Soft tissue sarcomas:

long-term aspects of combined modality treatment

Rijks*universiteit* Groningen

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Chapter 1

Introduction and aim of the thesis

Soft tissue sarcomas:
long-term aspects of combined modality treatment

Introduction and aim of the study

Soft tissue sarcomas are aggressive tumors that arise from mesenchymal tissues. The incidence is low and accounts for 3.6 per 100,000 per annum.[1] Mortality, on the other hand, is high; the average five-year survival rate is only 60%.[2,3] Although fewer than 1% of the malignant tumors in adults are soft tissue sarcomas, they are nevertheless responsible for 2% of all deaths caused by cancer.[1] The prognosis of poorly differentiated soft tissue sarcomas is in particular caused by frequent hematogenic metastases (30-40%) and not so much by locoregional recurrence (10-15%).[3]

In the past three decades, the combined modality treatment of soft tissue sarcomas has advanced considerably. Although surgery is the cornerstone of the sarcoma treatment, there is overwhelming evidence supporting adjuvant radiotherapy after narrow surgical excision of the tumor. On the other hand, there is no indication for (neo) adjuvant chemotherapy after surgical treatment of soft tissue sarcomas, with the exception of rhabdomyosarcoma, extraosseous Ewing's sarcoma / primitive neuroectodermal tumor (PNET), and extraosseous osteosarcoma.[3] Combined treatments have mainly contributed to improved locoregional tumor control and only to a lesser degree to survival. Conversely, the 'aggressive' surgical approach in the treatment of metastasized tumors has contributed to improved disease-free and overall survival.[3]

Surgery is the 'central discipline' in the multimodality treatment of the disease – which involves various disciplines including pathology, radiotherapy, medical oncology, rehabilitation medicine, genetics, and psychology.

Isolated limb perfusion (ILP) is a technique introduced in 1958 by Creech and colleagues.[4] Their aim with this regional cancer treatment was the local administration of a cytostatic agent at the highest dosage without introducing systemic side effects. The extracorporeal circulation system used was similar to the one employed in open heart surgery. The technique was first applied to patients with in-transit metastases of melanoma of the lower extremities who refused amputation. The cytostatic agent administered was melphalan. In 1961, the technique of isolated limb perfusion was introduced in the Netherlands by Zwaveling in Leiden. In 1964, Oldhoff and Schraffordt Koops successfully initiated the Groningen perfusion program in the Algemeen Provinciaal Stads en Academisch Ziekenhuis (APSAZ).[5]

The cancer centers in Rotterdam and Amsterdam soon followed. Hyperthermia was introduced in 1967 in the perfusion treatment by Cavalière.[6] At present, mild hyperthermia (39-40 °C) is widely used, since this causes less local toxicity than higher temperatures.[7] As the search for the optimum perfusion technique continued, other cytostatics such as dacarbazine (DTIC), adriamycin and cisplatinum were studied, but melphalan remained the most used and effective drug.[8] The early 1990s witnessed a breakthrough in this regional cancer treatment, when Lejeune and colleagues added Tumor Necrosis Factor alpha (TNFα) to melphalan as a perfusion agent in the isolated regional perfusion for locoregional advanced soft tissue sarcomas and melanomas.[9,10] This resulted in a high local response rate with acceptable locoregional and systemic toxicity and a high percentage of limb salvage. The results of the first multicenter trial of limb perfusion in the limb saving treatment of primarily irresectable soft tissue sarcomas of the extremities were reported in 1996. Medical centers in Lausanne, Amsterdam, Rotterdam, Berlin, Brussels, Tel Aviv, and Groningen participated in this trial. Use was made of a high dose of TNFα (3 or 4 mg) in combination with interferon gamma and melphalan. The technique allowed the salvage of the affected extremity in 84% of the cases.[10] The perfused tumors were extremely large, 20 cm on average. Resection was performed several weeks post perfusion. In 87% of the cases, a major tumor response was documented. It was then clear that ILP in combination with TNFα , interferon gamma and melphalan was safe and highly effective, and constituted a breakthrough in the treatment of locally advanced soft tissue sarcomas of the extremities.

Another aspect of the multimodality treatment is radiotherapy. In the early 1980s, Rosenberg was the first to show the value of adjuvant radiotherapy in the limb-saving treatment of sarcomas.[11] Yang and colleagues updated the study several years later, with a median follow-up of almost ten years. They found a significant decrease in locoregional recurrence after radiation, without affecting survival.[12] Unfortunately, adjuvant radiation in combination with surgery also has side effects, for instance greater stiffness and increased edema of the involved extremity.

Locally advanced soft tissue sarcomas of the extremities can be treated with isolated regional limb perfusion with high doses of cytostatics, followed by tumor resection, as outlined before. In general, these tumors can only be resected marginally. Adjuvant local radiotherapy might be indicated to increase the local tumor control rate.[13]

Radiation can also induce sarcomas, which are then called radiation-induced sarcomas. Radiation-induced sarcomas are biologically aggressive tumors.[14] These arise from a previous radiation site, usually after a period of around 10 years. In the past radiation was sometimes

used in the treatment of 'benign' tumors, but radiation sarcoma can also occur after radiotherapy for malignant tumors.

To what extent will a second primary tumor develop in patients treated for a sarcoma? A second primary tumor may develop both before and after the onset of the sarcoma. To what extent do other primary tumors affect the prognosis of primary non-resectable soft tissue sarcomas of the extremities that are being treated with isolated regional perfusion?

The limb-saving treatment of a 'primarily' non-resectable soft tissue sarcoma with isolated limb perfusion followed by delayed surgical resection and adjuvant radiation is highly intensive and may last for several months. What influence does such an intensive treatment have on the patient's quality of life?

The aim of this thesis is to gain insight into the various long-term aspects of the combined modality treatment of patients with sarcomas that emphasizes isolated limb perfusion, surgical resection and radiation therapy.

The aims of the thesis:
- Treatment options for radiation-induced sarcoma: what are the challenges in the treatment?
- What is the role of surgery in the multidisciplinary treatment of soft tissue sarcoma?
- During which periods, and through what causes, are patients at risk of losing an extremity with a locally advanced soft tissue sarcoma treated with isolated limb perfusion, surgery and radiotherapy?
- Is adjuvant radiotherapy indicated after isolated limb perfusion and resection for patients with a primarily irresectable soft tissue sarcoma in an extremity?
- What are the potentials of biological imaging in the prediction of long-term outcome of patients with a soft tissue sarcoma of the extremity treated with isolated limb perfusion?
- Do STS perfusion survivors differ from the general population in terms of quality of life and do post-traumatic stress symptoms occur that should be taken into account in the longer term?
- Is the incidence of other primary tumors increased in patients with locally advanced soft tissue sarcoma of the extremities and does this affect long-term survival?

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Chapter 2

Radiation-induced sarcoma: a challenge for the surgeon

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Chapter 2

Abstract

Background: Treatment of a radiation-induced sarcoma (RIS) remains an unsolved problem. To provide more insight into the disease process, its characteristics, outcome, and potential outcome determinants were defined.

Methods: Between 1978 and 2003, 27 patients - 20 females (74%) and seven males (26%) with a median age 44 years (range, 1-73 years) at the time of diagnosis of the primary - developed an RIS after a median interval of 8 years (range, 3-41 years). The histology of the RIS was 10 (37%) undifferentiated high-grade pleomorphic sarcomas, 7 (26%) angiosarcomas, 6 (22%) fibrosarcomas, 2 (7%) osteosarcomas, 1 (4%) pleomorphic rhabdomyosarcoma, and 1 (4%) pleomorphic leiomyosarcoma. Surgical resection was performed in 21 patients: 13 (62%) R0 (microscopically radical), 4 (19%) R1 (microscopically irradical), 2 (9.5%) R2 (macroscopically irradical), and 2 (9.5%) RX (unknown radicality). Six (22%) patients underwent no resection.

Results: The 5-year disease-free survival and overall survival rates were 27% and 30 %, respectively. The local failure rate after R0 resection was 54%. The distant failure rate for the entire group was 41%. Patients with an R0 resection had a significantly better survival rate (P<0.05) than patients with an R1, R2, or no resection.

Conclusions: RISs are aggressive malignancies with a high tendency for local recurrence and distant metastases. Previously applied treatment often hampers adequate resection. Therefore, radical surgical resection is the only chance to improve disease-free and overall survival, but it may also have a palliative role. Still, the overall prognosis remains poor.

Introduction

In The Netherlands, 69,000 new cases of cancer are diagnosed yearly, and 38,000 patients die from their malignancy.[1] The incidence of solid tumors is still increasing. Disease-free (DFS) and overall survival (OS) are increasing because of (1) progress in better preoperative staging by various imaging techniques, such as spiral computed tomography (CT), magnetic resonance imaging (MRI), ultrasound, and positron emission tomography, and (2) appropriate surgery in combination with adjuvant therapies such as chemotherapy, radiotherapy, and hormonal therapy. Therefore, cancer may now be viewed as a "chronic disease".

Because more cancer patients survive, there is an increased risk of a new malignancy or a secondary treatment-induced malignancy. The number of patients with a second malignancy reaches 10% in The Netherlands.[1] Types of treatment-induced malignancies may be distinguished between chemotherapy-induced and radiation-induced malignancies.

Surgical experience with radiation induced sarcoma (RIS) is limited, and the results of treatment of RIS are discouraging. With improved preoperative imaging techniques, including CT and MRI, and the increased experience in sarcoma surgery, along with plastic surgical reconstructions, more radical surgical operations are now possible. Whether this aggressive surgical approach has influenced the oncological outcome is yet to be determined. Therefore, a retrospective study and review of the literature was performed to investigate the short- and long-term outcome of surgical treatment of RIS.

Patients and methods

From 1978 to 2003, 27 patients - 20 females (74%) and 7 males (26%) with a median age 52 years (range, 20-83 years) - were diagnosed with RIS at the Groningen University Medical Centre. Patient records were retrieved from the sarcoma database of the Division of Surgical Oncology. To fill the required criteria, all patients must have received previous radiotherapy for a malignant or benign disease. The criteria required to fulfill the definition of RIS were: (1) different histopathologic features between primary lesion (i.e., the indication for initial radiotherapy) and the sarcoma; (2) sarcoma arising within the irradiated field; and (3) a latency period of at least 3 years.[2] The latency period was calculated from initial radiotherapy until the diagnosis of RIS. Sarcomas were reviewed on hematoxylin and eosin-stained sections with additional immunohistochemistry to evaluate tumor differentiation. They were classified with the most recent World Health Organization classification and graded according

to the French grading system.[3,4] Additional data reviewed were patient demographics, delivered radiation dose, latency period, treatment of RIS, local and distant failure, and survival after diagnosis of RIS.

Treatment for RIS in the absence of distant metastases was surgery. In cases of distant metastases, chemotherapy was considered. In cases of local failure after primary treatment for RIS, re-excision was preferred. Radiotherapy and chemotherapy were given only in select cases. Patient characteristics, tumor data, and treatment schedules are listed in Tables 1 to 3. DFS and OS was determined, and a comparison of survival after identifiable resection techniques was performed by using Kaplan-Meier survival curves with log-rank test. The achieved results were discussed, and the RIS literature was reviewed.

Table 1 Development of distant metastases in patients with RIS

Variable		*n*	**%**
Total number of patients		11	41
Anatomic site	Lung	8	73
	Liver	3	27
	Lymph node	4	36
	Bone	3	27
	Other soft tissue	3	27

RIS, radiation-induced sarcoma

Results

The median age of the 27 patients at the time of diagnosis of the primary lesion was 44 years (range, 1-73 years). The median latency period between radiotherapy for the primary lesion and RIS was 8 years (range, 3-41 years). The median patient age at diagnosis of RIS was 52 years (range, 20-83 years). The total delivered irradiation dose could be exactly retrieved in 24 cases (89%), and the median radiation dose was 50 Gy (range, 16-70 Gy). All three cases in which information on the irradiation dose was not retrievable involved a prolonged latency period after radiotherapy (>18 years). Eleven patients received adjuvant systemic therapy for the primary tumor: seven patients were treated with cytotoxic agents, and five received hormonal therapy. The shortest latency period was observed for a patient with a fibrosarcoma 40 months after irradiation with a dose of 60 Gy for a squamous cell carcinoma of the floor of

Table 2 Primary lesion and presentation of RIS

Primary lesion				Treatment				Presentation of RIS				
Patient no.	Age (y)	Sex	PTL	Surgery	Chemo	Hormonal	Radiation dose (Gy)	Histology	Location	Latency period (y)	Year of diagnosis	Distant disease
1	47	F	BC	BCT	No	No	50	Ang	Breast	7	1995	No
2	46	F	BC	BCT	No	No	70	Ang	Breast	4	1995	No
3	72	F	BC	BCT	No	No	70	Ang	Breast	7	1996	No
4	64	F	BC	BCT	No	No	50	Ang	Breast	4	1997	No
5	72	F	BC	BCT	No	No	70	Ang	Breast	6	1997	No
6	63	F	BC	BCT	No	Yes	70	Ang	Breast	4	1999	No
7	68	F	BC	BCT	No	Yes	70	Ang	Breast	7	2001	No
8	45	F	BC	BCT	Yes	Yes	70	UHGPS	Breast	5	1992	No
9	42	F	BC	BCT	Yes	No	70	UHGPS	Breast	7	2003	No
10	37	F	BC	AMP	Yes	Yes	40	UHGPS	Trunk	16	1997	No
11	44	F	BC	AMP	No	No	50	UHGPS	Axilla	4	1991	No
12	64	F	BC	AMP	No	No	50	UHGPS	Trunk	15	2000	Yes
13	54	F	BC	AMP	No	Yes	50	UHGPS	Trunk	9	2003	No
14	45	F	BC	AMP	No	No	67	Fib	Trunk	4	1995	Yes
15	21	F	H	None	No	No	40	UHGPS	Trunk	20	1994	No
16	28	F	H	None	Yes	No	40	UHGPS	Mediastinum	5	1998	No
17	16	M	H	None	No	No	60	Fib	Trunk	4	1991	No
18	18	F	H	None	Yes	No	?	Os	Trunk	32	1987	No
19	47	M	RC	APR	Yes	No	50	Fib	Pelvis	9	2002	No
20	68	M	SQ	RES	No	No	60	Fib	Head / Neck	3	1998	No
21	25	M	MA	RES	Yes	No	45	Fib	Head / Neck	36	2000	No
22	35	M	MY	None	No	No	16	Fib	Upper leg	17	1978	No
23	43	F	EN	HYS	No	No	?	UHGPS	Pelvis	40	1996	No
24	30	F	VC	None	No	No	30	UHGPS	Pelvis	41	1998	Yes
25	50	F	EN	HYS	No	No	?	PL	Pelvis	18	1980	No
26	1	M	RE	EN	No	No	45	PR	Head / Neck	21	2000	No
27	11	M	RH	LR	Yes	No	55	Os	Head / Neck	21	1997	No

RIS, radiation-induced sarcoma; F, female; M, male; PTL, primary tumor + localization; BC, breast carcinoma; BCT, breast-conserving therapy; Ang, angiosarcoma; UHGPS, undifferentiated high-grade pleomorphic sarcoma; AMP, amputation; Fib, fibrosarcoma; H, Hodgkin disease; Os, osteosarcoma; RC, rectal carcinoma; APR, abdominoperineal resection; SQ, squamous carcinoma, floor of mouth; RES, resection; MA, maxilla osteosarcoma; MY, myositis ossificans, thigh; EC, endometrial carcinoma; HYS, hysterectomy; VC, vulvar carcinoma; PL, pleomorphic leiomyosarcoma; RE, retinoblastoma, left and right eyes; EN, enucleation; PR, pleomorphic rhabdomyosarcoma; RH, rhabdomyosarcoma, soft palate; LR, local resection.

the mouth. The longest latency period was seen for a patient who developed a undifferentiated high-grade pleomorphic sarcoma 41 years after a squamous cell carcinoma of the vulva (radiation dose, 30 Gy).

Histology of the RIS was 10 (37%) undifferentiated high-grade pleomorphic sarcomas, 7 (26%) angiosarcomas, 6 (22%) fibrosarcomas, 2 (7%) osteosarcomas, 1 (4%) pleomorphic rhabdomyosarcoma, and 1 (4%) pleomorphic leiomyosarcoma. All patients were staged locally and distantly; three (11%) RIS patients had metastatic disease when the RIS was diagnosed.

There were 24 patients (89%) without distant metastases at the time of diagnosis of RIS. Thirteen underwent an R0 resection with median survival of 29 month (range, 5-307 months); seven of these patients developed a local failure (54%). In patients who did not develop a local failure after R0 resection, the median survival was 40.5 month (range 6-88 months). In patients who developed a local recurrence, the median survival was 20 month(range, 5-307 months). Four patients underwent an R1 resection with a survival ranging from 5 to 138 months. Two patients underwent an R2 resection and survived 4 and 14 months. Three patients underwent no resection (two of the three received palliative chemotherapy) and survived 7, 7, and 5 months. In two patients, the radicality of the first resection was not retrievable. In one patient, a local failure was diagnosed after 13 months, and an R0 resection was performed, after which the patient survived 149 months with no evidence of disease. The other patient died after 24 months. The three patients with distant metastases at the time of diagnosis of RIS survived 1, 6, and 15 months; the one who survived 15 months received palliative chemotherapy. During follow-up, eight patients (33%) developed metastases at single and multiple locations after a median of 8 months (range, 2-60 months). Details about the presentation of RIS, treatment, follow-up, and sites of metastases are listed in Tables 1-3.

DFS and OS were both 44% at 2 years and were 27% and 30%, respectively, at 5 years (Figs. 1 and 2). DFS was calculated by using the time period, in the group of patients with primarily no evidence of metastatic disease (n = 24), from establishment of the RIS diagnosis until their first recurrence (Fig. 1). The median OS after diagnosis of RIS was 15 months (range, 1-307 months). At the time of this review, nine patients were still alive with no evidence of disease , with a median follow-up of 66 months (range, 5-307 months). Seventeen patients (63%) died of their RIS, with a median survival of 14 months (range, 1-138 months). In one patient, the final cause of death was not retrievable (24 months). The local failure rate after R0 resection was 54%, and the overall distant failure rate was 41%.

Table 3 Treatment and follow up for radiation-induced sarcoma

Patient no.	Primary treatment sarcoma			Local failure			Distant failure (mo + location)	Survival (mo)
	Surgery (radicality)	Systematic therapy	Radiotherapy		Treatment			
				Appearance (mo)	Surgical	Other		
1	Excision (R0)	No	No	Yes (6)	No	RT:50Gy	No	DOD 13
2	Excision (R1)	No	No	Yes (91)	Yes:R0	No	No	NED 96
3	Amputation (R0)	No	No	Yes -LF1 (42) -LF2 (56)	Yes -LF1: R0 -LF2: no	No	No	DOD 60
4	Amputation (R0)	No	No	Yes -LF1 (2) -LF2 (6) -LF3 (12) -LF4 (24)	Yes: -LF1: R0 -LF2: R0 -LF3: R0 -LF4: R1	Yes: -LF1: - -LF2: - -LF3: - -LF4:90 Gy*	No	DOD 38
5	Amputation (R0)	No	No	Yes (2)	No	No	Yes (4 lung, mediastinal, spleen, liver, adrenal, and bone)	DOD 5
6	Amputation (R0)	No	No	No	No	No	Yes (19 bone 31 abdominal lymph nodes)	DOD 40
7	Amputation (RX)	No	No	?	?	?	?	DOUR 24
8	Amputation (R2)	No	No	NA	NA	NA	Yes (2 liver)	DOD 4
9	Resection (R1)	No	No	NA	NA	NA	No	NED 5
10	Excision: (R0)	No	No	Yes -LF1 (7) -LF2 (10) -LF3 (12)	Yes -LF1:R0 -LF2:R0	No	Yes (12 Lung + soft tissue metastases)	DOD 20
11	Excision (RX)	No	No	Yes (13)	Yes:R0	No	No	NED 149
12	No	No	No	NA	NA	NA	Yes (at diagnosis; lung)	DOD 1
13	Excision R1 Re-excision: no tumor (R0)	No	No	No	No	No	No	NED 6
14	No	Yes	No	NA	NA	NA	Yes (at diagnosis; lung, bone, lymph-nodes, mediastinal)	DOD 15
15	Excision (R0)	No	No	Yes (5)	Yes	Yes 60 Gy	Yes (8 lymph node and lung-metastases)	DOD 15
16	No	Yes	No	NA	NA	NA	No	DOD 7
17	R2	No	Yes	NA	NA	NA	Yes (6 sarcomatosis peritonei)	DOD 14
18	Excision (R1)	No	Yes 56 Gy	NA	NA	NA	Yes (X lung, lymph node, liver)	DOD 24
19	Exenteration (R0)	No	No	No	No	No	No	NED 16
20	No	No	No	NA	NA	NA	No	DOD 7
21	Resection (R0)	No	No	No	No	No	No	NED 41
22	Excision (R0)	No	No	Yes (7)	Yes: R0	Yes: chemo	No	NED 307
23	Hemipel-vectomy (R0)	No	No	No	No	No	No	NED 88
24	No	No	No	NA	NA	NA	Yes (at diagnosis; lung)	DOD 6
25	Excision (R1)	No	No	NA	NA	NA	Yes (60 lung)	DOD 138
26	No	Yes	No	NA	NA	NA	No	DOD 5
27	Resection (R0)	No	No	No	No	No	No	NED 66

RT, radiotherapy; DOD, dead of disease; NED, no evidence of disease (calculated from the moment radiation-induced sarcoma was diagnosed); LF, local failure; DOUR, dead of unknown reason; NA, not applicable; Chemo, chemotherapy; R1, macroscopically irradical; R2, X, not retrievable, microscopically radical; R0, microscopically radical.

