment volume (second order target volume) was 40–50 Gy. For the coning down volume (first order target volume) the median total dose was 59 Gy (range 45–72 Gy). A total of 18% (18/102) local failures was observed. In multivariate analysis, prognostic factors for the occurrence of a local failure were identified as follows: treatment of a primary or recurrent STS ($P = 0.02$), total dose ($P = 0.025$) and tumour grade ($P = 0.05$). Mode of surgery, tumour size (trunk versus extremity), pre- or postoperative radiotherapy, combined chemotherapy and tumour size (T1 versus T2) had no significant impact on the local relapse-free survival. These data give further evidence that combined surgery and radiotherapy is an effective modality in treatment of soft tissue sarcomas.

Key words: soft tissue sarcoma, radiation therapy, surgery
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INTRODUCTION

SINCE SOFT tissue sarcomas have been widely considered as radioresistant, radical and often mutilating surgery was assumed to be the only curative treatment modality [1]. Until the early seventies, the overall survival for extremity soft tissue sarcomas was only 25–30%. Conservative surgery for limb preservation led to unacceptably high rates of local recurrences in the range of 50–90%. Therefore, amputation was generally accepted as the treatment of choice. It guaranteed high local control rates during the limited life expectancy of these patients [2].

After surgery alone, local relapse rates depend directly on the extension of the surgical procedure. A simple tumour excision or shelling-out resulted in local failure rates between 60 and 90%. A wide resection with safety margins of 2–3 cm led to local recurrences between 25 and 60%. Only radical surgery, like compartmental resection and amputation, yielded low local failures of 15–20% and 7–18%, respectively [1, 3–6].

The introduction of megavoltage therapy and improvements in the definition of the target volume, supported by modern diagnostic imaging as well as development of sophisticated techniques in surgery, led to increased local control probabilities and a high percentage of limb preservation in soft tissue sarcomas of the adults. Advances in pathological tumour grading and typing and in chemotherapy, including neoadjuvant combined schedules, have also resulted in an improvement of overall survival [7].

This study presents the results of a retrospective analysis of 102 patients treated with a combined surgical and radiotherapeutic approach.

PATIENTS AND MATERIALS

Between January 1974 and December 1990, 369 adult patients (age 18–86 years) were referred to the Department of Radiation Therapy with the diagnosis of a soft tissue sarcoma. Desmoid tumours, sometimes described as fibrosarcomas grade 1, were not included in this study. Since 1978, a cyclotron unit was installed at the department, and, between 1978 and 1983, the majority of the patients with the diagnosis of a soft tissue sarcoma were irradiated with neutrons without defined selection criteria, like grading or residual tumour. The results were reported by Schmitt and colleagues [8] and, therefore, 188 patients were excluded from this analysis. Another 79 patients were treated with palliative intention because of symptoms or distant metastases at the time of diagnosis and were also excluded. 102 patients were irradiated curatively with photons and/or electrons.

First- and second-order target volume represents initial tumour volume plus 2 and 5 cm of surrounding tissue, respectively. The second-order target volume included the scar completely. The predominant radiation technique was the use of parallel opposed fields; in several cases, wedge field and single portal techniques were carried out. The median dose in the initial treatment volume (second order target volume) was 46 Gy (range 40–56, $n = 51$). For the coning down volume or first order target volume, the median total dose was 59 Gy (range

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Table 1. Malignant soft tissue sarcomas: histological subtypes

	No. of patients
Liposarcoma	17
Fibrosarcoma	15
Malignant fibrous histiocytoma	13
Leiomyosarcoma	12
Neurofibrosarcoma	10
Synovial sarcoma	8
Rhabdomyosarcoma	6
Malignant haemangiopericytoma	4
Angiosarcoma	3
Alveolar soft part sarcoma	1
Unclassified sarcoma	13
Total	102

45–72). The fractionation was 5 × 2 Gy or 4 × 2.5 Gy weekly. In 11 cases, the fractionation was 3 × 3 Gy weekly for the first order target volume. Dose specification was defined according to the ICRU report no. 29 [9]. Five dose groups could be differentiated: <50, 50–<55, 55–<60, 60–<65 and ≥65 Gy, respectively. The numbers of patients were equally distributed to these dose groups.