Figure 1 Percentage of disease-free survival (DFS) during follow-up of patients with primarily no evidence of metastatic disease (n = 24).
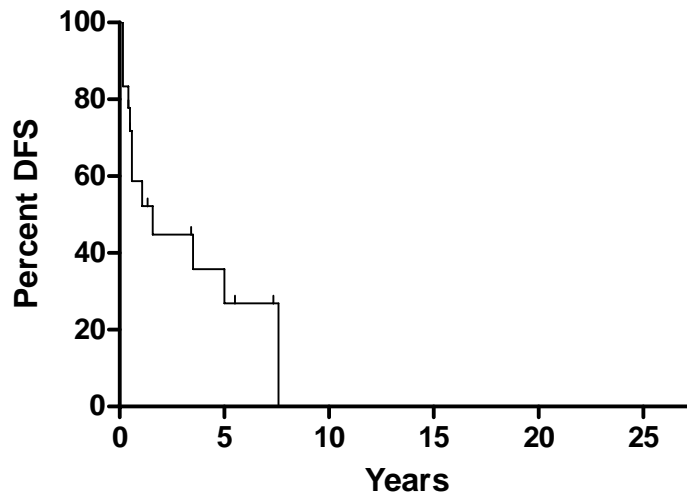
Figure 2 Percentage of overall survival during follow-up after radiation-induced sarcoma diagnosis of all patients (n = 27).
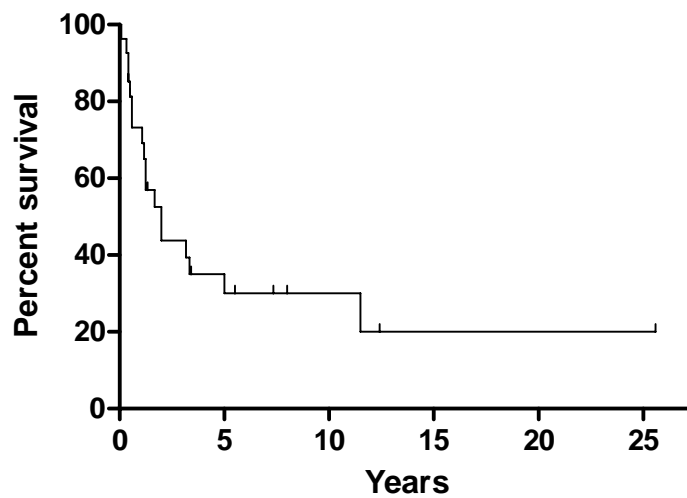
Patients who received an R0 resection had a significantly better survival than the patients without metastasis in whom only an R1 or R2 resection, or no resection, could be performed. (log-rank, 4.96; df =1, P = .026; relative risk, 8.6; 95% confidence interval, 8.2-8.9; nonradical resection group compared with the radical surgery group. (Fig. 3).

Figure 3 Radicality of resection and survival: a radical resection differs significantly (P = .026) from nonradical and no resection with respect to survival.
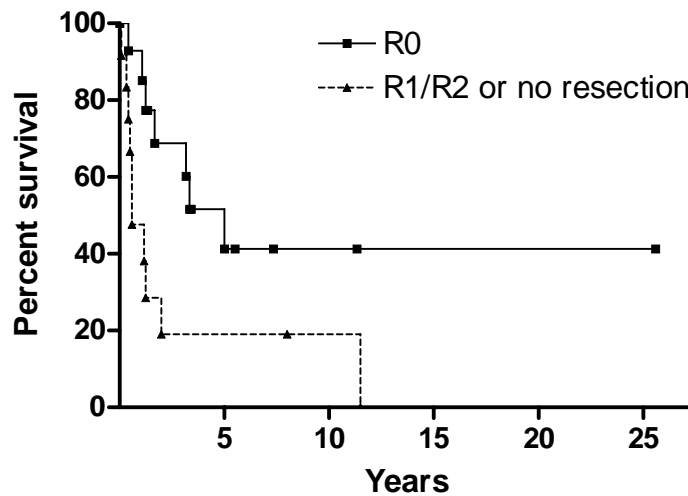
Discussion

The first RIS was described at the beginning of the 20th century, and the earliest comprehensive RIS study was by Cahan et al.[5] Since 1940, 16 studies have been published. The number of patients in the studies, latency period, survival time, number of patients dead of disease, 2- and 5-year DFS and OS, and percentage of local and distal failure are listed in Table 4.

Until now, RISs have been considered extremely rare, and the current incidence varies from .03 to .22%.[6-12] In this study, the median latency period between irradiation and diagnosis of RIS was 8 years, which is comparable to the roughly 10 years (range, 3 months to 50 years) in the published literature.[8,13-15] The development of RIS may be attributed to ionizing radiation, which may induce genomic instability.[16] The precise radiation-induced genetic mechanism is still unknown. The prognosis of RIS is poor and worse than the usual prognosis of a sarcoma.[11,17-23] The question of whether RIS of the soft tissue differs from RIS of the bone with respect to local growth pattern and metastatic potential remains unanswered.

We noticed an increased number of patients diagnosed with RIS over the last three decades (Fig. 4). The increase in RIS of soft tissue might be the result of an intensive cancer treatment combining (extensive) surgery with adjuvant or neoadjuvant chemotherapy and preoperative or postoperative radiation. Some chemotherapeutic agents, such as doxorubicin, might have the potential for causing radiation sensitization. A definitive relationship between latency period and radiation dose, with or without chemotherapy, as well as age at the time of RIS

diagnosis and survival, could be defined neither in this study nor in the available literature.[2,17,24,25]

Figure 4 Number of patients diagnosed with radiation-induced sarcoma over the last three decades.
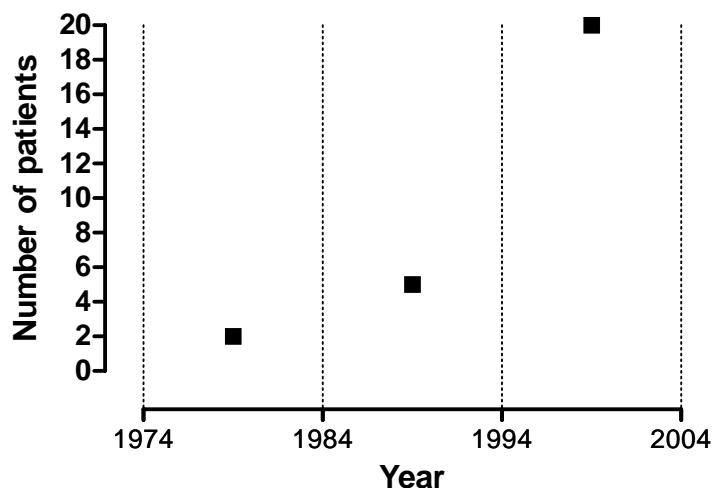
Another problem might be the difficult detection of a second malignancy within a previously irradiated area, causing a delay in diagnosis and, therefore, a more advanced stage of disease. When alterations occur within a previously irradiated area, the diagnosis of RIS must always be considered.[26]

Because of previously performed (intensive) treatment, RIS requires a so-called "tailored" cancer treatment with an optimal tumor staging, as well as information with respect to the local growth pattern of the RIS and involvement of the surrounding tissues. The current new radiodiagnostic imaging modalities of MRI and spiral CT might provide adequate information, and three-dimensional reconstruction enables excellent preoperative planning of the extent of the surgical resection and the need for reconstruction with plastic surgery, with the ultimate goal of achieving an R0 resection with low morbidity, e.g., primary wound healing. Adequate radical resection is sometimes difficult or even impossible. The reason for this is often the anatomical site of the tumor or extensive ingrowth in surrounding tissue. The important role of surgery has been underlined by many authors and confirmed in this study.[2,11,20,24] The group of patients with an R0 resection had a significantly longer median survival time, even in the group with local failure.

Table 4 Studies analyzing RIS

Study	Year of publication	No. of patients in study	Period of sarcoma diagnosis	Reason for radiation (n)	Latency, y, mean (range)	RIS of bone or ST	Mean survival (mo)	No. of patients DOD	2-y DFS (%)	2 y OS (%)	5 y DFS (%)	5 y OS (%)	LF (%)	DF (%)
Cahan[5]	1948	11	1940-1948	Irradiated bone	11 (6-22)	RIS of bone	24	7 (64%)	27	55	9	18		45
Arlen[31]	1971	50	1931-1970	Benign osseous lesions (35), soft part and visceral tumors (15)	9 (4-30)	RIS of bone		32 (64%)						
Weatherby[32]	1981	78	1930-1980	Benign and malignant osseous (45) and nonosseous lesions (33)	14.3	RIS of bone								
Huvos[14]	1985	66	1921-1983	Benign and malignant osseous and nonosseous lesions	12.8 (3.5-33)[α]	RIS of bone and ST	12	35 (53%) (+15 [23%])[β]				17		
Davidson[33]	1986	20	1954-1985	Malignant (15) and benign soft tissue disease (5)	16.8 (7-45)	RIS of ST					14			
Laskin[34]	1988	53	1954-1986	Breast, ovaria, testes, head, neck carcinomas and others	10 (2-40)	RIS of bone and ST		27 (51%) (+6 [11%])[β]		32				
Wiklund[17]	1991	33	1953-1988	Breast, female reproductive organs, childhood carcinomas	13.2 (3.4-22.8)	RIS of bone and ST	21.5	22 (67%) (+4 [12%])[β]		45		29		45
Brady[24]	1992	160	1943-1989	Breast, cervical carcinomas, lymphoma	10.3 (1.4-43)	RIS of bone and ST								
Mark[11]	1994	37	1987-1993	Breast carcinoma, Hodgkin's, retinoblastoma, acne, menorrhagia, and others	12 (0.25-50)	RIS of bone and ST					19			
Bloechle[26]	1995	11	1975-1993	Breast, cervical carcinoma, hemangioma, Hodgkin's, and others	15.8 (4-31)	RIS of ST		1 (9%) (+2 [18%])[β]			73			9
Strobbe[35]	1998	21	1987-1995	Exclusively breast carcinoma after BCT	6 (2.5-9)	Only angiosarcoma	24	7 (33%)	35	72				
Buis[23]	1998	42	1978-1996	Lymphoma and breast carcinoma	11 (2-37)	RIS of bone and ST					45	30		
Kirova[29]	1998	8	1983-1997	Breast carcinoma	10.3 (5-18)	RIS of bone and ST	24	6 (75%)						
Lagrange[2]	2000	80	1975-1995	Breast, cervical carcinoma, non-Hodgkin's, benign lesions, or other tumors	12 (3-64)	RIS of bone and ST	23	46 (57.5%)	54	69	32	39		
Blanchard[36]	2002	34	1975-2001	Exclusively breast carcinoma	12.5 (3-31)	RIS of bone and ST	33.1	22 (65%)					68	
Current Study	2004	27	1978-2003	Breast carcinoma (14), Hodgkin's (4), other soft tissue malignancies (7), osteosarcoma (1), myositis ossificans (1)	8 (3-41)	RIS of bone and ST	20	17 (63%) (+1 [4%])[β]	44	44	27	30	54	41

RIS, radiation-induced sarcoma; ST, soft tissue; DOD, dead of disease; DFS, disease-free survival; OS, overall survival; LF, local failure DF, distant failure; BCT, breast-conserving therapy.

α Median

β Dead of other or unknown causes

The prognosis for sarcoma patients after radical re-excision for a primary nonradical excision has been shown not to differ from that of patients after primary radical excision.[27] This study was too small to prove this for RIS as well.

The results of this study are similar to those in the review by Robinson and associates[25], which reported a median survival of 12 months with a survival rate at 2 years of 22% and at 5 years of 11%. Unfortunately, the overall results have only slightly improved since the 1940s, and most published studies provide only limited data; this hampers further insight into the described diseases. None of the reviewed studies showed a significantly beneficial effect of adjuvant chemotherapy, irradiation, or both.[14,28,29] This is not surprising, because effective reirradiation is impossible, and chemotherapy may have a role. However, the numbers of patients described in the subsequent studies were small. Recently, there has been evidence that most RISs show an extensive expression of the KIT protein. Although treatment with the KIT inhibitor imatinib might be considered for patients in whom radical surgery is not amenable, it is not likely this will be the final solution to this problem.[30]

As in previous reports, we found a wide variety in histopathological subtypes of RIS. With the increasing incidence of angiosarcoma of the breast after breast conserving therapy (BCT), this subgroup needs to be explored much more extensively. A cooperative international study is required to acquire more fundamental insight in this treatment-induced disease. If more information is obtained about these kinds of secondary malignancies and the patients who get them, prevention measures might be undertaken in patients who are candidates for BCT. Will the reduction of doses of intensity-modulated radiotherapy indeed fulfill the new hope in eradicating cancer, or will it, conversely, increase the risk of RIS in the surrounding healthy tissue?

In summary, RISs are aggressive malignancies with a high tendency for local recurrence and distant metastases. Previously delivered treatment hampers adequate resection and administration of radiotherapy. Therefore, RISs are a challenge for the surgical oncologist. A radical surgical approach is the only chance to improve DFS and OS, might offer palliation, and it is the only prognostic factor for long-term survival. Because the prognosis is poor, the options of new treatment strategies are being studied. More insight into the disease, especially angiosarcoma of the breast after BCT, might soon provide preventive measures in patients undergoing extensive combined cancer treatment.

Chapter 2

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Chapter 3

Role of surgery as primary treatment and as intervention in the multidisciplinary treatment of soft tissue sarcoma

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Chapter 3

Introduction

Soft tissue sarcomas (STS) are a rare group of cancers compromising ~ 1% of all malignancies. There has been a slight increase in incidence, and half of STS patients are over the age of 65 years.[1] The pathogenesis of most STS remains unknown. Genetic, environmental and immunological factors have been identified as risk factors. It is likely that the cause of STS is multifactorial.

STS may arise in any part of the body, predominantly in the extremities (45%; lower limb 29%, upper limb 16%), trunk (25%), head and neck (13%), and retroperitoneum (8%) [1]. The tumors are classified according to the World Health Organization Classification of Tumors, dividing STS into 19 categories and >50 subtypes. Some chromosomal abnormalities are unique to certain classes of STS. Classification and subtype prediction of adult STS such as synovial sarcoma, round-cell/myxoid liposarcoma, clear-cell sarcoma and gastrointestinal stromal tumors (GIST) recently became possible by functional genomics.[2]

The tumors are graded according to the French grading system, distinguishing low-, intermediate- and high-grade STS, and staged according to the American Joint Committee on Cancer staging system. More practical for daily clinical practice is to distinguish between low- and high-grade, and between tumor sizes <5, 5–10 and >10 cm, as suggested by Brennan.[3]

Insight into the disease and progress achieved with surgical technical skills and combined modality approach in these tumors have reduced the local failure rate and improved limb salvage figures. One-third to half of patients diagnosed with STS will die of their disease because of either metastatic disease or currently infrequently diagnosed locally recurrent disease.[4] The high-risk patient with extremity STS for distant metastasis and local recurrence is the patient with a large (T2), high-grade, deep lesion. The role of primary surgery as primary treatment and intervention in multidisciplinary sarcoma treatment is reviewed.

Landmarks in surgical treatment

In the past century, STS were simply resected, with local failure rates of 60% to 80%. There was a major movement in the late 1940's and early 1950's towards more radical surgical procedures, such as amputation or radical local resection, as first-line treatment. A sharp increase in local control was encountered. Up to the end of the 1970's, half of all limb sarcomas were treated by amputation. Although the local failure rate achieved with this surgical approach was only 10% to 15%, a large proportion of patients (30% to 40%) continued to die of metastatic disease.[4]

There have been several breakthroughs in the diagnostic imaging and treatment of STS during the last 30 years, resulting in improved limb salvage and survival rate. In the 1970's, computed tomography (CT) became available for local staging of STS and staging for distant metastases. Two decades later, magnetic resonance imaging (MRI), with or without contrastenhanced sequences, replaced CT in the local staging. Recently, spiral CT was introduced, providing the surgeon with optimal three-dimensional images and further facilitating preoperative treatment planning. Computer-assisted navigation systems have become available, which are extremely useful in the intra-operative treatment planning of sarcomas located in or near the pelvic girdle or vertebral column. Improvements in the radiodiagnostic of STS had a major impact in staging and in the planning of surgical treatment.[5]

In local treatment of STS there have been three successive major breakthroughs. In the 1970's, Simon and Enneking[6] developed the concept of compartment excision. At the same time, Rosenberg et al.[7] investigated the role of adjuvant radiation in the local treatment of limb sarcoma, showing no difference in local control and survival in patients treated with amputation compared with patients who received a limbsaving procedure. Compartment excision, in the meantime, has been replaced by wide local excision, but 5% to 10% of limb sarcomas still require an amputation. The third breakthrough was in the early 1990's, with the introduction of isolated limb perfusion (ILP) with tumor necrosis factor-α (TNF-α) by Lejeune in the treatment of primarily unresectable STS of the limb.[8]

Surgical resection of metastatic disease, by example isolated lung metastases, improved the disease-free and overall survival of patients.[9] The most recent breakthrough in sarcoma treatment was the introduction of the drug targeting therapy with imatinib in the treatment of disseminated gastrointestinal stromal tumors.[10] The role of (interval) surgery within drug targeting therapy is currently being explored.[11]

Surgical approach

The surgical approach in STS is determined by several factors: tumor location, size of tumor, depth of invasion (superficial or deep), involvement of nearby structures, and possibility of primary wound closure and/or plastic surgery reconstruction. Beside these factors, patient performance and stage of disease are additional important factors in the surgical decision process. Although a large proportion of patients receive combined modality treatment, patients with localized disease can be treated with surgery alone. However, precise clinical pathological criteria for selecting patients for unimodality therapy are currently lacking.

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Operative procedures in sarcoma surgery have been described excellently by Malawer and Sugarbaker.[12]

Biopsy

What kind of biopsy is appropriate in the diagnostic process and treatment of a patient with a soft tissue mass? After taking medical history and performing physical examination, the tumor is first locally staged with MRI or CT scan before any biopsy.[5] Positron emission tomography might allow differentiation between a benign and malignant tumor.[13] Based on the results of the imaging techniques, whether the appropriate biopsy technique is incisional, excisional, core-needle biopsy (CNB) or fine needle aspiration (FNA) is discussed.

The diagnostic accuracy of a CNB in referral centers is equivalent to incisional biopsies, although it may be difficult to differentiate a low-grade malignancy from a benign tumor mass.[14] In the event that a diagnosis is not clarified by CNB, additional CNB samples can be obtained without compromising the option to proceed with an incisional biopsy. An open biopsy ensures sufficient tissue for extensive immunohistochemistry and molecular (cyto)genetic techniques, especially in patients for whom neo-adjuvant treatment is foreseen. FNA and CNB are useful in the diagnostic process of a local recurrence or metastatic disease.

Careful attention should be paid to the biopsy site and the prevention of ecchymosis, e.g. tumor cell contamination. An inappropriately planned or poorly performed biopsy might seriously compromise subsequent surgical resection and even necessitate amputation. Therefore, core-needle and open biopsies should be carefully planned, and performed at the sarcoma center where the definitive surgery is to be undertaken. Surgical biopsy tracks are excised routinely with the tumor specimen at the time of the definitive resection of the tumor.