The staging system referred to was first introduced by Russell and colleagues [10], and later established as UICC 1987 classification [11]. The tumour grading system is based on a combination of mitotic index, amount of necrosis, histological type, degree of cellularity and pleomorphism as proposed by Costa and co-workers [12].

The quantitative data of local control and disease-specific survival were analysed with the life table method according to Kaplan and Meier [13] with the BMDP statistic program [14]. Significance values were calculated according to Mantel–Cox. A multivariate proportional hazard (Cox) regression was performed with standard software for the selection of prognostic factors with impact on the local failure, distant metastases and disease-specific survival rates.

RESULTS

The patients (60 males, 42 females) had a median age of 51.5 years (range 18–86), the median follow up was 48.5 months.

The most common histological types were liposarcomas (17%), fibrosarcomas (15%) and malignant fibrous histiocytomas (13%) (Table 1). Of all tumours, 56% were localised at the extremities, the rest at the head and neck and trunk region (Table 2). Two-thirds of the tumours were diagnosed in locally advanced stages (Table 3).

Table 2. Malignant soft tissue sarcomas: tumour sites

	No. of patients
Head and neck	6
Trunk	26
Intra-abdominal/retroperitoneal	13
Upper extremity	24
Lower extremity	33
Total	102

Table 3. Malignant soft tissue sarcomas: stages

	No. of patients
I A	7
I B	3
II A	16
II B	23
III A	12
III B	35
IV A	6
Total	102

Biopsies and partial tumour resection or simple excision with macroscopic or microscopic tumour residual was carried out in 16 and 50% of all patients, respectively. The residual tumour volume after partial resection ranged from 1 to 60 cm^3. In 30%, a locally wide and in 5% a compartmental resection/amputation was performed (Table 4). Megavoltage radiation with ^{60}Co or 5.7–15 MeV photons was used in 77% of all patients. Photons of ^{137}Cs and electrons alone or in combination with photons were applied in 9, 15 and 21 patients, respectively. The total dose was 50–<60 Gy and ≥60 in 35 and 49% of the patients, respectively. Doses less than 50 Gy were applied in 16% because of preoperative radiation (n = 4), combination with chemotherapy (n = 3) and other dose limitations, e.g. intraabdominal or retroperitoneal tumour sites (n = 9).

Local recurrences

Local control was defined as lack of local or regional tumour regrowth after complete resection or partial remission/no change after incomplete resection. A total of 18% (18/102) local failures was observed. Of 18 local recurrences, 83% (15/18) occurred within the first 2 years. According to the tumour stages, 10% (1/10) of the local failures were observed in stage IA/B, 15% (6/39) in stage IIA/B, 19% (9/47) in stage IIIA/B and 33% (2/6) in stage IVA. The corresponding 5-year local relapse-free survival rates for stages I to IVA patients were 85.7, 85.1, 75.9 and 62.5%, respectively, and for grades 1, 2 and 3/4 tumours 87.5%, 85.1% and 73.7%, respectively. The tumour grading had a significant prognostic impact on the local control probability in multivariate analysis (Table 5).

Table 4. Malignant soft tissue sarcomas: mode of surgery surgical procedure-local failure relationship

	No. of patients	%
Biopsy	0/3	—
Subtotal resection (macroscopic tumour residual)	4/13	31
Simple excision (microscopic tumour residual)	12/51	23
Wide excision	2/30	7
Compartmental resection	0/2	—
Amputation	0/3	—
Total	18/102	18

Table 5. Malignant soft tissue sarcomas: results (P values) of multivariate analysis

	Local recurrences	Distant metastases	Disease-specific survival
Primary/recurrent treatment	0.02*	—	<0.01*
Total absorbed dose	0.025	—	0.13
Grading	0.05	<0.01	0.039
Mode of surgery	0.098	0.17	0.1
Tumour site (trunk vs. extremity)	0.11*	0.35*	<0.02*
Size (T1 vs. T2)	0.43	0.037	0.023
Pre/postoperative RT	0.48*	—	—
Combination of chemotherapy	0.97*	0.68*	—

* Two-sided *t*-test.

There was no significant difference between local control rates at 5 years for T1 (≤5 cm) and T2 (>5 cm) tumours (UICC classification of 1987) (Table 5). Radiation for primary tumours had a better prognosis than for recurrent sarcomas ($P = 0.02$) (Table 5), although the median size of primary tumours was larger (8 cm, range 1–21) compared with recurrent soft tissue sarcomas (4.5 cm, range 0.5–16) ($P = 0.002$, one-sided *t*-test). The local relapse-free 5-year survival was 94/91% for primary T1/T2 and only 61/55% for recurrent T1/T2 tumours, respectively ($P = 0.0002$) (Figure 1). Tumour size alone had no significant impact on the local relapse-free survival in each group.

No significant influence on local control rates was found according to the extent of the surgical procedure by multivariate analysis (Table 5). The 5-year local control rates were 66.5% (biopsy or partial resection), 73.6% (simple excision), 94.4% (wide excision) and 100% (compartmental resection or amputation). Since none of the 3 patients treated with biopsy and radiation therapy suffered a local failure, these cases are described in detail.

Patient 1 was a 26-year-old female with a high-grade malignant angiosarcoma located at the tonsillar fossa. The carotic arteria was surrounded by the tumour. Lateral opposed fields with ^{60}Co were given to a total dose of 50 Gy (4 × 2.5 Gy/week). Additionally, chemotherapy with doxorubicin, cyclophosphamide and vincristin was given because of the high risk situation (three courses pre-irradiation, two courses postirradiation). A minor response was observed without tumour progression after 90 months.

Patient 2 was a 86-year-old male with a grade 2 neurofibrosarcoma located at the lower right leg. Tumour extension was 5 cm in diameter and radiation therapy was carried out with a single portal electron beam to a total dose of 51 Gy (3 × 3 Gy/week). Complete remission was observed after 51 months, but the patient suffered an ulceration with chronic osteomyelitis, probably caused by the high single fractions.

Patient 3 was a 51-year-old male with an alveolar rhabdomyosarcoma grade 3 located at the paravertebral thoracal region with a maximum tumour extension of 12 cm. Six courses of chemotherapy were given, initially according to the CYVADIC scheme, leading to a partial remission. Radiation therapy was carried out ap-pa with ^{60}Co to a total dose of 42 Gy (5 × 2 Gy/week), and the patient is well with a tumour residual of 5 × 2 cm^2 after 88 months. No metastatic disease occurred in these 3 patients.

No difference in 5-year local relapse-free survival was observed after wide excision versus compartmental resection/amputation nor after simple versus subtotal resection, respectively. However, univariate analysis revealed a different prognosis for simple tumour excision versus wide excision in favour of the more extended surgical technique ($P = 0.02$) (Figure 2).

By multivariate analysis, the tumour site was only a significant prognostic factor for disease-specific survival ($P < 0.02$) (Table 5), but not for local relapse-free survival. By univariate analysis, the 5-year, local control rate was 86% for sarcomas of the extremities as compared to 71.3% for trunk sarcomas ($P = 0.04$).

Of the 18 local failures, 72% (13/18) occurred in the first order target volume (coning down volume). Of the local recurrences, 11% (2/18) were observed in the second order target volume (initial target volume) and 17% (3/18) outside the treatment volume (geographic miss). The median dose for infield relapses (first and second order target volume) was 50 Gy (range 45–64 Gy). The local failure rates decreased with increasing dose. In the dose range <50 Gy, between 50 and <65 Gy and

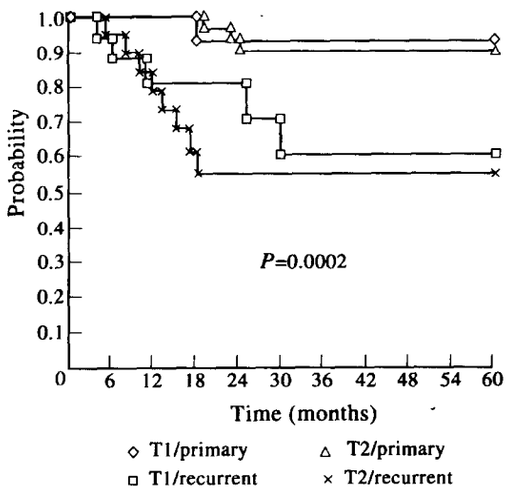

Figure 1. Local relapse-free survival: tumour size and treatment for primary/recurrent sarcoma.