Whoops approach

Sarcomas are still diagnosed after an unplanned excision, the so-called 'whoops approach'. The pathology report will describe an R1 (microscopically involved margin) or R2 (macroscopically involved margin) resection requiring further therapy. If further surgery may render a patient disease-free (R0 resection) or an R2 might become an R1 resection, reresection is essential. If this aggressive surgical policy is applied, these patients are not apparently at risk for a worse outcome as compared with patients primarily referred to a multidisciplinary sarcoma unit.[15] The study from the Memorial Sloan-Kettering Cancer Center (MSKCC) even suggests that patients undergoing two operations (excision followed

by second re-excision) have improved survival compared with patients treated with a single definitive operation.

Local resection

In the late 1970s, compartment excision was advocated, while today the consensus is that in sarcoma surgery, a wide local resection, R0 resection with a 2 cm margin, is an adequate resection. In the majority of sarcoma resections, a 2 cm margin is impossible to achieve due to anatomical structures, and an R1 resection is the best achievable resection margin. R2 resections should be avoided. Adjuvant radiation after R1 resection improves the local control rate (see also radiotherapy and chemotherapy below). Positive microscopic resection margins significantly decrease the local recurrence-free survival rate and independently predict distant recurrence-free survival and disease-specific survival rates in STS treatment.[16] If local resection of a sarcoma of the limb is impossible, amputation or disarticulation of the involved limb should be performed to render the patient disease-free. Sometimes extensive ablative surgical resections are required.

Surgical treatment of retroperitoneal STS is a challenge for the surgical oncologist, although the majority of these tumors are unresectable. Only radical tumor resection, often with resection of nearby organs, can render a patient disease-free.[17] The surgical margins are always minimal and the local failure rate is high, especially in high-grade tumors.[18] Palliative surgical procedures may be performed to address symptoms (intestinal obstruction, bleeding). Chemotherapy is ineffective, post-operative radiotherapy may cause radiation enteritis and preoperative radiotherapy is hardly used. Drug targeting therapy with imatinib changed the prognosis of GIST.

Ablative surgical procedures

Forequarter amputation

Sarcomas of the shoulder girdle are frequently large and deepseated at initial presentation, and difficult to manage. For a small group of patients, a forequarter (interscapulothoracic) amputation is the only treatment option, and in a few cases a Tikhoff–Lindberg procedure, which allows for preservation of the limb, is feasible. On the other hand, for some patients an extensive resection with a part of the thoracic wall is necessary to achieve free surgical margins. Interthoracoscapular amputation is one of the most major ablative surgical procedures, which can be performed with curative or palliative intent, with minimal treatment-related morbidity. The prognosis does not differ from STS in general.[19,20]

Hindquarter amputation

The majority of STS of the upper thigh and buttock can potentially be treated with local excision, preserving the limb. For a few sarcomas of the lower limb or buttock region, a curative or palliative hindquarter amputation is unavoidable. The prognosis of these sarcomas after curative surgical treatment is not different from sarcomas in general. Wound healing disturbances are a major problem in the treatment of sarcomas in this anatomical region.[21]

Buttockectomy

Locally advanced soft tissue tumors of the buttock region represent a group of tumors with specific difficulties common to pelvic tumors, often large and deeply attached at initial presentation, and in the past treated with a hemipelvectomy. The majority of patients might now be treated with a complete *en bloc* resection of the gluteus muscles.[22] This procedure can be converted into an anterior hemipelvectomy if the tumor penetrates the deep margin of the muscle or infiltrates the bone. Involvement of the sciatic nerve is currently not longer an indication for a hemipelvectomy, since resection of the sciatic nerve is well tolerated, requiring only a brace.[23]

Hind foot amputation

Less than 10% of lower extremity sarcomas arise in the foot. In this location, limb-saving surgery is seldom possible and below-knee amputation is indicated. For selected tumors located at the forefoot, different hindfoot amputations are available, being excellent alternatives to a below-knee amputation.[24]

Interval surgery

Interval surgery is defined as a surgical procedure followed by induction treatment with chemotherapy and/or radiation for a solid tumor followed by surgery. The goal of the combined treatment strategy in STS is to improve the limb salvage rate, local tumor control and/or survival. Interval surgery is applied in the treatment of bone sarcomas, extra-osseous Ewing's sarcoma, primitive neuroectodermal tumor and rhabdomyosarcoma. There is a limited experience with interval surgery for STS with isolated limb perfusion, neo-adjuvant chemotherapy, intra-arterial chemotherapy and preoperative irradiation.

Isolated limb perfusion

In the first trial of ILP for STS, Krementz[24a] showed an early response rate of 83% after melphalan; however, complete regression of the tumors was rarely seen. The results achieved with ILP were not better than for surgery and adjuvant radiation therapy.[25] Other perfusion agents were investigated. Doxorubicin and cisplatin were also ineffective, while doxorubicin combined with melphalan was too toxic.[26-28] The resurrection of interest in the ILP technique came with the introduction of tumor necrosis factor (TNF)-α and melphalan into the perfusion of primarily unresectable STS of the limb [8]. After a so-called TNF perfusion, a remarkable shrinkage of the tumor was encountered within 6–12 weeks, and unresectable sarcomas became resectable.

A large European study proved the ILP concept in the limbsalvage procedures for unresectable STS with TNF-α and melphalan. The objective response rate was 76%. A limb salvage rate of 71% was achieved, with minimal treatment-related morbidity.[8] An independent review committee considered that 80% of all enrolled patients in this study met the criteria for irresectability.[29] Further analysis showed that ILP patients survived as long as matched controlled conventionally treated patients.[29] Since the resection margins in these tumors are minimal and viable tumor cells are often encountered at the periphery of the tumor, radiation is indicated to ensure local tumor control. Adjuvant radiation is well tolerated after ILP and extensive surgical resection.[30] TNF perfusion has now been used for over a decade, and in surviving patients the long-term treatment-related morbidity necessitating amputation is low.[31] The outcome of the ILP procedure in 'elderly' sarcoma patients is in general not different from in 'younger' sarcoma patients.[32] Perfusions in elderly limb sarcoma patients, on the other hand, sometimes cannot be performed due to atherosclerotic changes in the main arteries and/or severe comorbidity.

Why do all perfused sarcomas not respond to a TNF-α ILP? Multidrug resistance (MDR) is a major issue in chemotherapy treatment. Two groups investigated the expression of MDR in patients undergoing TNF perfusion treatment and showed that temperature and drugs were unable to induce MDR-positive sarcomas.[33,34] This is an important finding, since systemic doxorubicin-based polychemotherapy is currently being investigated in STS patients after TNF perfusion as an adjunct within the European Organization for Research and Treatment of Cancer (EORTC) trial 62931.

ILP with TNF-α provides the ability to avoid amputations and further increase the preservation of functional limbs, and is currently available in over 30 centers in Europe. In 2002, a total of 350 TNF perfusions were performed.

Neo-adjuvant chemotherapy

The idea behind neo-adjuvant chemotherapy for locally advanced STS is: (i) tumor cytoreduction to render local surgery less extensive; (ii) early treatment of occult metastatic disease; and (iii) *in vivo* evaluation of the tumor's chemosensitivity. The EORTC performed a randomized phase II trial with doxorubicin 50 mg/m^2 and ifosfamide 5 g/m^2 versus local therapy alone. Owing to slow accrual, the trial was not extended to a phase III trial. There was no difference in the 5-year survival rate: 64% in the no-chemotherapy arm versus 65% for the control arm, and no conclusions could be drawn from the trial.[35] The trial showed no increase in surgical morbidity or improved local control. Based on the meta-analysis study, as well as recent data from Italy, there is still interest in the use of preoperative chemotherapy in the treatment of locally advanced STS.[36,37] The question is whether surgeons and their patients are willing to participate in such a trial.

Drug targeting therapy

Complete surgical resection is the most important prognostic factor for patients with GIST. Local recurrences and metastatic disease are frequently encountered after surgery for GIST. Recently, a breakthrough in the treatment of disseminated GIST was observed with the introduction of imatinib. The preliminary results are impressive. The role of surgery is currently unknown for patients treated for metastatic GIST, as well as for patients who are unresectable and receive induction imatinib therapy. It is clear that in the near future, the role of surgery in locally advanced and metastatic GIST, as well as the role of imatinib, will be defined.[11]

Intra-arterial chemotherapy

The idea behind the intra-arterial chemotherapy was the 'first pass through effect' of the cytostatic agent. In the late 1970's, Eilber et al.[38] developed, for locally advanced limb sarcoma, a 3-day regimen of continuously intra-arterial doxorubicin with preoperative high-dose fractionation radiation schedules of different dose levels. The initial results in the early 1980's were so promising that the treatment was adopted by the Groningen University Hospital. The treatment was indeed effective, but the treatment-related morbidity was too high. Severe long-term treatment-related morbidity was encountered; 60% of the survivors developed serious functional problems varying from fibrosis to pathological stress fractures and invalidating neuropathy.[39] Since 1975, 753 patients have been treated at the University of

California at Los Angeles for a primary or recurrent sarcoma of the limb; 498 patients received neo-adjuvant therapy with intra-arterial doxorubicin and different radiation dose schedules. The study showed only a benefit of neo-adjuvant treatment in patients with recurrent sarcomas. Three-quarters of all recurrences were diagnosed within 36 months. When a local recurrence occurred, an amputation was unavoidable in 38% of cases.[38] Intra-arterial chemotherapy has no advantage over systemic drug delivery, and doxorubicin acts in this treatment mainly as a radiation sensitizer.

Preoperative radiation therapy

External beam radiotherapy delivered either pre- or postoperatively is highly effective in preventing local recurrences in patients who have a high risk for local failure, without any significant change in overall survival.[40] Adjuvant radiation is mostly used after marginal resection of STS, with a substantial treatment-related morbidity, especially after extensive surgery, such as reduced limb strength, range of motion, fibrosis and edema. Locally advanced sarcomas might be treated with preoperative radiotherapy. A retrospective non-randomized comparison of pre- versus post-operative radiotherapy from the MD Anderson Cancer Center suggested that local control might be improved for patients with measurable disease treated with preoperative radiation.[41] A randomized trial of pre- versus post-operative radiotherapy in STS of the limb showed that preoperative radiotherapy was associated with a significant increase in wound healing complications, and did not warrant the further use of preoperative radiation in STS.[42] In contrast, preoperative radiotherapy is well accepted in the treatment of retroperitoneal sarcoma, to improve the local control rate while reducing the radiation induced morbidity, and sophisticated treatment schedules in which preoperative radiotherapy is combined with doxorubicin and intraoperative radiotherapy are promising for the surgical oncologist and radiation oncologist.[43] To further optimize the effectiveness of radiation treatment in locally advanced sarcoma, molecular target agents are currently being developed for cytoprotective or cytotoxic pathways, and clinical trials are already under way.[44]

Surgery for recurrent disease

Local recurrence

The most significant independent factor for recurrence is surgical margin, followed by deep tumor location and tumor grade.[16] Local control after inadequate resection or recurrent

sarcoma is equal to that of primary sarcomas, if negative margins can be obtained by surgery.[15]

Metastasectomy

Approximately 30% to 40% of patients with high-grade sarcomas develop hematogenous metastases, predominantly to the lungs. Less than 3% of STS patients develop lymphogenic metastases. Patients with clear cell sarcoma, embryonal rhandomyosarcoma, epitheloid sarcoma and angiosarcoma are especially at risk, and the incidence in these tumors might be as high as 20%.[1] Although the lungs might be the primary site for distant failures in three-quarters of patients, other sites of metastasis include the skin and soft tissues of the head and neck, trunk, and extremities. The median survival after the diagnosis of metastatic disease from primary extremity sarcoma is ~ 1 year, with no difference between pulmonary and non-pulmonary metastases.[45]

Pulmonary metastases from STS are in general diagnosed with conventional X-rays and further staged with CT. If resection of all metastatic disease seems possible, a unilateral, bilateral or median sternotomy is advised. Approximately 60% to 80% of these patients might be rendered disease-free after surgical resection of the lung metastases, with a 5-year survival ranging from 20% to 40%. Long-term survival is possible in selected patients, but is exceedingly rare [46]. The EORTC experience showed a 3-year survival rate of 54% among patients undergoing complete resection of metastatic disease confined to the lungs, comparable to the MSKCC experience, with a 3-year actuarial survival of 46%.[47] Despite successful metastasectomies, a large proportion of patients will recur in one or both lungs. A second or even a third thoracotomy might be considered to render the patients disease-free.[48] Lymphogenic metastases are treated with a radical lymphadenectomy with a 5-year survival rate of >30%. Soft tissue masses are generally easy to resect, and resection might improve local control and quality of life. The only curative treatment option for metastatic disease is surgery, which can be performed with minimal treatment-related morbidity and mortality.

Surgery for complications

The risk for complications is related to the extent of surgery, the overall and local condition of the sarcoma patient and the eventually applied adjuvant treatment. Two different complications might be distinguished: short- and long-term. The short-term complications are mainly wound infections and wound healing disturbances, and may cause delay in adjuvant treatment when indicated. The long-term complications are treatment-related and are mainly

caused by radiation treatment. Complications are frequently seen after extensive surgery, especially fibrosis. Plastic surgery reconstruction should be used liberally in sarcoma surgery. The management of late (wound) complications requires much surgical expertise, and adequate treatment is seldom possible.

Plastic surgery reconstruction

The tactical and technical surgical parameters in sarcoma surgery are well defined in order to diminish the complication rates during tumor biopsy and definite resection. Reconstructive plastic surgery procedures by tissue transfer and microvascular surgical techniques play a key role in coverage of major defects and prevention of wound healing problems, and should be used more liberally; prevention is better than cure.

Conclusions

During the last two decades, considerable progress has been made in the diagnostic imaging of STS and use of combined modality treatment strategies. The extent of local resection and role of adjuvant radiation treatment are well defined. Preoperative radiation treatment in locally advanced STS has several advantages, but increased risk for wound complications has hampered further implementation. The optimal sequence of radiation and surgery remains complex. The reintroduction of ILP with TNF-a and melphalan was a breakthrough in limb salvage for primarily unresectable STS. The ILP technique is complex, and is only available in a few cancer centers in Europe. In the combined modality treatment, surgery is still the cornerstone of successful STS treatment. Further research in STS with new experimental approaches in multimodality treatment strategies with new chemotherapeutic agents and drug targeting therapies are under way, and may change the role of primary surgery to interval surgery in the future. Considering the increased insights in the tumor biology of STS and the improved surgical techniques, combined with intensive adjuvant treatment strategies, attention should be paid now to minimizing long-term treatment-related complications, as well as quality of life issues in these cancer survivors.

Chapter 3

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Chapter 4

Isolated limb perfusion with TNF and Melphalan for locally advanced soft tissue sarcoma: three time periods at risk for amputation

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Chapter 4

Abstract

Background: The aim of this study was to investigate the long-term limb salvage rate and overall survival after isolated limb perfusion (ILP) with Tumor Necrosis Factor alpha (TNF) and melphalan for locally advanced soft tissue sarcoma (STS).

Methods: From 1991-2003, 73 patients (36 male, 37 female, median age 54 (range 14 – 80) years) years with biopsy proven STS underwent 77 perfusions followed by delayed surgical resection, with or without adjuvant radiation. Limb salvage and overall survival curves were calculated using the Kaplan-Meier method.

Results: A total of 21 amputations (28%) were performed. Overall 1, 5 and 10 years limb salvage was 80.1 ± 4.8, $68.2 \pm 6.5\%$ and $60.6 \pm 9.2\%$ respectively. Three time episodes were at risk for amputation. The first period was within 1½ year after perfusion mainly due to massive necrosis of the tumor and overlying skin resulting in a soft tissue deficit or recurrent disease (n=17). The second time period was within 5 years with 2 amputations performed for late local recurrence. The third episode occurred ten years after perfusion, 2 amputations performed for critical leg ischemia. Another two patients developed a pathological fracture of the femur due to radiation osteonecrosis. These 4 patients received adjuvant radiotherapy. Overall 1, 5 and 10 years survival was $82.9 \pm 9.2\%$, $58.7 \pm 13.1\%$ and $42.5 \pm 18.2\%$ respectively.

Conclusions: ILP with TNF and melphalan followed by delayed surgical resection and adjuvant radiation treatment is an effective limb salvage treatment regimen for locally advanced STS. However, we observed late morbidity with 2 amputations performed for critical leg ischemia and 2 pathological fractures of the femur in patients receiving adjuvant radiotherapy.

Introduction

Limb salvage in patients with locally advanced extremity soft tissue sarcomas (STS) continues to be a challenge. Survival in these patients is determined by the development of distant metastases and is not improved with the amputation of the affected limb.[1,2] Besides amputation, an extensive surgical procedure followed by radiation therapy is a treatment option.[3] Rosenberg et al. showed the same disease free and overall survival as amputation in the early eighties with this treatment regimen.[1] Preoperative therapies to improve limb salvage rates have been propagated. Suit et al. reported already in 1981 on the use of preoperative radiation therapy.[4] Eilber et al. combined preoperative (intra-arterial or systemic) chemotherapy and radiation therapy to improve resectability rates.[2,5] In a randomized trial O'Sullivan et al. reported a greater risk of wound complications in the preoperative radiotherapy group compared with the postoperative radiotherapy group.[6] The use of brachytherapy may also improve local control and avoid amputation.[7] The current treatment strategy of high grade limb sarcomas is wide local resection with the goal to achieve a R0 resection with a 2 cm margin. In case the margin is less than 2 cm, or a R1 resection (microscopically involved margin), adjuvant radiation therapy with 50-70 Gy is indicated to reduce the risk of local failure.[3] The question whether radiotherapy should be given preoperative or postoperative is still unanswered.[6]

Another strategy for limb salvage in locally advanced extremity STS is to perform an isolated limb perfusion (ILP) with cystostatic agents. Originally developed for the treatment of melanoma of the limb in 1957, the procedure was also applied in the treatment of STS of the limb. In their first experience, Krementz et al. showed an early response rate with melphalan alone of 83%, however complete regression of the tumor was hardly seen.[8] Other perfusions agents in the treatment of limb STS were therefore investigated. Rossi claimed efficacy of doxorubicin, while another study proved that doxorubicin alone was ineffective and combined with melphalan too toxic.[9,10] Cisplatin showed also to be less effective than melphalan in the limb perfusion setting of sarcomas and carboplatin too neurotoxic.[11,12,13]

With the addition of Tumor Necrosis Factor alpha (TNF) to the perfusion circuit, Lejeune et al. made a step forward in the treatment of locally advanced extremity soft tissue sarcoma (STS).[14] A large European multi-center study proved the ILP concept in the limb salvage procedures for locally advanced STS with TNF and melphalan. The objective response rate was 75% and a limb salvage rate of 82% was achieved with a minimal treatment related morbidity.[15] Since 1991, patients with locally advanced STS of the limbs, have been treated at

the University Medical Center Groningen by ILP with TNF, melphalan with or without interferon gamma (IFN) as perfusion agents, followed by delayed surgical excision and postoperative radiation therapy if a marginal resection or non radical resection was performed. Recently we encountered long-term local morbidity and therefore the aim of the present study was to analyze the limb salvage rate and survival in patients with locally advanced STS of the extremities that were treated in our center and to report the late effects of this treatment modality.

Patients and methods

Patient Characteristics

From the time period 1991-2003, 73 patients with soft tissue sarcoma of the extremity underwent 77 perfusions with a combination of TNF and melphalan, with (19) or without IFN (58). Thirty-six males and 37 females, with a median age of 54 (range 14 - 80) years were treated. Tumors were considered unresectable because of size, their multicentricity in the limb, or fixation to the neurovascular bundle and or bone and therefore amputation was the only alternative treatment option. Perfusion was performed at the iliac level in 32 cases (42%), at the popliteal level in 23 cases (30%), at the femoral and axillary level in each 11 cases (14%). There were 60 primary (82%) and 13 recurrent (18%) sarcomas. Sixty two sarcomas were located in the leg (85%) and 11 in the arm (15%). All patients were treated after informed consent was obtained according to the institutional guidelines.

Nineteen different histological types of STS were distinguished. The pathological grade of the tumor was scored following the criteria of Coindre et al. as well as the stage of the tumor according to the American Joint Committee on Cancer (AJCC)[16] (Table 1).[17] Median tumor size was 16.2 (range 8.3 – 23) cm. In case of multifocal disease, the largest diameter was used.

Perfusion technique

The perfusion technique employed at the University Medical Center Groningen is based on the technique developed by Creech et al.[18]and described elsewhere.[19] The major modifications during the last thirty years were the use of modern thermal blankets, improvement in leakage monitoring, the introduction of a membrane oxygenator and heat exchanger, to ensure an

optimal perfusion at 39-40°C. Since an extensive wash out procedure with 6 L of saline is used systemic inflammatory response syndrome (SIRS) is hardly seen.[20] Postoperatively patients can be monitored on the recovery ward instead of the intensive care unit.

Assessment of Tumor Response, tumor remnant and follow-up

Responses were assessed by standardized World Health Organization (WHO) criteria and based on physical examination, and or MRI/CT investigations.[21] Complete response (CR) was defined as the disappearance of all measurable disease in the limb for longer than 4 weeks, partial response (PR) as regression of the tumor size by greater than 50% for longer than 4 weeks, no change (NC) as regression of less than 50% of the tumor in the limb or progression of less than 25% for longer than 4 weeks.

Resection of the tumor remnants was performed between 2 – 15 weeks after perfusion (median 8 weeks). After resection, response was also made on pathological examination. The tumor remnants were measured in three dimensions and the percentage of necrosis estimated in relation to the complete tumor volume. Representative tumor sections were taken, encompassing macroscopically different tumor areas, including necrosis. As a general rule, one section per centimeter largest diameter with a minimum of three was taken. Based on an integration of gross and microscopic findings, a final estimate of the percentages of viable and necrotic or regressive tumor was made.

Excision margins were also evaluated on pathological examination and classified as radical when the resection margins were free of tumor cells (complete resection; R0), or as R1 when resection margins were microscopically involved or as R2 when resection margins were macroscopically positive involved. Postoperative radiotherapy (60 - 70 Gy) was considered indicated in case of <95% necrosis on pathological examination of the tumor or with marginal or microscopically positive resection margins. All patients were followed after perfusion treatment in a standardized protocol. Median follow-up was 27 (range 2 – 138) months.

Statistical Analysis

Survival and limb salvage curves were calculated according to the Kaplan-Meier method and Log-rank test.[22] Values of P ≤ 0.05 were considered to be statistically significant. Graph Pad Prism® version 2.0 for Windows statistical software was used.

Results

Tumor response

A clinical complete response was observed after 19 ILP's (25%), a PR after 53 ILP's (69%) and NC after 5 ILP's (6%) local progression was never observed. Resection of the remnant tumor was performed in 68 patients (93%). The pathological response is illustrated in Figure 1. After 17 ILP's (23%) no viable tumor cells were found on pathological examination. In 29 ILP's (37%) 90% or more necrosis was found on pathological examination. Adding both groups together a good response to ILP was found in 60% of the patients. In 17 ILP's (22%) an intermediate response was found on pathological examination (necrosis 50-80%). After 8 ILP's (10%) less than 20% of necrosis or no necrosis was found on pathological examination. In 5 patients (7%) tumor response was not assessed because of progression of distant metastases in 4 patients and a local recurrence in one patient that necessitated a second perfusion resulting in 90% necrosis of the tumor. No correlation could be demonstrated between grade and percent necrosis of the tumor after perfusion (Pearson's correlation). Post operative radiotherapy (total dose 60-70 Gy, 25 x 2 Gy daily and 10-20 Gy boost) was given in 37 patients with microscopically involved or marginally free resection margins. Radiation therapy started within 5-6 weeks after tumor resection. Radiation treatment was delivered through a multiple-field technique with CT treatment planning on a linear accelerator, 6-15 MV.

Amputations and limb salvage

A total of 21 amputations (28%) were performed. Table 2 presents the time interval between ILP and amputation and the rationale for amputation. Overall 1, 5 and 10 years limb salvage was 80.1 ± 4.8, $68.2 \pm 6.5\%$ and $60.6 \pm 9.2\%$ respectively (Figure 2). When analyzing the limb salvage curve, a distinction in 3 time episodes was observed at risk for amputation. The first period was observed within the first one and a halve year after perfusion (17 patients) due to a perfusion induced massive necrosis of the tumor and overlying skin resulting in a soft tissue deficit (6 patients), tumor recurrence after perfusion (5 patients), wound complications after ILP followed by radiotherapy (2 patients), a microscopically involved resection margin with the rejection of the patient for adjuvant radiotherapy of the foot (2 patients), one patient with an insufficient clinical response and in one patient an arterial trombosis occurred with no

vascular reconstruction possibilities 2 months after resection of a local recurrence in the groin. The second time period was within 5 years after ILP, with 2 amputations performed for late local recurrent disease (37 and 58 months after perfusion). The third episode occurred around ten years after perfusion. Amputation was performed for critical leg ischemia with neuropathy due to treatment induced atherosclerosis of the remaining tibial artery which was not suitable for arterial reconstruction (110 and 125 months after perfusion). An example of the clinical appearance of patient no 21 is shown in Figure 3. In this patient a popliteal ILP was performed at the age of 18 years for a chondrosarcoma. After marginal resection this patient received 66 Gy adjuvant radiotherapy. Ten years after ILP an amputation was performed because of critical leg ischemia. No recurrent disease was found on pathological examination of the amputated specimen. Another two patients developed a pathological fracture of the femur due to radiation induced osteonecrosis (78 and 129 months after perfusion). All of these 4 patients with late post ILP complications received high dose post-perfusion radiotherapy (60 - 70 Gy).

Systemic metastases and survival

Twelve patients presented with distant metastases at time of ILP (16% stage IV AJCC), 50% of these patients had lung metastases whereas remarkably the other halve had lymphe node metastases. Eleven of these patients died of disease after a median period of 9 (range 2 - 54) months), one patient is alive with no evidence of disease after 11 months. During follow-up 25 patients (36%) developed distant metastases at a median interval of 9 (range 2 - 100) months. A significant difference ($P < .001$) was observed between patients with no distant metastases at the time of ILP (mets -) compared with patients with metastases at the time of ILP (mets +) (Fig. 4). Overall 1, 5 and 10 year's survival for all patients was $82.9 \pm 9.2\%$, $58.7 \pm 13.1\%$ and $42.5 \pm 18.2\%$ respectively (Figure 4).

Discussion

The results of an European multi-center trial performed in the nineties, lead to the approval of using TNF for ILP in patients with locally advanced extremity sarcomas by the European Medicine Evaluation Agency.[15] Currently ILP with TNF is available in more than 30 Centers and in 2002, 350 so called TNF-perfusions were performed. As one of the first centers that participated in the TNF ILP experience and practice for over a decade we recently

encountered long-term treatment related morbidity necessitating amputation of the perfused limb 10 years after treatment. For this reason we analyzed our results of ILP with TNF and melphalan and describe our results in the present study.

We observed an overall response rate of 82% which is in the range of the 63 - 91% response rates reported in the literature.[15,23-25] Although a suggestion has been made for a relation between the grade of a sarcoma and the response to TNF ILP we could not demonstrate a correlation between grade and the percent necrosis after ILP with TNF. This is in concordance with the results of the Amsterdam group.[23] Various reports have shown that a limb salvage rate of 81-86% can be achieved in patients with locally advanced limb sarcoma.[15,23-25] An independent review committee reconsidered the unresectability criteria of all enrolled patients in the European study. Eighty percent of the patients in this study met indeed the criteria for unresectability and survival curves based on a match control study with cases of the Scandinavian Soft Tissue Sarcoma Databank showed that TNF ILP had no negative effect on survival.[26]

We used the Kaplan-Meier method to calculate limb salvage as this method adjust for censored observations, i.e. patients who were alive and well at the time of last contact or patients who have died of distant metastases but with preserved limb function. Using this method we calculated a 1 year limb salvage rate of 80% with amputations performed mainly because of post perfusion related complications or early local recurrence in the first year after ILP. A second curve in limb salvage was observed within 5 years after TNF ILP in two patients with late local recurrences. A third bent in the limb salvage curve was observed around ten years after ILP. This was a new observation in two patients that presented with critical leg ischemia with ulceration and continuous pain. Besides ILP with TNF and melphalan, both patients received adjuvant radiotherapy (66 and 70 Gy) after marginal tumor resection.

What seems to be the cause of this late morbidity? Analysis of the functional and long-term morbidity in 97 patients with stage I melanoma treated with ILP with melphalan as the sole perfusion agent in our own center, showed after a median follow up of 36 (range 12-76) months, no patients with critical leg ischemia.[27] The Rotterdam and Amsterdam perfusion group reported a long-term morbidity consisting of muscle atrophy or fibrosis in 11% of the patients after ILP with melphalan, however cases of critical leg ischemia are not described.[28] The fact that in our series no muscle atrophy or fibrosis was found might be explained by the

fact that we always perform a lateral fasciotomy after ILP to prevent a compartment syndrome. With a literature search for late morbidity after ILP with TNF and melphalan, no studies could be retrieved.

The clinical importance of late morbidity after radiotherapy has evolved since the publication of Eifel et al. who retrospectively reviewed the medical records of 1784 FIGO stage IB patients receiving primary radiotherapy at the MD Anderson Cancer Center between 1960 and 1989.[29] She showed that after 5 years, there was a small but continuous risk of experiencing major complications of radiotherapy, i.e. urinary, rectal and small bowel complications, all the way to 20 years of follow-up. Johansson et al. described a high occurrence of severe neuropathy closely linked to the development of fibrosis around the nerve trunks, after aggressive postoperative telecobalt therapy received in 1963-1965 in a group of 71 breast cancer patients that were initially treated with modified radical mastectomy.[30] Radiotherapy damage to the vascular system was demonstrated by Hopewell in an experimental setting, arteries of the hamster cheek pouch, showed localized constrictions after irradiation.[31] These constrictions were caused by clones of endothelial cells and may be the predominant factor influencing the degeneration of the capillary bed after radiotherapy.[32] Evidence of this occlusive effect of vessels by proliferating endothelial cells after radiation have also been reported by other investigators.[33]

Another argument to subscribe the observed late morbidity, at least in part, to the radiotherapy is the fact that another two patients receiving adjuvant radiotherapy after ILP with TNF and melphalan, developed a pathological fracture of the femur (78 and 129 months after ILP with TNF and melphalan). Radiotherapy induced osteonecrosis is a well known phenomenon after radiotherapy. Lin et al. described 12 fractures of the femur after surgery and irradiation for STS of the thigh. Treatment of these fractures was difficult and demanding with only 4 bony unions after a mean follow-up of 37 months.[34] When we add up the evidence of developing fibrosis after ILP with melphalan and the development of fibrosis after radiotherapy, the combination of the two regiments could explain the observed late morbidity rate in the present series.

Overall survival for all patients showed a steadily decline with a ten year percentage of 42%. Even after 110 and 120 months patients die of distant metastases. Sixteen percent of the patients had metastases at the time of ILP. A significant difference in survival was observed comparing these patients with pulmonary or lymphe node metastases with patients lacking metastases at time of ILP. Five- year overall survival of 59% in this series is higher than the

reported 5 year survival of 48% in the Amsterdam experience and the reported 32% of Lejeune et al.[23,24] This in an unexpected observation since selection criteria for ILP with TNF between the institutes are comparable.

Patients with high-grade tumors and diameters greater than 5 centimeter have a great tendency to metastasize. These patients could theoretically benefit from neo-adjuvant chemotherapy. A quantitative meta-analysis of data from 14 trials of doxorubicin-based adjuvant chemotherapy showed indeed a benefit from systemic adjuvant chemotherapy of 6% for local relapse-free interval, however there was no overall survival benefit at 10 years.[35] Delaney et al. developed a regimen of preoperative chemotherapy consisting of mesna, adriamycin, ifosfamide, and dacarbazine (MAID) interdigitated with radiotherapy followed by resection and postoperative chemotherapy with or without radiotherapy to improve outcome in patients with high grade extremity STS. Compared with a historical group of control patients, outcome in the MAID group was superior.[36] In an update of 64 patients 5 required amputation because of disease, 3 had unresectable disease and 1 patient refused surgery. Estimated three-year survival and local-regional control were 75.1% and 79.3%, respectively. These results are comparable with the results of the present study.[37] However, systemic therapy is associated with systemic toxic effects in contrast with the mild systemic side effects observed after ILP with TNF and melphalan.

Since 1992 we have not changed the indication for TNF perfusion. Patients who were candidates for amputation of the involved limb, based on the preoperative MRI, were offered an ILP with TNF and melphalan with the ultimate goal to preserve the limb with a locally advanced soft tissue sarcoma. After ILP patients received a delayed surgical resection and adjuvant radiation therapy in those patients with marginal or microscopically positive resection margins. This treatment resulted in a high limb salvage rate in patients with locally advanced STS, however late morbidity can occur especially when adjuvant postoperative radiotherapy is applied. Therefore continuous follow-up of these patients is warranted.

Table 1 Histological grade of the tumors according to Coindre et al.[17] and stage of the tumors according to AJCC.[16]

Grade	Number	%
I	10	14
II	23	32
III	40	54
Stage		
I	10	14
II	1	1
III	50	69
IV	12	16

Table 2 Amputations performed in 21 patients sorted on interval duration.

N	Diagnosis	Age (years)	Interval (months)	Rationale for amputation	Current status
1	PUS	60	0	Postperfusion necrosis[38]	NED 120 months
2	Angiosarcoma	74	1	Local recurrence	DOD 11 months
3	Fibrosarcoma	76	1	Postperfusion necrosis	NED 2 months
4	PUS	67	2	Postperfusion necrosis	DOD 9 months
5	Epitheloid sarcoma	21	2	Postperfusion necrosis	DOD 54 months
6	Leiomyosarcoma	17	2	Insufficient clinical response	DOD 7 months
7	Liposarcoma	60	2	R1 resection, RT not possible	AWD 10 months
8	PNET	62	3	Local recurrence	DOD 17 months
9	Synovial sarcoma	39	3	Postperfusion necrosis	DOD 50 months
10	PUS	63	3	Postperfusion necrosis	NED 72 months
11	Angiosarcoma	80	4	Local recurrence	DOD 10 months
12	Synovial sarcoma	65	4	R1 resection, RT not possible	NED 6 months
13	Epithelioid sarcoma	22	6	Local recurrence *	DOD 39 months
14	Haemangiopericytoma	50	8	Wound complications after ILP with radiotherapy *	AWD 65 months
15	PUS	71	12	Wound complications after ILP with radiotherapy *	NED 14 months
16	PUS	61	15	Arterial occlusion	AWD 17 months
17	Synoviosarcoma	42	18	Local recurrence	NED 20 months
18	Liposarcoma	53	37	Local recurrence	DOD 110 months
19	Liposarcoma	39	58	Local recurrence	DOD 120 months
20	PNET	56	110	Critical leg ischemia	NED 118 months
21	Chondrosarcoma	18	125	Critical leg ischemia	NED 134 months

NED = no evidence of disease; AWD = alive with disease; DOD = death of disease; PUS = pleomorphic undifferentiated sarcoma; PNET = malignant peripheral nerve sheath tumor; R1 resection = microscopically involved resection margin; RT = radiotherapy; * patients with a second TNF melphalan ILP

Figure 1 Percentage of necrosis estimated on pathological examination of the resected tumor remnant in relation to the number of patients.
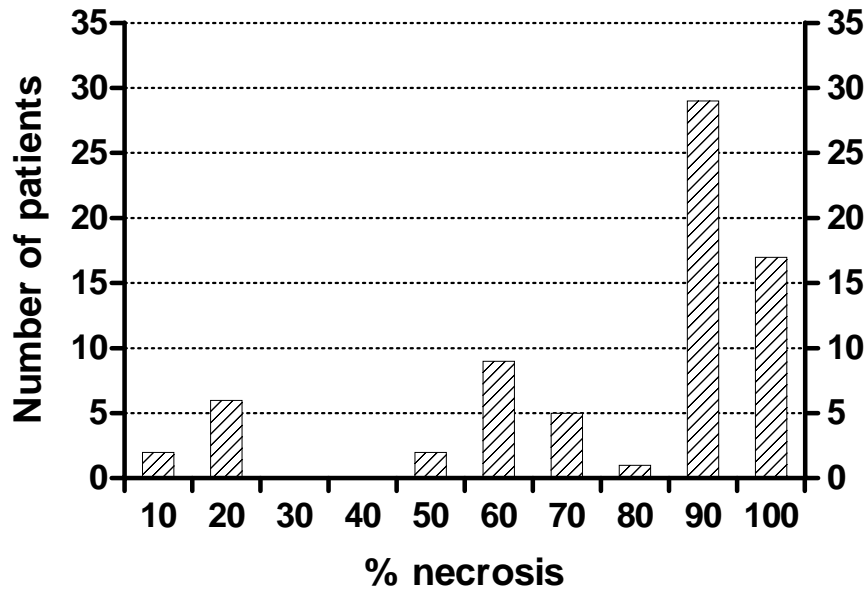

Figure 2 Limb salvage curve in patients with locally advanced soft tissue sarcoma treated with TNF and melphalan isolated limb perfusion.
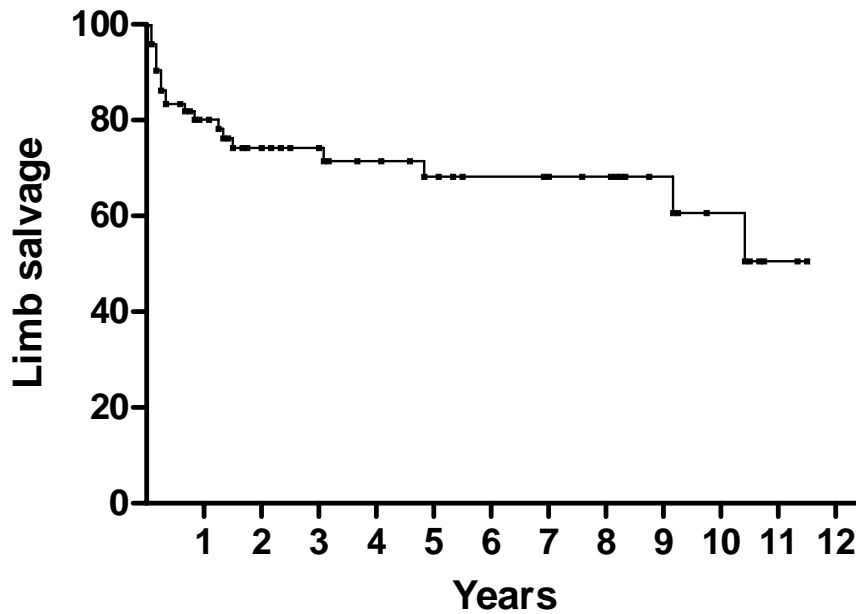
**Figure 3** Clinical appearance of the lower leg of patient no 21 (Table 3) before amputation for critical leg ischaemia.

Figure 4 Overall survival in patients with locally advanced soft tissue sarcoma treated with ILP, TNF and melphalan. A significant difference was observed between patients with no distant metastases at the time of ILP (mets -) compared with patients with metastases at the time of ILP (mets +).
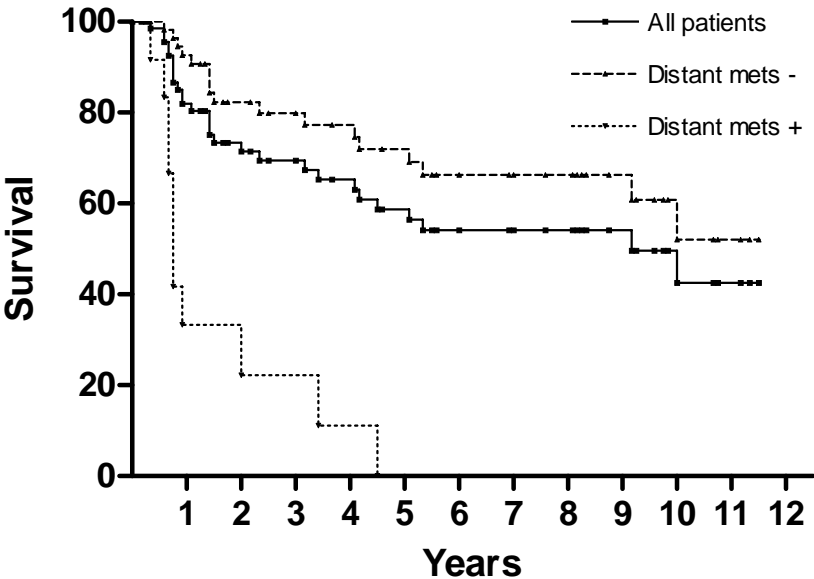
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Chapter 5

Isolated limb perfusion with TNF and Melphalan for locally advanced soft tissue sarcoma: the value of adjuvant radiotherapy

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Chapter 5

Abstract

Background: The aim was to investigate the value of adjuvant radiotherapy for locally advanced soft tissue sarcoma (STS) after hyperthermic isolated limb perfusion (ILP) with Tumor Necrosis Factor alpha (TNF) and Melphalan followed by limb-saving surgery.