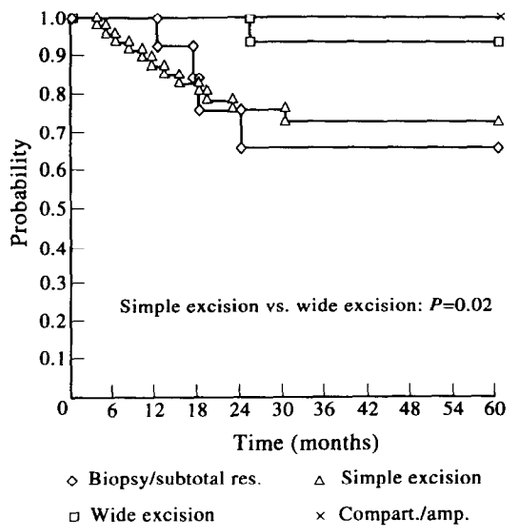

Figure 2. Local relapse-free survival: mode of surgery.

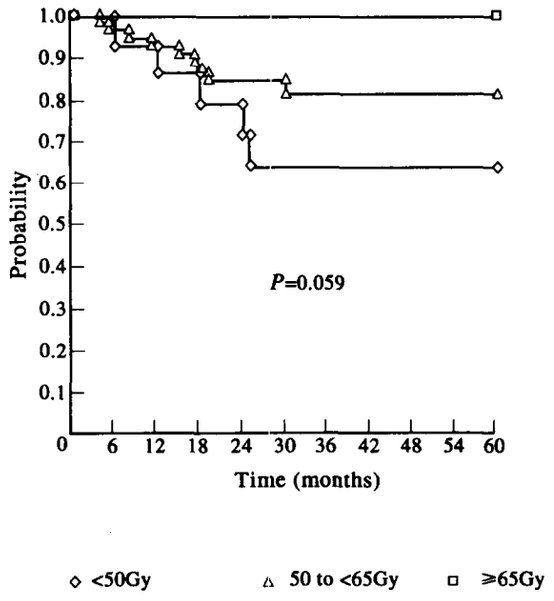

Figure 3. Local relapse-free survival: dose of the infield relapses.

≥65 Gy, 31% (5/16), 16% (10/63) and 0% (0/23) of the local relapses, respectively, were found. A trend towards better long-term local control (5 years) with higher doses was found with 65, 82.6 and 100% (P = 0.059) for all local recurrences (Figure 3). Investigating dose dependency, we excluded the three outfield recurrences and the two second order target volume recurrences because, in these cases, no correct dose description could be carried out. By multivariate analysis, decreasing dose was a significant prognostic factor for the occurrence of a local failure (P = 0.025) (Table 5).

Only 14 patients were additionally treated with chemotherapy (mainly the CYVADIC regimen). In this group of patients, no local recurrence was observed compared with 20% (18/88) without chemotherapy. By multivariate analysis, chemotherapy was not a prognostic indicator in terms of local relapse-free survival (Table 5).

Comparison of pre- and postoperative radiation therapy revealed no differences in local control probability. After preoperative radiation with 45 Gy (median, range 40–54), the local recurrence rate was 11% (1/9) versus 18% (17/93) in the postoperatively irradiated patient group (P = 0.48) (Table 5).

Distant metastases

The overall frequency of distant metastases was 20.6% (21/102). With respect to tumour grading, the rates of distant metastases increased from grade 1 to 2 to grade 3/4 from 0% (0/11) to 7.7% (3/39) to 34.6% (18/52), respectively. Thus, tumour grading was a major prognostic factor for the development of metastases, which could be substantiated by multivariate analysis (P < 0.01) (Table 5). The metastases-free survival rates at 5 years were 100% for grade 1, 87.7% for grade 2 and 58% for grade 3/4 tumours (P = 0.003).

Tumour size also had a prognostic impact on the development of distant metastases. Tumours of ≤5, >5–10, >10–15 and >15 cm in diameter showed increasing frequencies of metastases of 5.4% (2/37), 27.8% (10/36), 29.4% (5/17) and 33.3% (4/12), respectively (P = 0.04). In contrast to the UICC classification of 1987, the European Organization for Research and Treatment of Cancer (EORTC) suggested an 8-cm discrimination border as prognostically more significant in terms of distant metastases rates. An analysis according to a threshold size of 8 cm revealed a metastases rate of 11.5% (7/61) for up to 8 cm tumours and 34.1% (14/41) for larger than 8 cm tumours (P = 0.005). The corresponding rates according to the UICC classification were 5.4% (2/37) for T1 and 29.2% (19/65) for T2 tumours (P = 0.037) (Table 5).