Methods: From 1991-2003, 73 patients, median age 54 (range 14-80) years underwent 77 ILP's followed by resection in 68 patients (93%). Radiotherapy was administrated in case of marginally or microscopically positive resection margins. Local recurrences were scored and calculated according to the Kaplan-Meier method and Log-rank test.

Results: After residual tumor mass resection 58% received radiotherapy (EBRT+group) and 42% did not (EBRT-group). The median follow-up was 28 (range 2-159) months. A significant better local control rate was observed in the EBRT+ compared with the EBRT-group (P<.0001). When only R0 resections in non-metastased patients were considered the significance remained between both groups (P=.0003). In the EBRT-group, a R1 or R2 resection resulted in earlier relapse of local disease compared with R0 resections (P=.0475).

Conclusions: Adjuvant EBRT reduces the risk for local recurrence after delayed resection in STS patients treated with ILP and TNF and is indicated when resection margins are close or microscopically positive and seems, also beneficial after a R0 resection.

Introduction

Soft tissue sarcomas (STS) comprise a heterogeneous group of malignant mesenchymal tumors, generally classified according to their resemblance to normal tissue. Currently 19 histological types and over 50 different subtypes can be recognized. Many histological types reveal different biological behavior, but even within a single histological group considerable divergence in the malignant potential has been noticed. During the last decade it has become evident that the studies in STS provide more insight in tumor behavior, when they were specified for histological type and grade.[1]

A major difficulty in the management of STS is the low incidence, as well as their insidious presentation. During the last two decades there have been improvements in the radiodiagnostic evaluation of these tumors. The development of magnetic resonance imaging (MRI) with or without angiography and spiral computer tomography (CT) facilitates the surgeon in planning the surgical procedure as well as the radiation oncologist in planning the pre or postoperative radiation treatment. More extensive surgical procedures became possible with the reconstructive surgical techniques with implants and/or tissue transfer with the ultimate goal to improve the outcome, e.g. limb saving operations, decrease local failure rate and increase disease free and overall survival, without increasing long-term morbidity. The role of (neo)adjuvant chemotherapy in the treatment of soft tissue sarcomas is limited with the exception of the Ewing sarcomas, primitive neuro ectodermal tumors (PNETs) and rhabdomyosarcomas.[1]

Although limb saving surgical procedures are feasible in the majority of patients with soft tissue sarcomas of the limb, a small proportion of patients can only be treated with an amputation. Since the early nineties these patients are candidates for the so-called hyperthermic isolated limb perfusion (ILP) with Tumor Necrosis Factor alfa (TNFα) and Melphalan followed by delayed resection. Eggermont and co-investigators investigated this new treatment approach and documented in a large European study an objective response rate of 76% and a limb-salvage rate of 71% with minimal treatment related morbidity.[2] This treatment approach is also applied at the University Medical Center Groningen since 1991. We recently investigated the overall limb salvage rate of these patients and described long term morbidity resulting in late amputations years after therapy. The role of adjuvant radiotherapy in this late observed morbidity was discussed as a possible contributing factor.[3]

The goal of the present study was to investigate the primary role of the radiotherapy as an adjunct to prevent local recurrence after ILP with TNFα and Melphalan.

Patients and methods

During the time period July 1991- December 2003, 73 patients, 36 males (49%) and 37 females (51%) with a median age of 54 (range 14-80) years with locally advanced primary or recurrent STS were eligible for an ILP with TNFα and melphalan, followed by delayed resection and adjuvant external beam radiotherapy. The sarcomas were graded according to the French grading system and the histology was based on the most recent World Health Organization's Classification of Tumors (Table 1).[4,5] All patients had the same preoperative workup to stage the disease locally and to detect possible distant metastases: magnetic resonance imaging (MRI) of the affected limb and computed tomographic (CT) scans of the lungs.[6] Patients without metastatic disease were treated with curative intent, while patients with metastatic disease were eligible for a so called 'palliative perfusion' when they had a life time expectancy of minimum six months and the intention of the treatment was limb salvage.

Table 1 Classification of the locally advanced soft tissue sarcomas in this study: Primary/recurrent, grade and histology.

Primary/recurrent soft tissue sarcoma	%
Primary STS	88
Recurrent STS	12
Grade	
Grade I	14
Grade II	32
Grade III	43
Histology	
Pleomorphic undifferentiated sarcoma (non otherwise specified)	32
Synovial sarcoma	14
Myxoid liposarcoma	10
Leiomyosarcoma	8
Myxofibrosarcoma	6
Fibrosarcoma	4
Malignant peripheral nerve sheath tumor (MPNST)	4
Epitheloid sarcoma	3
Myxoid chondrosarcoma	3
Angiosarcoma	3
Other*	13

Legend
Other* = embryonal rhabdomyosarcoma, well differentiated (lipoma like) liposarcoma, pleomorphic liposarcoma, primitive neuroectodermal tumor (PNET), clear cell sarcoma, malignant solitary fibrous tumor, Ewing sarcoma, malignant myoepithelioma of soft tissue, pleomorphic rhabdomyosarcoma.

According to the AJCC staging system there were 10 stage I, 1 stage II, 50 stage III and 12 stage IV tumors.[7] All patients were treated after informed consent was obtained according to the institutional guidelines.

Perfusion technique

ILP was performed under general anesthesia. The major artery and vein of the limb were clamped after heparinization with 3.3 mg heparin/kg body weight (Thrombolique, Organon BV, Oss, The Netherlands). Collateral vessels were ligated and a tourniquet was applied to compress the remaining minor vessels. The perfused limb was wrapped in a thermal blanket to reduce heat loss. The perfusion technique of the axillary, iliacal and popliteal vessels was previously extensively described.[8,9] Leakage of the perfusion circuit to the systemic circulation was measured with radio labeled iodide and technetium.[10] The extremities were perfused for 90 minutes under mild hyperthermia (39-40°C) with TNFα (Beromun®, Boehringer, Ingelheim, Austria) and Melphalan (L-phenylalanine mustard; Glaxo- Wellcome company, Italy). The following doses were used: 3 mg TNFα (arm), 4 mg TNFα (leg) or 3 mg TNFα (popliteal perfusion) and 10 mg/l Melphalan (limb volume, leg) to 13 mg/l Melphalan (limb volume, arm). In the beginning of the study, 18 patients also received a dose of 0.2 mg Interferon (Boehringer, Ingelheim, Austria) subcutaneously 1 and 2 days before perfusion, followed by 0.2 mg INFγ injected into the arterial line at the start of perfusion. At the end of the perfusion the heparin was antagonized with prothrombin and a fasciotomy was performed. Patients received subcutaneous low-dose molecular heparin until full mobilization.

Clinical and pathological response

Complete clinical response (CR) was defined as disappearance of all measurable disease in the limb for longer than 4 weeks; partial response (PR) as regression of the tumor size by greater than 50% for longer than 4 weeks, no change (NC) as regression of less than 50% of the tumor in the limb or progression of less than 25% for longer than 4 weeks. After resection were the tumor remnants measured in three dimensions and based on an integration of gross and microscopic findings, the percentage of necrosis was estimated. The histopathological response of ILP was standardized and scored according to the World Health Organisation (WHO) criteria.[11] The resection margins of the tumor were classified as radical when the resection margins were free of tumor cells (complete resection; R0), or as R1 when resection

margins were microscopically involved or as R2 when resection margins were macroscopically positive involved. Resection margins were perioperatively marked with clips to facilitate adjuvant radiotherapy when indicated.

Radiation treatment

Postoperative radiotherapy (60-70 Gy) was considered indicated in case of <95% necrosis on pathological examination of the tumor or with marginal or microscopically positive resection margins. EBRT was given with a daily dose 2 Gy (25x2Gy) and an additional boost dose of 10 Gy (after R0 resection) or 20 Gy (after R1-R2 resection) (2 Gy/day). Radiation therapy started within 5-6 weeks after tumor resection. Radiation treatment was delivered through a multiple-field technique with CT treatment planning. Radiotherapy was given on a linear accelerator, 6-15 MV. When indicated, patients received rehabilitation service as well as physiotherapy.

Follow-up

All patients were clinically followed after treatment according to a standardized protocol at three months intervals during the first year, four month intervals during the second year, than every six months and after five year once a year. A chest X-ray was performed after each visit. Primary end point in this study was local recurrence. Disease free and overall survival (DFS and OS), regional and distant metastases were also scored. Analyses of endpoints were calculated according to the Kaplan-Meier method and Log-rank test.[12] Values of P < .05 were considered statistically significant. Graph Pad Prism® version for Windows statistical software was used.

Results

Ten perfusions were performed for a sarcoma tumor grade I (14%), 24 perfusions for grade II (32%), 43 perfusions for grade III (54%). Sixty perfusions were performed for primary (88%) and 17 perfusions for recurrent sarcomas (12%); 61 'curative perfusions' and 12 'palliative perfusions'. Sixty-two sarcomas were located in the lower limb (85%) and 11 sarcomas in the upper limb (15%). Perfusion was performed at the iliac level in 32 patients (42%), at the popliteal level in 23 patients (30%), at the femoral level in 11 patients (14%) and axillary level in 11 patients (14%). Four patients underwent a second perfusion: in two of these patients there was an insufficient response after the first perfusion. In two other patients a

complete response was achieved however the tumor recurred for which a second perfusion was performed.

The median tumor size before an ILP was performed was 16.2 (range 8.3-23) cm. Resection of the residual tumor was performed after a median post-perfusion time of 8 (range 2-15) weeks in 68 patients (93%). After ILP complete clinical response was observed in 19 patients (25%), a partial response in 53 patients (69%) and no response in 5 patients (6%). Resection of the remnant tumor was performed in 68 patients. In four patients no resection was performed due to progression of distant metastasis and one patient with complete response refused further surgery.

The median follow-up of the patients treated with ILP was 28 (range 2-159) months and a flowchart of the 73 ILPs is presented in Figure 1.

Local control rate

From the 68 patients another 4 could not complete the combined modality treatment schedule because they were amputated shortly after resection of the STS. This amputation was due to vascular disturbances, wound healing disturbances or the tumor did not respond after the perfusion treatment. After residual tumor mass resection 37 of the 64 patients (58%) received EBRT (EBRT+group) and 27 patients (42%) did not (EBRT-group). The five years local control rate was 96.5 ± 3.5% in the EBRT+group and 52 ± 23% in the EBRT-group (P<0.0001) (Figure 2).

When only patients with curative intention, i.e. without distant metastases at the time of perfusion, were selected, the local tumor control rate was 96.5 ± 3.5% in the EBRT+group (n=35) and 56 ± 25% in the EBRT-group (n=20) (P<0.0001) (Fig. 3).

When R0 resections were considered in the curative treated group, the local tumor control rate was 100% in the EBRT+group (n=29) and 55 ± 31% in the EBRT-group (n=15) (P=0.0003) (Figure 4).

In the EBRT-group of patients treated with a curative intention, a R1 or R2 resection (n=3) resulted in an earlier relapse of local disease compared with R0 resections (n=15)(P=0.0475): with at 2 years a difference of 57 ± 28% versus 33 ± 33% (Figure 5).

In the EBRT+group of patients treated with curative intention, a R0 resection (n=29) resulted after 5 years in 100% local tumor control rate versus 75 ± 25% in a R1 resection (n=6) (P=0.01) (Figure 6).

Figure 1 A flowchart of the patients from entry all the way to the final group.
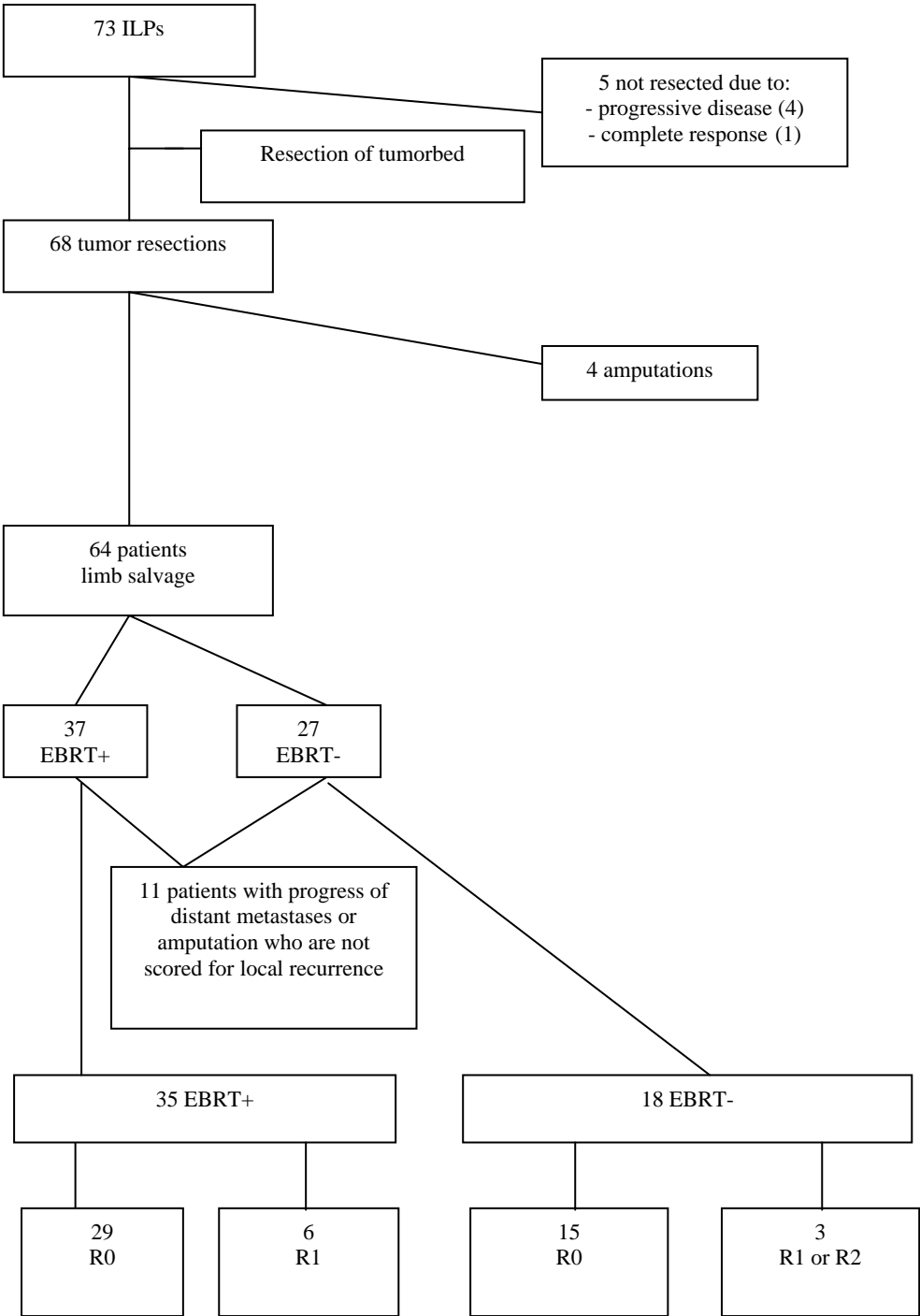
Figure 2 Local tumor control rate in all patients: five years local control rate EBRT+group (n=37) 96,5 ± 3,5% versus 52 ± 23% EBRT- group (n=20) (P<0.0001).
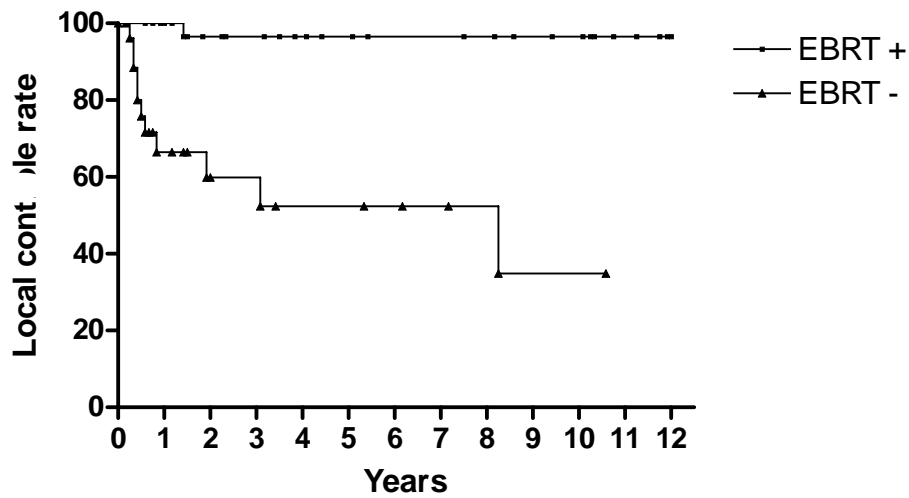
Figure 3 Local control rate in patients treated with curative intent: five years local control rate EBRT+group (n=35) 96.5 ± 3.5% versus 56 ± 25% EBRT- group (n=20) (P<0.0001).
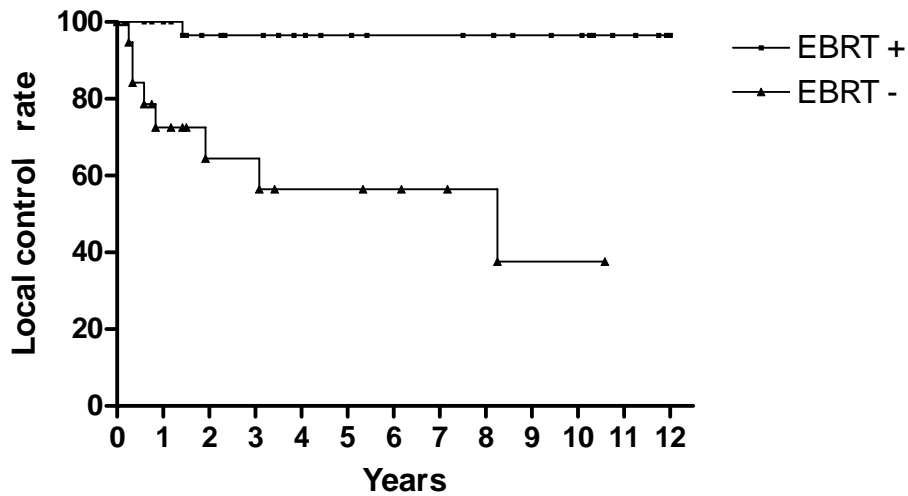
Figure 4 Local control rate in patients treated with curative intention and R0 resections: five years local control rate EBRT+ R0 group (n=29) of 100% versus 55 ± 31% EBRT- R0 group (n=15) (P=0.0003).
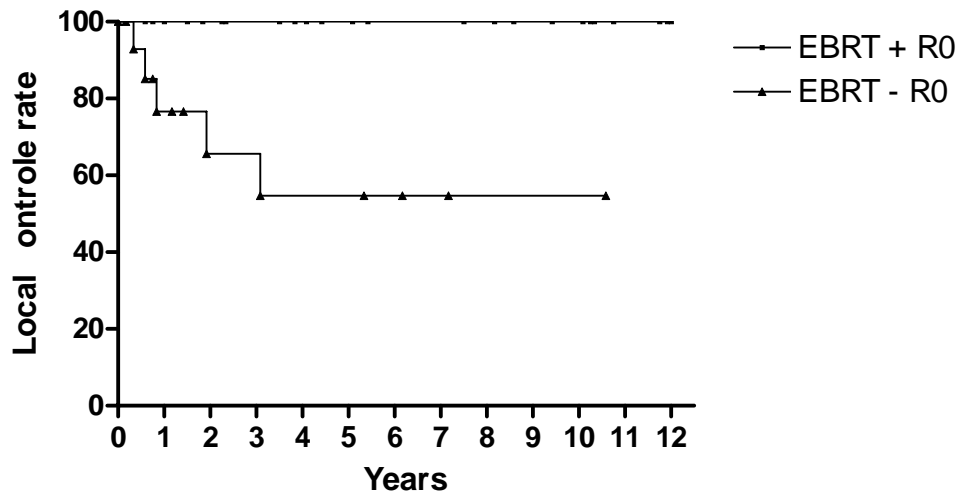
Figure 5 Local control rate in patients treated with curative intention without adjuvant radiotherapy: EBRT- R0 (n=15) versus R1 or 2 resections (n=3): 2 years local control rate 57 ± 28% versus 33 ± 33% (P=0.0475).
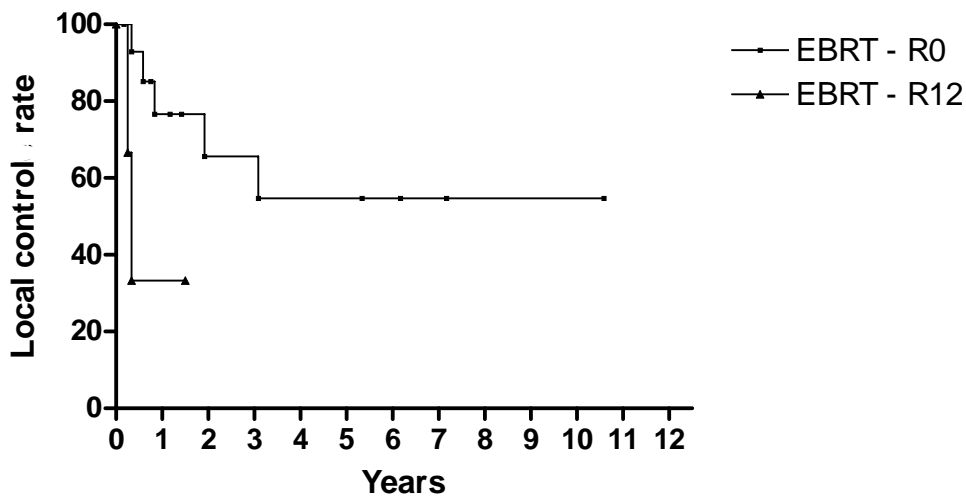
Figure 6 Local control rate in patients treated with curative intention, EBRT+ R0 (n=29) versus EBRT+ R1 resections (n=6): 5 years local control rate 100% versus 75 ± 25% (P=0.01).
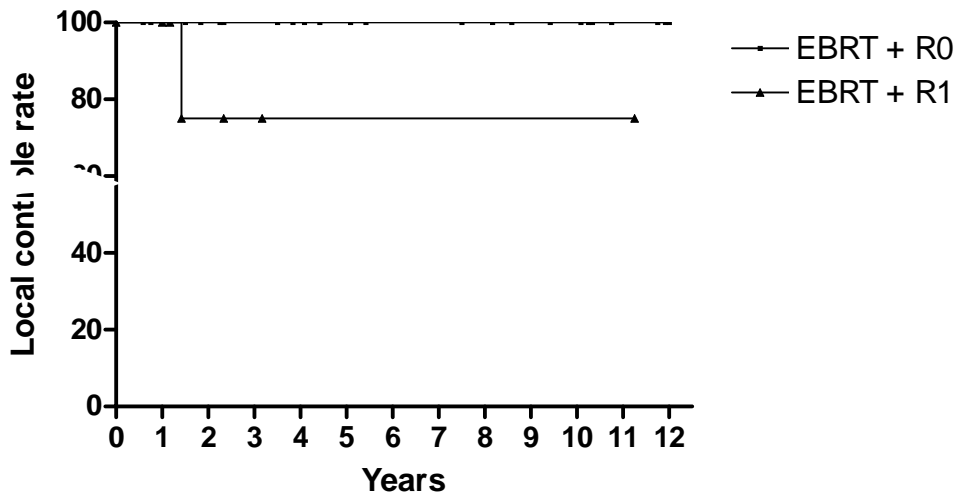
Metastasis and overall survival

Twelve patients presented with distant metastasis (Stage IV) at the time of ILP (16%). There was a significant difference in survival between the group of patients with and without distant metastases at the time of ILP (P< .001). During follow-up 25 patients (36%) developed distant metastasis at a median interval of 9 (range 2-100) months. A total of 21 amputations (28%) had to be performed in the whole series. The overall 1, 5 and 10 years survival was 83.1 ± 4.4%, 61.4 ± 6.4% and 47.5 ± 7.5% respectively (Figure 7).

Figure 7 Overall survival in all ILP patients: the overall 1, 5 and 10 years survival was 83.1 ± 4.4%, 61.4 ± 6.4% and 47.5 ± 7.5% respectively.
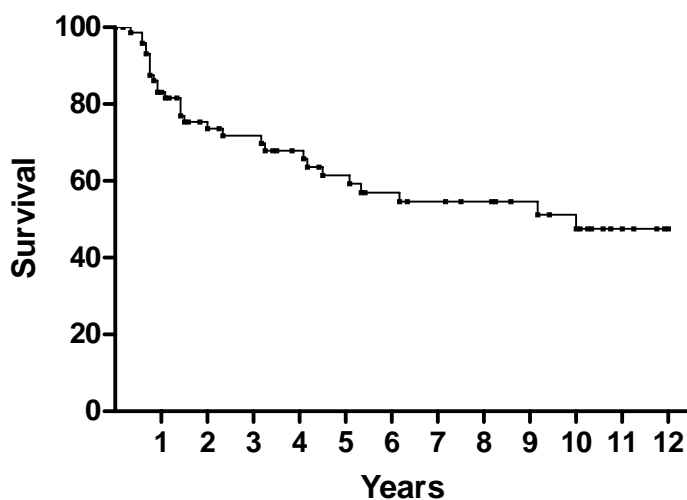
Discussion

The goal of adjuvant radiotherapy in this combined limb saving treatment modality was to decrease the local recurrence rate. From previous studies we know that survival figures in extremity sarcoma patients are not influenced by limb saving procedures.[13,14,15] Adjuvant radiation treatment improves local tumor control in limb saving treatment of STS.[16,17] The first goal of the applied combined modality treatment of ILP was to increase the limb salvage rate in patients with extremity sarcomas, who were locally irresectable by standard surgical treatment. Indeed we were able to achieve a limb salvage rate of 72%. Tumors with microscopically or macroscopically involved margins received adjuvant radiation as well as marginal resected tumors with less than 95% necrosis on pathological examination. From an earlier study we know that adjuvant radiation after ILP and delayed tumor resection of locally advanced extremity STS was feasible.[18] In this study we demonstrated unequivocally that adjuvant radiation treatment should be used in this combined modality treatment, even after radical resections.Radiation can improve local control after marginal resection (R1 or R2). Trovik showed a local failure rate in R1 and R2 resection of 39% without irradiation compared to 24% with irradiation.[19] There is also a relation between the delivered radiation doses and local tumor control in sarcoma treatment. Fein et al demonstrated that boost therapy with a total dose >62.5Gy resulted in a 5-year local control rate of 95% compared to 78% for patients receiving less than 62.5Gy (p=0.008).[17]

The value of adjuvant radiotherapy in limb saving sarcoma surgery was first demonstrated by Rosenberg et al. in the early eighties.[15] Yang et al updated their initial experience and described after a median follow-up of 9.6 years a highly significant decrease in the probability of local recurrence after irradiation (p=0.0028), without difference in overall survival. Adjuvant irradiation resulted in significantly worse limb strength, oedema, and range of motion. But these deficits were often transient and had few measurable effects on activities of daily life or global quality of life.[16]

Despite the advantage of decreasing the local recurrence rate, the clinical importance of acute and late morbidity after radiotherapy may not be underestimated. Two patients in our series developed late radiation induced complications after ILP and adjuvant radiotherapy. A pathological fracture of the femur at 78 months and 129 months and in both patients this resulted in pseudarthrosis. Treatment of these fractures might be difficult.[20] Therefore a study was designed by Sullivan and co-workers in the nineties to overcome the postoperative

radiation morbidity. Postoperative radiotherapy was compared with preoperative radiotherapy and a disadvantage of the preoperative radiotherapy with increased risk of wound complications was shown.[21] Recently, Eggermont and co-workers demonstrated that ILP can also be safely applied in pre-irradiated limbs.[22] There is often a discussion with respect to 'unresectability' of these kind of extensive sarcomas and the type of treatment to be performed. Instead of ILP, preoperative radiotherapy might be an option, to reduce 'tumor volume'and 'tumor aggressiveness' and to render a patient resectable for cure. A disadvantage of this treatment option is the increased risk for woundcomplications.[21] Another point of discussion might be if ILP patients with a good clinical/pathological response (>95% necrosis) and 'good' surgical margins need adjuvant radiation. We showed that indeed these patients need adjuvant radiation, since the local control rate in this group was only 56% without adjuvant radiation. Our PET studies in sarcomas after ILP showed in these tumors often an active rim on the outside of the tumor.[23] This was the rim with viable tumor, inside full necrosis, outside viable tumor cells. It is well known that a 'good' surgical margin in sarcoma surgery is often an inadequate margin for local tumor control.[15,16]

Therefore 'wide' local tumor resections are advocated, but these 'wide' local resections were impossible in these perfused patients. The results of this study emphasize the key role of adjuvant radiation in reducing the risk of local recurrences in the combined modality treatment of ILP for locally advanced STS of the extremities. Although we observed in an earlier publication about the risks of late morbidity of radiation in a perfused limb, the contributing effect of radiotherapy should outweigh this risk since patients with locally advanced soft tissue sarcoma are at a high risk of dying of distant metastases.

Conclusion

ILP followed by delayed surgical resection is an effective limb salvage treatment regimen for locally advanced extremity STS. Adjuvant EBRT reduces the risk for local recurrence significantly and is indicated when resection margins are close or microscopically positive and seems, also beneficial after a R0 resection**.**

Chapter 5

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Chapter 6

Prognostic value of 18F-fluorodeoxyglucose-uptake in locally advanced soft tissue sarcomas treated with regional chemotherapy

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Chapter 6

Abstract

Background: Evaluating the potential role of standardized uptake value (SUV) in patients with locally advanced, non-metastased, high-grade, extremity soft tissue sarcoma.

Methods: Thirteen patients scheduled for hyperthermic isolated limb perfusion (ILP), referred for a 18F-Fluorodeoxyglucose (FDG) Positron Emission Tomography (PET)-scan were eligible. The SUV in the sarcoma lesion was calculated before and six weeks after ILP. After the second scan, surgical resection was performed. Survival data were assessed.

Results: Univariate analysis showed prolonged overall survival in those with a low SUVmax value after perfusion (144 ± 8months) compared to those with a high SUVmax (33 ± 8 months) (p=0.004), but SUV max was not an independent prognostic factor (p=0.08).

Conclusion: Patients with a high grade locally advanced STS with a high SUVmax postperfusion showed a decreased overall survival compared to patients with a low SUVmax. The opportunities of SUV measurements in diagnosis and treatment evaluation of STS patients needs further exploration.

Introduction

Over the past thirty years there has been a tremendous progress in the local management of these malignancies. Improved developments in diagnostic imaging and surgical treatment with adjuvant radiotherapy are the cornerstones of this evolution: almost 90% of extremity STS can be treated today with limb salvage surgery with or without adjuvant radiation.[1,2] For patients with primary irresectable STS, hyperthermic isolated limb perfusion (ILP) with Tumor Necrosis Factor alpha (TNF) and Melphalan became available in the early nineties. This treatment has resulted in a long term limb salvage rate of 82%.[3] Survival of extremity-STS-patients is not influenced by these limb salvage procedures.[4] The 5-year survival rate of soft tissue sarcomas (STS) of the extremities is 60-70%.[1,2] Identification of prognostic factors may allow the development of individualized strategies leading to improved results.

A possible way to identify prognostic factors is Positron Emission Tomography (PET). PET visualizes the uptake of radiolabeled tracers.[5] 18F-Fluorodeoxyglucose (FDG), a radiolabeled glucose analogue is a tracer that measures the glucose metabolism which is increased in cancer cells.[6] An accelerated rate of glucose transport and an increased rate of glycolysis are among the most characteristic biochemical markers of malignant transformation.[7] FDG uptake has been found to be associated with cell viability and particularly with cell proliferative activity.[8-10] The currently most widely used radiotracer in oncology is FDG.[11] A systematic review and meta-analysis indicated that FDG-PET can discriminate between benign and malignant soft tissue tumors and low and high-grade sarcomas based on the Standardized Uptake Value (SUV).[12] SUV of PET assesses the degree of tracer accumulation. In patients with breast cancer, head and neck carcinoma, pancreatic cancer and lung cancer, high FDG uptake showed a significantly lower disease-free and overall survival. The SUVmean or SUVmax turned out to be significant prognostic factors in several univariate and multivariate analyses.[7,13-19] However, studies have also been published where the SUV had no prognostic value with respect to disease-free or overall survival.[17,20]

No studies evaluating consecutive values of FDG-uptake prior and after regional chemotherapy have been performed in patients with a soft tissue sarcoma of the extremity. The potential role of the SUV was analyzed in predicting relevant aspects of long-term outcome in patients with STS treated with regional chemotherapy with isolated limb perfusion.

Chapter 6

Patients and Methods

Patients

All STS patients with a high grade STS in the extremity, more than 5 cm in diameter and without distant metastases, who where referred to Groningen University Medical Center from 1991 to 1995 and who underwent a hyperthermic iolated limb perfusion (ILP) and FDG-PET imaging prior and 6 weeks post ILP were eligible for this study. The SUV in the sarcoma lesion was calculated before resection: the first FDG-PET before ILP and the second FDG-PET after ILP. ILP of the affected limb was performed with TNF alpha and Melphalan and followed by delayed surgical resection.[3,21] The histopathological response of ILP was standardized and scored according to the World Health Organisation (WHO) criteria.[22] Complete histopathological response (CR) was defined as disappearance of all measurable disease in the limb for longer than 4 weeks; partial response (PR) as regression of the tumor size by greater than 50% for longer than 4 weeks, no change (NC) as regression of less than 50% of the tumor in the limb or progression of less than 25% for longer than 4 weeks. Extensive histopathologic examinations of the resected specimens were performed. The percentage of necrosis was estimated on the basis of macroscopic evaluation of necrotized tissue and histologic examination results of tissue surrounding the necrotic area, tissue without identifiable nuclei being considered necrotic. If clinically no tumor was detectable anymore (clinical CR) but resection of the tumor bed showed vital tumor cells, the final outcome was downgraded to a PR. A clinical PR could only be upgraded to a CR if histologic analysis showed 100% necrosis of the tumor remnant. Likewise, a clinical minimal regression of <50%, but still rendering the tumor resectable, could be upgraded to a PR if the tumor remnant was found to be necrotic for 50% or more. A clinical regression of >50% would qualify for a PR even if necrosis in the tumor remnant would be <50%, as >50% of the tumor mass had disappeared.[23] The tumor was histopathological classified using the most recent World Health Organization's Classification of Tumors and graded according to the French grading system.[24,25] In case of marginal resection margins postoperative radiotherapy (60-70 Gy) was started 5-6 weeks after tumor resection. Patients were included in the study if they had a perfusion after the first PET and a resection after the 2nd PET. The medical records of these patients were reviewed and the following information was retrieved: age at the time of perfusion, sex, FDG-uptake prior to, and after ILP, characteristics of the sarcoma (localization, type, grade, percentage of necrosis after perfusion), limb salvage, period of follow-up, local recurrence of the tumor, disease free survival, overall survival and characteristics of the metastases if they occurred during follow-up (localization, time of

appearance). The technique of hyperthermic ILP with TNF ad Melphalan was extended described earlier.[26]

Positron emission tomography

FDG was routinely produced by a robotic system with a radiochemical purity of > 98% according to the procedure described by Hamacher et al.[27] All PET scans were performed using a ECAT 951/31 PET camera (Siemens/CTI, Knoxville, TN). Patients fasted for at least 6 hours prior to PET scanning. Serum glucose levels (FDG-PET) were measured and were all within normal range. After a 20-min transmission scan for attenuation correction, 300-350 MBq of FDG was injected intravenously and dynamic images were acquired for 16 time frames for a total of 50 min (ten 0.5 min, three 5 min and three 10 min).

PET data analysis

To measure the standardized uptake value (SUV), the last three time frames were summed using standard ECAT software. A region of interest (ROI) was drawn around the tumor in all planes to establish the plane with maximum FDG. A threshold of 70% of the maximum pixel value within the tumor was used. In this plane, SUVmax and SUVmean were determined using the injected radioactivity, measured radioactivity and patient weight. (SUV = radioactivity concentration in tissue (Bq/kg) / (injected dose (Bq) / patient weight (kg)). In the post-ILP PET scans, this procedure was repeated.

Statistics

The clinical data of the patients were analyzed using the Statistical Package for the Social Sciences (SPSS) for Windows (Version 12.0; SPSS INC., Chicago, IL). For the survival analysis patients were divided into two groups based on the median SUVmax. The relationships between SUV and patients' characteristics were assessed by the Student's t-test or analysis of variance as appropriate. Survival data were analyzed using the Kaplan-Meier method and the differences in cumulative survival rate were assessed using the log-rank test. Univariate and multivariate analysis (Cox proportional hazard model) were performed to determine independent prognostic predictors. All variables with $p<0.2$ in the univariate analysis were entered in the multivariate analysis. All p-values are 2-tailed and considered significant if $p<0.05$.

Results

Thirteen patients met the inclusion criteria; eight males and five females with median age of 53 (range 18-80) years. The STS was located in the upper extremity in 1 patient and in the lower extremity in 12 patients. The histology of the sarcomas is presented in Table 1.

Table 1 Histology and grade of the soft tissue sarcomas in this study

Histology	Grade
Embryonal rhabdomyosarcoma	3
Dedifferentiated liposarcoma	2
Fibrosarcoma	3
2X Synovial sarcoma	3, 3
Malignant peripheral nerve sheath tumor (MPNST)	2, 3
Myxoid Chondrosarcoma	2
Primitive neuroectodermal tumor (PNET)	3
Angiosarcoma	3
3X Pleomorphic undifferentiated sarcoma	2, 3, 3

The median size of the tumor was 16.2 cm. Median pre perfusion SUVmax was 5.6 (range 2.1-12.2) and median post perfusion SUVmax was 3.1 (range 0.9-12.2). The median follow-up time after PET scanning was 65 (range 10-152) months. At last follow-up, five patients were alive and eight were dead as a result of the disease. During follow-up one patient developed a local recurrence and nine patients distant metastases. Characteristics of the patients' sarcomas and SUVmax are summarized in Table 2. There were no significant differences in patient and sarcoma characteristics.

Univariate survival-analysis for various patient characteristics is presented in Table 3. Patients with a high SUVmax after perfusion had a significant lower overall survival as compared to those with low SUVmax (33±8 months versus 144±8 months; p=0.0004) (Figure 1). We also performed a univariate analysis for disease free- and limb-survival but no significant findings were retrieved.

Because of possible interrelation between prognostic factors, multivariate analysis was performed. All variables with p<0.2 in the univariate analysis were entered in the multivariate analysis: sex, metastases during treatment, local recurrence, pathological response, radicality of performed resection (microscopically radical (R0), macroscopically radical but microscopically irradical (R1) or macroscopically irradical (R2)), and SUVmax after perfusion. Multivariate Cox regression showed that SUVmax after perfusion did not have a

significant independent impact on survival (p=0.084), but a trend can be shown towards increased survival with lower SUVmax.