Tumour site, mode of surgery and a combination with chemotherapy had no influence on the distant metastases rates (Table 5).

Survival

18 patients died of disease. By multivariate analysis, the following unfavourable prognostic factors were determined in terms of disease-specific survival: treatment of a recurrent tumour, sarcomas located at the trunk, tumour size greater than 5 cm and higher tumour grading (Table 5). The survival rates according to Kaplan and Meier at 5 and 10 years were identical with 100, 85.6 and 49.7% for grade 1, 2 and 3/4 sarcomas, respectively (P = 0.05). Mode of surgery and dose were not prognostic factors for survival (Table 5).

Side-effects

Severe side-effects were observed in 16% (16/102) of all patients. During the early treatment period of 1974 to 1982, the late morbidity rate was 22% (10/45). This was much higher compared with the period of 1983 to 1990 (10.5%, 6/57). Fibroses grade III (WHO score), lymphoedema and ulcerations, which required reconstructive surgery, occurred in 7, 4 and 2%, respectively. In 1 patient each, osteomyelitis, adhesion ileus and a contracture was seen. The ulcerations, contracture and osteomyelitis could be attributed, at least in part, to the use of high single fractions of 2.5–3.0 Gy, the relative high total dose levels of 50–73 Gy and single radiation portals with superficial overdosage during the early treatment period. The adhesive ileus occurred after 56 Gy/28 fractions through parallel opposed portals of 9 × 12.5 cm^2, and thus could hardly be related to the radiation alone. Eighty-two per cent (47/57) of the patients with soft tissue sarcomas of the extremities had no significant functional deficits.

DISCUSSION

In order to preserve function and to avoid amputation for soft tissue sarcomas of the extremities, mainly combined treatment modalities, consisting of surgery and postoperative radiation therapy, have been established. The extent of surgery in the presented series is a significant prognostic factor. Biopsies or partial tumour resections in combination with radiation therapy lead to local failure rates as high as 31% compared to 23% after simple excision and only 7% after wide excision. Results from similar studies broadly support these findings [3, 15, 16], indicating the necessity to reduce the tumour cell burden as far as possible by an adequate surgical procedure before radiation therapy. Therefore, wide excisions should be performed whenever possible without significant impairment of function.

The efficacy of radiation therapy is demonstrated by comparing the published results of combined modality treatments to surgery alone. With the same level of radical surgery, local control rates were much higher if radiation therapy was additionally used [1, 17, 18]. The only published prospective trial on 43 patients, which compares radical surgery (amputation) with wide tumour resection and additive radiation revealed no significant

differences in local control at 9 years follow-up ($P = 0.22$) [19]. In the presented study, local control after biopsy or partial resection combined with postoperative radiation reached 66%, probably caused by the small number of cases (especially three local controls out of three sarcomas following biopsy alone), but demonstrating that radiation therapy alone can achieve local control in a considerable proportion of macroscopic disease. This was also shown in the studies of McNeer and associates [20], Tepper and Suit [21], and Windeyer and colleagues [22] for treatment of moderately advanced sarcomas by radiation therapy alone.

The results of multivariate analysis of 'infield' recurrences showed a significant dependency on the dose. Above 65 Gy, no local recurrences were seen. This supports the hypothesis discussed by other authors, that a considerable proportion of soft tissue sarcomas must be regarded as radiosensitive [23]. Soft tissue sarcomas irradiated as monolayer or spheroid culture *in vitro* proved to be relatively radiation sensitive as compared to cultures from squamous cell carcinomas, breast cancers and gliomas [24–26]. The available evidence is incompatible with the older notion that soft tissue sarcomas are radioresistant. On the contrary, they appear to be more radiation sensitive than most other solid tumours. The reported poor results for radiation therapy alone in the treatment of locally advanced soft tissue sarcomas [21, 27] are likely to be a consequence of the often extremely large tumour burden compared to other solid tumours curable by radiation therapy alone, rather than the consequence of a low radiosensitivity of soft tissue sarcomas.