Table 2 Characteristics and SUVmax in patients with soft tissue sarcoma of the extremities

Characteristic		*Patients N*	*Mean SUV$_{max}$ ±SE pre perfusion*	*p-value*	*Mean SUV$_{max}$ ±SE post perfusion*	*p-value*
Sex	Male	8	7.0±1.3		4.6±1.2	
	Female	5	5.2±1.3	0.362	2.7±0.6	0.226
Age	<50 y	6	5.8±1.1		2.7±0.5	
	>50 y	7	6.6±1.4	0.693	4.9±1.3	0.164
Location	Arm	1	5.9		4.4	
	Upper leg	5	6.4±1.3		4.8±1.9	
	Lower leg	7	6.2±1.5	0.991	3.2±0.6	0.648
Grade	II	4	6.8±2.1		4.0±0.8	
	III	9	6.0±1.0	0.709	3.8±1.1	0.943
Local recurrent disease at start of treatment	No	10	6.6±1.2		4.1±0.9	
	Yes	3	5.3±1.2	0.584	3.2±1.5	0.663
Pathologic response rate	Complete	6	6.1±1.4		2.7±0.5	
	Partial 50%	2	5.0±0.4		7.7±4.5	
	Partial 90%	4	7.0±2.8		3.1±0.4	
	No response	1	7.6	0.910	6.1	0.107
Radiation	No	9	6.7±1.0		4.4±1.1	
	Yes	4	5.4±1.9	0.509	2.7±0.2	0.344
Resection	R0	11	6.3±1.0		3.2±0.4	
	R1	1	5.3		12.2	
	R2	1		0.769	3.3	0.0005

SE = standard error
SUV = standard uptake value

Table 3 Univariate Kaplan-Meier survival analysis: differences in survival (log-rank test)

Variable		Patients N	Mean survival ±SE (months)	p-value
Sex	Male	8	60±20	0.119
	Female	5	114±16	
Age	<50 y	6	104±22	0.282
	>50 y	7	62±20	
Location	Arm	1	51	0.826
	Upper leg	5	79±28	
	Lower leg	7	91±22	
Grade	II	4	62±27	0.459
	III	9	93±19	
Local recurrence at start of treatment	No	10	82±19	0.986
	Yes	3	86±29	
Pathologic response rate	Complete	6	103±16	0.156
	Partial 50%	2	38±28	
	Partial 90%	4	85±34	
	No response	1	17	
Radiation	No	9	62±17	0.117
	Yes	4	127±22	
Resection	R0	11	96±17	0.001
	R1	1	10	
	R2	1	18	
Development of metastases during treatment	No	4	138±11	0.058
	Yes	9	59±18	
Median SUV$_{max}$ pre perfusion	<=5.6	6	104±22	0.443
	>5.6	7	73±23	
Median SUV$_{max}$ post perfusion	<=3.1	6	144±8	<u>0.0004</u>
	>3.1	7	33±8	

Figure 1 Kaplan-Meier overall survival for STS patients with a high post perfusion SUVmax or low post perfusion SUVmax after hyperthermic isolated limb perfusion. P= 0.0004
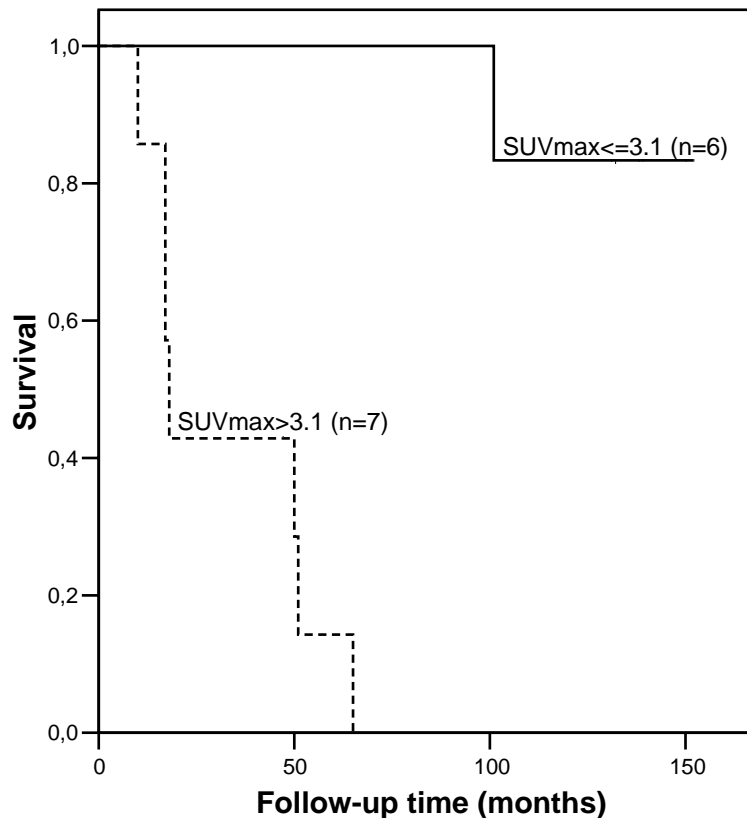
Discussion

There is an increased interest with respect to the potential of SUV-measurements with FDG-PET in patients treated with combined modality treatment. This pilot study shows that SUVmax of FDG-PET after regional chemotherapy with isolated limb perfusion might be a predictor for survival in patients with locally advanced high grade soft tissue sarcoma of the extremity. Biological studies have shown a correlation between SUVmax and tumor cellularity, mitosis and level of Ki-67 (a proliferative marker) and a moderate correlation with tissue levels of p53 (a cell growth regulation product).[19] Data in clinical studies suggest SUV to be an important prognostic factor, e.g. in patients with pancreatic, prostate, gastric cancer, head and neck and non-small-cell lung cancer and melanoma.[5,7,16,28-30]

In a selective group consisting of only high-grade sarcomas of the extremities without metastatic disease treated with regional chemotherapy through ILP we found that SUVmax was an independent predictor for survival in univariate analysis. A study in patients with bone

and soft tissue sarcoma (n=209) showed after a mean follow up of 19 months that SUVmax was a statistically significant independent predictor of patient survival.[19] We can support this result with our findings reported after a longer period of follow up and in a less heterogeneous but smaller group as only high grade soft tissue sarcomas in the extremities were considered and the type of treatment was more standardized. Studies with more patients are needed to affirm the finding of both biological imaging studies.

Conclusion

Biological imaging with FDG-PET opens new frontiers in treatment evaluation of cancer treatment. In this pilot study patients with a high grade locally advanced STS with a high SUVmax postperfusion showed a decreased overall survival in univariate analysis compared to patients with a low SUVmax. The opportunities of SUV measurements in diagnosis and treatment evaluation of STS patients needs to be further explored.

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Chapter 7

Quality of life after hyperthermic isolated limb perfusion for locally advanced extremity soft tissue sarcoma

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Chapter 7

Abstract

Background: Quality of life (QoL) and post traumatic stress symptoms (PTSS) were studied in patients with soft tissue sarcoma (STS) of the extremities treated with isolated limb perfusion (ILP), delayed resection with or without adjuvant irradiation.

Methods: Forty-one patients received a questionnaire including the Rand-36 and Impact of Event Scale (IES).

Results: 39 STS survivors, 16 male (41%) and 23 (59%) female, median age 59 (range 15-78) years participated in the questionnaire survey (response rate 95%). Median age at perfusion was 49 (range 14-72) years. No significant differences were found in mean scores between STS survivors and the reference group with the exception of a worse physical functioning. Amputated patients showed significantly worse physical and social functioning, and more role limitations than patients whose limbs were saved. Eleven patients (28%) had a PTSS score of zero, 8 patients (20.5%) had a score $\geq$ 26 suggesting the need for psychological counselling. None of these 8 patients had lost their limb. Patients who indicated that the choice of treatment was made by the surgeon rather than collaboratively showed significantly decreased social functioning, more role limitations and intrusion. Greater treatment satisfaction was significantly related to better social functioning, more vitality, better general health perception, less intrusion, avoidance, and total IES.

Conclusions: Even though STS-survivors' QoL was only different from a reference group in physical functioning, one fifth of the patients suffered from PTSS. An amputation, the physicians' decision rather than the patients' decision for the perfusion treatment and a low satisfaction with the performed treatment negatively influenced QoL.

Introduction

For decades soft tissue sarcomas (STS) were known for their poor long-term outcome with respect to local tumor control, survival as well as functional outcome. Developments in diagnostic imaging and surgical treatment with adjuvant radiotherapy are the cornerstones of the evolution over the past thirty years. Nowadays, STS patients have 5-year survival rates of 60-70%.[1,2] For patients with primarily irresectable locally advanced STS, the so-called hyperthermic isolated limb perfusion (ILP) with Tumor Necrosis Factor alpha (TNFα) and Melphalan, became available in the early nineties with a limb salvage rate of 82%.[3] Survival of extremity-STS-patients is not influenced by limb salvage procedures.[4]

The limb salvage treatment of STS with ILP is a combined modality treatment of regional chemotherapy followed by delayed extensive surgical resections with or without surgical reconstructions and/or adjuvant high dose radiation therapy sometimes followed by systemic chemotherapy with curative or palliative intent. ILP treatment is time consuming and has an uncertain outcome. The risk of loosing a limb after limb salvage procedure is determined by the risk of perioperative complications, local recurrences, and short and long-term treatment induced morbidity.

Patients who are alive after treatment for a potential fatal disease are often analyzed in terms of overall and disease free survival. However, less attention is paid to their quality of life (QoL) in these years gained. Health is defined by the WHO as a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity. Medical oncologists were one of the first physicians to implement QoL measurements into practice as the question raised to which extent quantity of life was gained at the expense of quality of life.[5] The need to investigate the QoL and the psychological consequences of this combined treatment became increasingly clear as more patients with extremity STS became long-term survivors. It is often hypothesized that for many people with cancer, the survivor advantages of the intensive treatment far outweigh the potential long-term side effects.[6] Findings in the literature are inconsistent concerning that matter: worse, equal or even better QoL in cancer survivors than in healthy comparison group have been reported.[7,8] However, specific subgroups at risk for a worse QoL have been identified such as survivors who are single, less educated, less involved in decision making or less satisfied with the received medical treatment.[9,10] Little is known about the QoL of patients with locally advanced, primary irresectable STS of a limb who underwent a TNF based ILP as an intentional limb saving treatment.

The present study was conducted to gain insight into the QoL in this intensively treated group of patients and into aspects possibly affecting these patients' QoL. The study investigates if STS-survivors differ in QoL from a reference group and evaluates if QoL and stress response symptoms in STS-survivors are related to A) socio-demographic aspects (sex, age, education level, employment and marital status and to B) disease- (time period since perfusion, limb survival, local recurrence, presence of metastases, co-morbidity) and treatment-related aspects (i.e., involvement in the choice of treatment, satisfaction with treatment).

Methods

Procedure and patients

All patients with locally advanced STS who underwent ILP with TNFα and melphalan and an intentional limb salvage treatment during the time period 1991-2003 were eligible for the study. None of the patients had metastases at the time of the ILP treatment. Patients who were alive received a letter explaining the aim of the study, an invitation to participate in the questionnaire survey and a prepaid return envelop.

All patients underwent a complex diagnostic and therapeutic pathway. Before treatment started the option of amputation or an intentional limb saving treatment with ILP was discussed. This study focuses on the STS patients who received the intentional limb saving tumor treatment. The affected limb received an ILP with TNFα and Melphalan followed by delayed resection The technique is described previously.[11] Most patients received adjuvant radiotherapy (60-70 Gy).[11] During the whole range of the intentional limb saving procedure it was possible that patients still lost their limb due to irresectability, vascular complications, wound healing disturbances or radiation induced complications.[3] The TNFα based ILP-containing treatment and the series of patients were recently extensively described.[3,11] All patients were treated following the institutional guidelines.

Measurements

Socio-demographic (sex, age, education level, employment and marital status) and disease related data (time period since perfusion, limb survival, local recurrence, presence of metastases at the time of questionnaire completion, co-morbidity) were assessed from all patients.

On a five options scale, patients could fill in their perception of actual involvement in the decision for treatment. Answers ranged from the doctor only (1) to the doctor and myself in

equal extent (3) to me only (5).[12] In addition patients were asked to score their satisfaction with treatment received on a five-point scale from 'very good' to 'very bad'. Patients were invited to indicate reasons for satisfaction and for dissatisfaction.

Health related quality of life was investigated with a Dutch-language version of the Rand 36[13], a multidimensional self-report questionnaire identical to the Short Form (SF)-36[14] but using a different scoring method. The Rand 36 consists of the following domains: physical functioning (10 items), social functioning (two items), role impairment due to physical problems (four items), role impairment due to emotional problems (three items), mental health (five items), vitality (four items), pain (two items), general health perception (five items) and health change (one item). After recoding and transformation, scores on the subscales could range from 0 to 100. Higher scores indicate a better QoL. Internal consistency of the subscales for the respondents in the present study was good (alpha ranged from 0.70 to 0.92). Normative data are available for the healthy Dutch population. The normative data compromise the mean scores of a group of 1063 men (35%) and women (65%) from a random sample of the population register of a municipality in the Netherlands (number of inhabitants = 108 000). The mean age of the persons in the total random sample was 44 (range 18-89) years.[13]

Post traumatic stress symptoms (PTSS) were measured with the Dutch version of the Impact of Event Scale.[15,16] This scale is often used in studies on cancer patients.[17] In this study information was obtained about the degree to which confrontation with the treatment for a sarcoma was influencing the current daily life of the respondent. Fifteen items measured intrusion (intrusively experienced ideas, images, feelings or bad dreams about the event) (7 items) and avoidance of unpleasant feelings or memories of the event (8 items) using the answer categories: not at all (0), rarely (1), sometimes (3) and often (5). (Intrusion: range 0-35, avoidance: range 0-40) Items of the two subscales are summed to compute a total score. (range 0-75) A total score of more than 26 is a strong indication of clinically significant PTSS, for which psychological help is recommended. Internal consistency of this questionnaire was good (alpha was 0.84 for intrusion, 0.76 for avoidance, and 0.85 for the total IES score).

Statistics

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) for Windows (Version 12.0; SPSS INC., Chicago, IL). Unpaired t-tests were computed to compare STS-survivors with the reference group in the domains of quality of

life. Pearson correlations, unpaired T-tests, and non-parametric Mann-Whitney and Kruskal-Wallis tests were conducted to examine effects of socio-demographics and treatment- and disease related variables on the outcome measures.

Correlation coefficients < 0.30 indicate a weak association, those between 0.30 and 0.50 a moderately strong association and those > 0.50 a strong association.[18]

Results

Forty-one of the 73 patients (57%), who had been treated with intentional limb salvage procedure for locally advanced, irresectable STS at the Department of Surgical Oncology at the UMCG since 1991 were still alive. Thirty nine patients, 16 male (41%) and 23 (59%) female, median age 59 (range 15-78) years participated in the questionnaire survey (response rate 95%). Median age at perfusion was 49 (range 14-72) years. Median time since perfusion was 7 (range 1-13) years. A fifth of the patients had completed primary school only and only one patient had a university degree. The median education level was lower secondary school. A little over one third of the patients had a job and one third was retired. Over two third of the STS-survivors was married or cohabiting (69%). (Table 1).

Successful limb salvage was achieved in 30 patients, while 9 patients underwent an amputation of the affected limb. Amputation of the affected limb was due to massive necrosis after ILP, local recurrence or critical leg ischemia.[3] The decision to amputate was not influenced by the presence of metastases. At the time of the present study, 4 of the 9 patients (44%) whose limb was amputated had metastases. Of the 30 patients whose limb was saved, 6 patients (20%) had metastases at the time of questionnaire completion. Thirty-three patients had a sarcoma in the lower limb (31% thigh, 21% knee and 33% lower leg) and 6 in the upper limb (15%). Three patients had local recurrence and 10 patients had distant metastases at the time of filling in the questionnaire (Table 1). The vast majority did not suffer from comorbidity.

Nine patients responded that the choice was made by the physician alone and two patients indicated that the choice was made by themselves. Almost half of the patients judged that the physician mainly made the choice of treatment with their participation. Thirty patients were very or rather satisfied with the treatment, 3 patients were not, and 6 scored the answer as neutral. Involvement in treatment choice and satisfaction with treatment were not significantly related. (Table 2).

Table 1 Socio-demographic and disease related characteristics

	N	%
Sex		
Male	16	41
Female	23	59
Age		
Median 59 years		
(range 15-78) years		
Highest education completed		
Primary school	8	21
Lower vocational degree	3	8
Lower secondary school	9	23
Middle secondary school	6	15
High secondary school	4	10
High vocational degree	8	21
University	1	2
Employment		
Paid job	13	33
Voluntary job	2	5
Housekeeping	8	21
Retired	12	31
Student	1	2
Unemployed	3	8
Marital status		
Single/divorced/widowed	12	31
Married/cohabiting	27	69
Location of STS		
Upper limb	6	15
Lower limb	33	85
Limb Survival		
No	9	23
Yes	30	77
Local recurrence		
No	32	82
Yes	3	8
Unknown	4	3
Metastases		
No	29	74
Yes	10	26
Comorbidity		
No	35	90
Yes	4	10

Independent t-tests showed no significant differences in mean scores between the STS survivors and the reference group in most aspects of QoL, except in physical functioning (p<0.001) and role limitations due to physical problems (p=0.01). A tendency for a worse social functioning was found (p=0.09) (Table 3). Eleven patients (28%) had a total stress response symptom score of zero. Eight patients (20.5%) had a score $\geq$ 26 suggesting that psychological counselling was needed.

No significant differences were found between male and female patients in QoL and PTSS. Younger STS-survivors scored better on physical functioning than older ones (r=-0.34, p=0.035). Educational level was not significantly related to QoL and PTSS in STS patients.

Table 2 Treatment choice and satisfaction and relationship between the two variables.

	Frequency	%
Choice of treatment made by…		
physician only	9	23
mainly physcian	19	49
physician and patient equally	6	15
mainly patient	3	8
patient only	2	5
Satisfaction with treatment		
Very satisfied	20	51
Rather satisfied	10	26
Neutral	6	16
Rather unsatisfied	1	2
Very unsatisfied	2	5
Correlation coefficient*	r=-.19	not significant

* correlation coefficient between the choice of treatment and satisfaction with treatment

Table 3 Quality of life of STS-survivors who underwent ILP and a reference group and comparison between the two groups.

QoL	STS Survivor Mean (SD)	Reference group Mean (SD)	t	p
-Physical functioning	55.6 (30.0)	81.9 (23.2)	-5.42	<.001
-Social functioning	79.8 (25.1)	86.9(20.5)	-1.75	0.09
-Role limitations- physical	61.6 (41.4)	79.4(35.5)	-2.62	0.01
-Role limitations- emotional	87.0 (26.8)	84.1(32.3)	0.63	0.53
-Mental health	76.7 (16.4)	76.8 (18.4)	-0.04	1
-Vitality	64.6 (18.9)	67.4 (19.9)	-0.90	0.37
-Pain	82.2 (21.2)	79.5 (25.6)	0.78	0.44
-General health perception	69.1 (19.1)	72.7 (22.7)	-1.13	0.26
-Health change	57.1 (25.6)	52.4 (19.4)	1.14	0.26
Stress response	**Mean (SD)**			
-Intrusion	6.9 (7.1)			
-Avoidance	5.3 (6.7)			
-Total	12.2 (13.1)			

There was a significant difference in only one domain of QoL when patients employed for wages were compared with the rest: they suffered from significantly less pain (Mann-Whitney U test= -2.47, p= 0.014). Having or not having a partner did not affect functioning in STS survivors. A Mann-Whitney test showed that those whose limb was amputated reported significantly worse physical (U=-2.41, p=0.016) and social functioning (U=-2.27, p=0.023), and they reported more role limitations due to physical (U=-2.39, p=0.017) and emotional (U=-2.45, p=0.014) problems than those whose limb could be saved. No significant

differences were found in mental health, vitality, pain, general health perception and avoidance, intrusion and total IES between the two groups. No significant relationships were found between time since initial treatment and the various QoL domains and PTSS.

If patients had metastases at the time of the survey, they reported significantly worse physical functioning (U=-2.13, p=0.034), and more role limitations due to physical (U=-2.14, p=0.032) and emotional (U=-2.92, p=0.004) problems. There were no differences in the other areas of QoL nor in intrusion, avoidance and total stress response symptoms. None of the nine amputated patients had a score $\geq$ 26 on the total IES. Of the ten patients with metastases two had a score $\geq$ 26. The effects of incidence of local recurrence and chronic diseases on QoL and STS could not be examined because only a few patients had experienced local recurrence (n=3) or suffered from co-morbidity (n=4).

Kruskal Wallis tests showed that those who were less involved in the decision for treatment had significantly higher scores on intrusion (Chi-square=11.37, p=0.023). Also, they tended to report more total IES (Chi-square=9.12, p=0.058) and a worse social functioning (Chi-square=9.17, p=0.057). Greater treatment satisfaction was related to a better social functioning (r=-0.36; p=0.024), more vitality (r=-0.32; p=0.046), and a better general health perception (r=-0.36; p=0.028). Higher treatment satisfaction was significantly associated with less intrusion (r=0.57; p<0.0001), avoidance (r=0.35; p=0.27) and total IES (r=0.58; p<0.0001). These correlation coefficients ranged from moderately strong to strong.

Fourteen patients (36%) indicated additionally why they were satisfied with the treatment, 18 (46%) why treatment had discouraged them, and 7 patients (18%) mentioned both positive and negative aspects of treatment. Positive experiences mentioned by 16/21 of the patients were that they were satisfied with the final result and the fact that the course of treatment was as explained and therefore expected. The remaining 5/21 mentioned they experienced the treatment positively because they had expected worse and because they had suffered little pain. Discouraging arguments mentioned were the intensity of treatment (20/25), long recovery period (9/25) and/or the fact that they had been seriously ill as a consequence of the treatment (6/25).

Discussion

The aim of the current study was to gain insight into the QoL and PTSS of patients with locally advanced, primary irresectable STS of a limb who underwent an intensive and extensive sarcoma treatment that consisted out of a TNFα based ILP followed by delayed

surgical resection ± adjuvant high dose external beam radiotherapy as an intentional limb saving treatment.