These findings are especially encouraging for the use of combined treatment modalities in the treatment of soft tissue sarcomas of the trunk, since surgery with sufficiently wide safety margins is frequently compromised by a considerable loss of function. The high local control rate of 70% at 5 years for soft tissue sarcomas of the trunk, although lower than those observed for the limb, confirms the efficacy of the combined approaches even for unfavourable tumour sites.

Size was not prognostically significant for local tumour control, whereas grade, total dose and surgical procedure were significant. This again emphasizes that appropriate surgery and sufficient doses of radiation are more important than the local extent of the lesion. Even large sarcomas can be managed without detectable loss of local control when proper treatment is offered.

The local control rates were significantly higher for primarily treated soft tissue sarcomas, although the median tumour size was larger (8 cm) in this group of patients compared with recurrent tumours (4.5 cm). This observation was also made by Avizonis and colleagues [28], Robinson and colleagues [29] and Gaynor and colleagues [30]. Specifically, they identified one or more local recurrences as an unfavourable prognostic factor for local tumour control. The reason for this inverse relationship could not be attributed to a topographic miss of the tumour, because 83.3% (15/18) of all local failures occurred inside the target volume. However, normal tissue after multiple tumour resections may be altered by bradytrophic scar formations and fibroses, resulting in a significant hypoxia, thus promoting radioresistance. This might explain that small recurrent soft tissue sarcomas had a worse prognosis than larger primary tumours.

Patients receiving chemotherapy exhibited no higher local control rates in multivariate analysis. Controversial observations were made in several randomised and non-randomised studies, testing the value of adjuvant chemotherapy [31, 32]. Rosenberg and associates [33] were the first to show, in a prospective clinical trial, the benefit of an adjuvant chemotherapy in terms of disease-free- and overall survival. Unfortunately, after 5 years, the survival advantage disappeared, whereas the benefit in the disease-free survival remained stable in this study. Although this benefit did not translate consistently into better survival, it could be exploited for further enhancement of local control in large unresectable sarcomas, especially of the trunk. Neoadjuvant chemotherapy in combination with radiation and surgery has not yet been tested in larger series, although it appears to be a promising approach for large unresectable soft tissue sarcomas.

Although advances in surgery and radiation therapy led to, on average, high local control rates, survival depends crucially on distant metastasis. Grade and tumour size were the only significant parameters for development of distant disease, whereas mode of surgery, tumour site and chemotherapy were non significant. Grading and tumour size as significant prognostic factors have been reported by several authors, and are undoubtfully of major importance for the development of distant metastases [30, 34, 35]. Gaynor defined, from multivariate analysis, that the combination of multiple factors with negative prognosis had a clear impact on the rate of distant metastases and the overall survival. These involved >5 cm high-grade tumours with deep infiltration. The metastases rate of these tumours were approximately 70% and the overall survival at 5 years only 23%.

Since most patients die of distant disease, adjuvant chemotherapy has been intensively tested in order to improve survival. In the presented series, chemotherapy was only given in a selected subgroup of high risk patients with undifferentiated or subtotally resected tumours. Therefore, a comparison between the high-risk group treated with additionally chemotherapy and the lower risk group for the assessment of potential survival benefit from chemotherapy is not possible. More than 10 larger randomised studies [31] have examined the value of adjuvant chemotherapy. Only four trials, three for soft tissue sarcomas of the extremities [33, 36, 37] and one for non-extremity sarcomas [38], have demonstrated a significant improvement of survival. The late onset of adjuvant treatment in these studies, usually after completion of radiation therapy, has been blamed for the overall disappointing results. Currently, strategies with an earlier onset of chemotherapy and a restriction to only high-grade tumours are under investigation, however, a benefit has not yet been proven.

As mentioned before, the most important factor influencing overall survival was the development of distant metastases. However, local tumour control was also a significant factor in the studies reported by Suit and Miralbell [39]. In our study, primary or recurrent treatment, tumour site, tumour size and grading had a significant influence on the survival rates. Abbas and associates [3] also identified tumour size, extension of tumour and histological type as significant prognostic factors, which was also supported by Potter and colleagues [16] and Pao and Pilepich [40].

If radiation therapy is used in combined treatment modalities to preserve function, severe side effects have to be kept as low as possible. The overall complication rates (grade 3) noted in the presented study was 16%. An analysis of the first treatment period during 1974 to 1982 compared with the years 1983 to 1990 showed a clearly higher rate of late radiation damage in the earlier period than later on. According to our data, the most important unfavourable factors for the development of late sequelae is the use of higher doses per fraction in a radiation

schedule, e.g. 4 × 2.5 Gy per week (boost series were sometimes given with 3 × 3 Gy per week). Single radiation portals and electrons for the whole treatment series also negatively influenced the late normal tissue results. Whereas two ulcerations, a contracture and an osteomyelitis could be attributed to these factors, the occurrence of a late adhesion ileus could not be explained by radiation factors.

One of the most sophisticated investigations assessing late effects of radiation in the treatment of sarcomas was published by Stinson and associates [41]. In this study, relatively high rates of side effects were observed after combined therapy of extremity soft tissue sarcomas. The incidence of fibroses (moderate or severe) was 57%, oedema (grade 3) 19% and chronic contractures 20%. However, looking at the functional integrity of the extremity, 84% of their patients and 82% of our patients had no significant functional deficits.

In summary, these data give further evidence that radiation therapy is an effective modality in the treatment of soft tissue sarcomas. The presented results and recently published clinical and experimental data indicate, in contradiction of older notions, that soft tissue sarcomas are relatively sensitive to radiation. Surgery should be performed with wide safety margins whenever possible, although close margins or even minimal residual disease is tolerable if mutilation or significant loss of function is otherwise at risk provided radiotherapy with doses above 60 Gy can be delivered, including a sufficient safety margin. Neoadjuvant chemotherapy in combination with radiation therapy and surgery should be tested in patients with locally advanced, unresectable sarcomas in order to improve local control and survival, and in patients with large high grade sarcomas with a substantial risk of distant metastases to improve survival. The rate of late effects can be minimised by using multiple ports, doses per fraction ≤2 Gy, and by avoiding electron beam treatments for the whole course of radiation therapy.

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Sudden Tumour Regression With Enhanced Natural Killer Cell Accumulation in a Patient With Stage IV Breast Cancer

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Spontaneous regression of advanced breast cancer is a rare phenomenon. Efforts have been made in order to explain it by means of immunological mechanisms. Corticosteroids have demonstrated important efficacy in the treatment of breast cancer. We present a patient with stage IV breast cancer in whom large tumour masses dramatically regressed during treatment with dexamethasone alone. In this patient, histological and hormonal findings, with results of analyses on surface and intracellular blood cells markers demonstrated significant redistribution of lymphocytes and accumulation of natural killer cells in tumour masses. It seems that dexamethasone has acted through the hypophyse against cancer.

Key words: spontaneous regression, breast cancer, dexamethasone, surface and intracellular markers, natural killer cells

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INTRODUCTION

SPONTANEOUS REGRESSION in metastatic cancer is a very rare event reported in the literature as case reports. Its occurrence has been estimated to be less than 1 in 100 000 cases [1]. Although this phenomenon has remained an enigma, efforts to explain its mechanism and characteristic features have focused on non-specific stimulation of the immune system [2].

Endocrine therapy has been found to be an important therapeutic option in the treatment of breast cancer. It has, for instance, been observed that after removal of the ovaries in premenopausal women the disease has regressed [3]. Also, similar responses following adrenalectomy or hypophysectomy in postmenopausal women have been observed [4]. Furthermore, other hormones such as progestins, androgens and corticosteroids have also demonstrated antitumour effect [5–8].

Corticosteroids have been used either as primary treatment or in combination with other therapies in the treatment of breast cancer. When prednisolone alone has been given, an objective response rate of no more than 14% has been achieved [5]. When corticosteroids were combined with other endocrine treatments after mastectomy and radiotherapy in early breast cancer, significant reductions in local recurrence rates and prolonged survival rates were achieved [9].

In advanced cases, dexamethasone has been found to be useful in relieving acute symptoms caused by brain metastases or by tumours compressing the spinal cord. Dexamethasone successfully prevents adverse effects such as tissue oedema caused by radiotherapy.

The disadvantages of dexamethasone and other corticosteroids are their various side-effects, such as hypertension, peptic

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