Physical functioning and role limitations due to physical problems were the only domains in which our group of patients scored significantly lower than the reference group. The problems perceived in the physical domains could be explained by the resection of a large muscular compartment and often adherent structures in the affected part of the limb that the sarcoma patients had undergone. Obviously, such invasive surgery affects the physical functioning of these sarcoma patients. On the other hand, functioning in the remaining QoL domains in these patients was the same as in the reference group. It has been suggested that patients with cancer seem to change their internal standards and their expectations about life during treatment. Other studies also postulate that cancer patients evaluate QoL according to their new expectations and different standards.[5,19] The limitations patients experienced in physical functioning do not seem to affect functioning in the other QoL domains.

The finding of a surprisingly high percentage of 20.5% of the patients having clinically elevated PTSS is in contrast to literature showing a prevalence of clinically high PTSS among people with cancer varying from 3% to 12% depending on the cancer treatment.[20-23] The 20.5% PTSS rate found is this study is comparable with more traditional traumatic events such as rape, war, disaster and accidents in general samples.[21]

To distinguish those in our group of patients who had more problems concerning QoL and PTSS, we investigated the effects of socio-demographic, disease and treatment related variables.

Socio-demographics

Younger STS-survivors scored better on physical functioning than older STS-survivors. Some other QoL studies also showed that the physical autonomy score was affected by age.[24,25] In the other QoL domains and PTSS we found no associations with age. This is in contrast with the literature reporting that younger age is a risk factor for psychosocial distress, anxiety and depressive symptoms among cancer survivors.[19,26]

Other socio-demographics such as sex, education level, marital status were not related to QoL and PTSS in our studies. This is different from findings in literature that show that women tend to develop somatic complaints more quickly after negative life events[24,27]; a higher educational level is associated with a higher QoL in the general population[19,24]; and that having a partner has been identified as a predictor of better well-being in the general population, in particular in men.[19,26] There was a significant difference in one domain of QoL

when patients employed for wages were compared with the rest: they suffered from significantly less pain. This can be a chance finding. Another suggestion is that work distracts and reduces pain sensation. More research is needed to evaluate this finding.

Illness related

Patients with an amputated limb had a worse QoL score in physical and social functioning, and in role limitations due to physical and emotional problems. This is in contrast with the literature that showed no differences in QoL between patients whose limb was amputated and patients treated with conservative surgery and adjuvant radiation treatment.[28-30] These studies, however, describe patients who were randomised between amputation and limb saving treatment. In our group, all treatments started intentionally with a limb-saving purpose. Our results suggest that once the patients are on the pathway where limb-saving treatment seems possible, an eventual amputation actually may make a difference resulting in a decreased perception in some of the QoL domains.

Even though more quality of life problems were found in patients whose limb was amputated it appeared that none of these patients had a posttraumatic response symptom score indicative of need of professional psychosocial care. A hypothesis for this phenomenon may be that the loss of a limb has released patients from the insecurity of a possible loss in the future. The threat of local recurrence and further damage to the limb due to long-term effects of radiation or vascular incompetence may be like a sword above the head that may fall at any moment. An equal percentage of patients with metastasised disease had a clinically elevated PTSS score as found in the complete study group (20%). Metastasised patients did have problems in physical functioning and role limitations due to physical and emotional problems.

We found no effect of time in relation to QoL suggesting physical functioning problems are of a more permanent nature. In Lamperts study patients with lower extremity STS were more at risk to become disabled than patients with STS in other areas of the body.[31] In our own data the number of upper extremity STS patients (n=3) was too small to detect significant differences in QoL and PTSS compared to patients whose affected limb was a lower extremity.

Choice of treatment

This study shows that those patients who indicated that the surgeon made the treatment choice rather than they themselves, showed a decreased social functioning, more role limitations due to physical problems and higher levels of intrusion. This is in agreement with other studies

reporting that patients benefit from participating in medical decision making.[10] Despite all the reasonable doubts patients may have, it seems important that the patient is at least involved in the final decision for his or her treatment. Other studies also mention that patients who perceive that they have decisional control in their treatment may regain control-perception over the disease as well, which may ultimately lead to a higher QoL.[32-36] It may be that greater attention should be paid to the communication of treatment options and its consequences to the patient so that the patient is better able to make an informed decision.

Our results also showed that patients who were more satisfied with treatment reported less PTSS and a better QoL, a finding in line with earlier research.[10,37-40] In contrast to other studies no significant relationship was found between decision involvement and treatment satisfaction in the current study.[10,39]

In the light of data indicating that 20.5% of the STS survivors experience PTSS symptoms even years after treatment and that patients, in particular those whose limb was amputated, had problems in the physical QoL domains, identifying ways to prevent or relieve these symptoms should be considered. A suggestion would be a multimodal rehabilitation program including a physical and a psychosocial program that might help reduce the problems in the physical domains and the psychosocial distress in these patients. An intensive multi-focus rehabilitation program for cancer patients after completion of their cancer treatment appeared to have immediate and longer term beneficial effects on physiological functioning and quality of life.[41] Furthermore, attention should be paid to the issue of collaborative decision making that may be better achieved with informing the patient more comprehensively about treatment options and possible consequences. Attention to communication issues may also increase patient satisfaction.

The inclusion of a validated generic QoL questionnaire and the high response rate (95%) are the strengths of this study. On the other hand only 41 patients (57%) of the original study population of 73 patients were eligible since the remaining 32 patients were deceased at the time of the survey. In addition, the present study is a retrospective cross-sectional study. The measurement of quality of life in STS patients is a dynamic rather than a static process that requires reassessment. Consecutive quality of life measurements may give insight into change over time and causal relationships between variables.

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Chapter 8

Other primary neoplasms in patients with soft tissue sarcomas of the extremities treated with isolated limb perfusion

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Chapter 8

Abstract

Purpose: To investigate the incidence of other primary neoplasms (OPN) in patients with a locally advanced soft tissue sarcoma (STS) of the extremities and their effect on survival.

Patients and methods: A retrospective cohort of 73 patients, median age 54 (range 14-80) years diagnosed with locally advanced STS, all treated by isolated limb perfusion and delayed surgical resection was studied. Medical records were examined for clinical characteristics of the STS and OPN, therapeutic interventions, morbidity and survival.

Results: Seventeen patients of the 73 treated with ILP (23%) had an OPN: 8 OPNs before STS diagnosis (47%), 1 synchronously, 1 between two OPNs, and 7 OPNs after STS diagnosis (41%). The median follow-up period after STS-diagnosis was 48 (4-162) months. The 5-year survival of the non-metastasized STS-only group (79 ± 13%) was not significantly different from the STS-OPN group (83± 17%) (p=0.46), whereas the 5-year survival rate of the OPN-STS group (13 ± 13%) was significantly decreased versus the STS-only group (P<0.0001). The most frequent types of OPN were breast cancer, squamouscell carcinoma and urinary tract (kidney and bladder) cancer.

Conclusion: Patients with locally advanced STS have a high risk to be diagnosed with an OPN. The overall survival in non-metastasized STS patients is significantly decreased if patients had an OPN before an STS.

Introduction

Soft tissue sarcomas (STS) occur at approximately 3.6 per 100.000 per year in The Netherlands. They may arise in any part of the body, but their predominant location are the extremities. The incidence increases with age and half of the patients are over 65 years of age, but STS are also common among children.[1] The only curative treatment for local and even recurrent disease is surgery. For the majority of STS, chemotherapy seems to be ineffective, with some exceptions, e.g. Ewing sarcomas/ primitive neuroectoderm tumors (PNET) and embryonal rhabdomyosarcomas for which chemotherapy can increase curation rate.[2]

Over the past thirty years, enormous progress has been made in the local management of STS. Developments in diagnostic imaging, adjuvant radiotherapy and the introduction of hyperthermic isolated limb perfusion (ILP), are the cornerstones of the improved limb salvage rate.[3] Nowadays almost 90% of patients with extremity STS can be treated with limb salvage treatment, with a 5-year survival rate of 60-70%.[2,4] Tumor size, histology, grade, primary tumor site, and presence of metastatic disease are the most important prognostic factors for survival.[1] With the improving prognosis of STS patients, long-term follow-up data on local recurrences, distant disease and survival are becoming available.[2,3] Several recent studies suggested that patients with STS are at increased risk of development of an other primary neoplasm (OPN). Genetic tumor syndromes such as neurofibromatosis type 1, familial adenomatous polyposis, retinoblastoma and Li-Fraumeni syndrome are known to be associated with STS.[2,5-11] But also in STS patients without these well defined genetic syndromes, an increased risk of developing other malignancies - either before or after the sarcoma diagnosis - has been noted, most notably of the breast and kidney.[12,13]

The aim of the study was to investigate the incidence of OPNs in a patient cohort with locally advanced STS of the extremities treated with ILP and resection, as well as the effect of OPNs, diagnosed either before or after sarcoma treatment, on the overall survival of these sarcoma patients.

Patients and Methods

Patients

The incidence of OPN in a retrospective cohort of 73 patients, diagnosed with a locally advanced STS of the extremity from January 1991 till December 2003 and referred to the University Medical Center Groningen for a combined treatment consisting of ILP and delayed surgical resection was studied.

These 73 patients, 36 males and 37 females with a median age of 54 (range 14-80) years received a treatment that consisted of 60 minutes ILP (39-40 °C) with Tumor Necrosis Factor alpha (TNFα) (Beromun®, Boehringer Ingelheim, Austria) (3 mg TNF upper limb or 3-4 mg lower limb) and Melphalan (L-phenylalanine mustard; Glaxo-Wellcome Company, Italy) ((10 mg/l Melphalan (limb volume, leg) to 13 mg/l Melphalan (limb volume, arm)). The perfusion technique was described previously.[14]

After ILP, delayed tumor resection was performed after 6-8 weeks, unless there was an indication for earlier intervention. The patients included in this study were recently described in detail elsewhere with respect to limb salvage and the value of adjuvant radiation in the local sarcoma treatment.[3,15] Postoperative radiotherapy (60-70 Gy) was considered indicated in case of <95% necrosis on pathological examination of the tumor or with marginally free or microscopically positive resection margins. Patients with metastatic disease at time of diagnosis of STS were excluded in the overall survival analysis in this study.

The medical records of all patients were reviewed and the following information was retrieved: age at diagnosis of STS, sex, characteristics of the sarcoma (localization, type, grade), duration of follow-up, characteristics of the OPN (age at diagnosis, type, location, treatment), diagnosed before or after the sarcoma treatment, the characteristics of metastases if they occurred during the treatment (localization, age at detection) and overall survival. All ILP patients were followed at regular intervals in the outpatient clinic. No patient was lost for follow-up.

The STS's and OPN's were histopathologically classified using the most recent World Health Organization's Classification of Tumors and the STS were also graded according to the French grading system.[16,17]

Statistical analysis

The disease status at the latest follow-up (i.e. death due to the STS, death due to the OPN, death to other cause, alive with disease and no evidence of disease) was analyzed. Overall survival calculated from STS treatment onwards was scored in the non-metastasized treated STS patients grouping those with STS-only and those with STS and an OPN before or after the STS. Analyses were performed according to the Kaplan-Meier method and the Log-rank test.[18] Endpoints were either death or date of last follow-up. A P-value of less than 0.05 was considered statistically significant. Graph Pad Prism® version for Windows statistical software was used. Differences between groups were assessed by analysis of variance or Chi-Square as appropriate.

Results

Data of seventy-three patients with primary, locally advanced STS of a limb who underwent ILP and surgery were analysed. In 17 patients (23%) a total of 19 OPNs were diagnosed: 10 females (59%) and 7 males (41%). The time interval between the diagnosis of the OPN prior or after STS-treatment is represented in Figure 1.

Figure 1 Cancer events depicted chronologically: age related in penetrance in 17 patients with soft tissue sarcoma (STS) and another primary neoplasm (OPN). Every line indicates one patient.
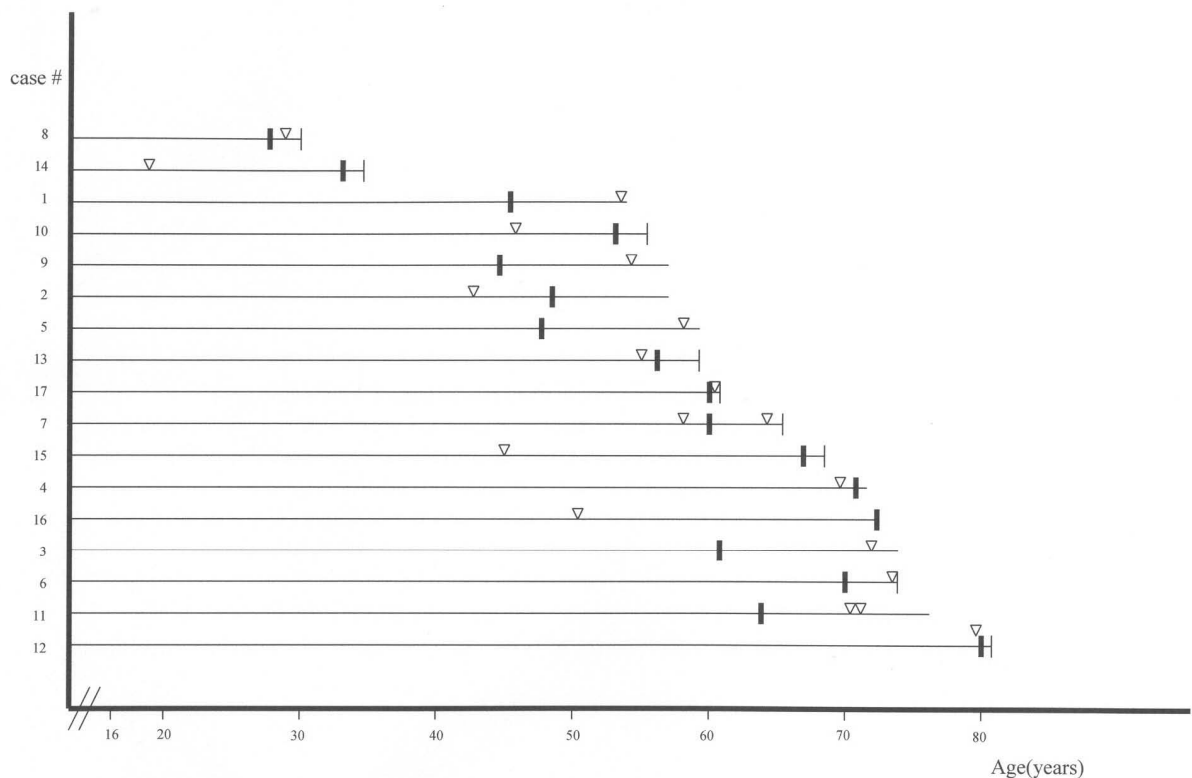
▌Age at which STS was diagnosed

▏Age of death

▽ Age on which OPN was diagnosed

Eight patients had OPNs before STS diagnosis (47%) with a median time interval of 84 (range 15-145) months, 1 synchronously, 1 between two OPNs, and there were 7 patients who developed a OPN after the STS (41%) with a median time interval of 68 (range 1-273) months. We distinguished three groups; those without OPN (='STS-only'), those with STS followed by OPN (='STS-OPN group') and those with OPN followed by STS ('OPN-STS

group'). The patient with an STS between the two OPN's could not be included in either of the two latter groups. The various types of OPNs, their order of appearance and their treatment are represented in Table 1, indicating that breast cancer, squamous cell carcinoma, renal cancer and colorectal cancer were detected more than once.

Table 1 Types of other primary neoplasms (OPNs) in STS patients and their treatment

First neoplasm	Second neoplasm	Treatment of OPN
STS	adenoca breast	BCT
STS	adenoca breast	ablatio
STS*[pt1]	adenoca breast	ablatio
STS	renal clear cell cancer	nephrectomy
STS	adenoca colon	none
STS *[pt2]	melanoma upper arm as well as basocellular carcinoma nose	local excision
STS	MPNST neck (C1-C3)	laminectomy and XRT
STS	adenocarcinoma parotic gland	local excision and lymphadectomy
adenoca breast	STS	BCT
squamouscell carcinoma mouth	STS	local excision
squamouscell carcinoma larynx**	STS	local excision
squamouscell carcinoma mouth	STS	XRT
renal clear cell cancer	STS	partial nephrectomy
adenoca rectum	STS	LAR + CT
Hodgkin's disease	STS	splenectomy, XRT, CT
endometrial carcinoma*[pt1]	STS	hysterectomy
cervical carcinoma	STS	total exenteration
bladder cancer	STS	intravesical CT

Legend
-BCT = breast conserving therapy
-CT = chemotherapy
-LAR = low anterior resection
-MND = modified neck dissection
-MPNST = malignant peripheral nerve sheath tumor
-XRT = radiation therapy
*[pt] = indication of the two patients with a double OPN
** = patient with STS and OPN diagnosed simultaneously

There were more breast cancers in the STS-OPN group and there more skin tumors in the OPN-STS group. Renal cell cancer and colon cancer were divided equally in both groups. There was one patient who had a second STS as OPN. Since the first tumor was a fibrosarcoma in the leg and the second tumor was a malignant peripheral nerve sheath tumor (MPNST), diagnosed 15 months later in the cervical vertebrae C1-C3, this last one was considered as an OPN. Demographic data and clinical characteristics of the patients are summarized in Table 2.

Table 2 Demographic and clinical data of 73 patients with a locally advanced soft tissue sarcoma (STS) of the extremities: 56 patients with only an STS (**A**) and 17 patients had an STS and another primary neoplasm (OPN) (**B**).

	All patients	A: Patients with only an STS	B: Patients with STS and OPN
All n=	73	56	17
Sex			
males	36 (49%)	29 (52%)	7 (41%)
females	37 (51%)	27 (48%)	10 (59%)
male: female-ratio	1:1	1:1	2:3
Median age STS diagnosis	54 (range 14-80) yrs	52 (range 14-78) yrs	60 (range 28-80) yrs
Overall survival (after STS-diagnosis) in non metastasized patients			
1 year	83.0 ± 10.0%	93,3 ± 6,7 %	79,8 ± 20,2 %
5 years	63.1 ± 14.1%	78,9 ± 13,3 %	49,7 ± 26,7 %
10 years-	48.0 ± 17.2%	60,0 ± 19,6 %	41,5 ± 26,7 %
Median size of the STS	16.2 (range 8.3-23) cm	14 (range 8.3-20) cm	17.5 (range 10.2-23) cm
Tumor grade			
grade I	6 (14%)	4 (7%)	2 (12%)
grade II	24 (32%)	18 (32%)	6 (35%)
grade III	43 (54%)	34 (61%)	9 (53%)
Histology in %			
pleomorphic undifferentiated sarcoma (not otherwise specified)	24 (33%)	17 (31%)	7 (41%)
synovial sarcoma	10 (14%)	9 (17%)	1 (6%)
myxoid liposarcoma	7 (9%)	4 (7%)	3 (17%)
leiomyosarcoma	6 (8%)	5 (9%)	1 (6%)
myxofibrosarcoma	4 (5%)	4 (7%)	0 (6%)
fibrosarcoma	3 (4%)	2 (3%)	1 (6%)
MPNST	3 (4%)	2 (3%)	1 (6%)
epitheloid sarcoma	2 (3%)	1 (2%)	1 (6%)
myxoid chondrosarcoma	2 (3%)	2 3(%)	0 (0%)
angiosarcoma	2 (3%)	1 (2%)	1 (6%)
embryonal rhabdomyosarcoma	1 (1%)	0 (0%)	1 (6%)
others*	9x1 (10%)	9x1 (16%)	0 (0%)
Metastases			
No metastases	36 (49%)	31 (55%)	5 (29%)
Metastases at diagnosis STS	12 (17%)	11 (20%)	1 (6%)
Metastases during follow-up	25 (34%)	14 (25%)	11 (65%)
Resection			
R0	56 (77%)	44 (79%)	12 (70%)
R1	12 (16%)	9 (16%)	3 (18%)
R2	3 (4%)	2 (4%)	1 (6%)
No resection	2 (3%)	1 (2%)	1 (6%)

Legend:
* = well differentiated (lipoma like) liposarcoma, dedifferentiated liposarcoma, pleomorphic liposarcoma, primitive neuroectodermal tumor (PNET), clear cell sarcoma, Ewing sarcoma, malignant myoepithelioma of soft tissue, pleomorphic rhabdomyosarcoma
R0 = microscopically radical resection; R1 = macroscopically radical resection (but not microscopically radical);
R2 = macroscopically irradical resection, MPNST = malignant peripheral nerve sheath tumor

There were relatively more women in the group with an OPN than in the STS-only group. The median age at STS-diagnosis in the group with an OPN was also higher compared to the STS-only group. No significant differences could be found with respect to median tumor size, tumor grade, and performed surgery (R0, R1, R2) between the two groups, although in the group with an OPN there were relatively more pleomorphic undifferentiated sarcomas and myxoid liposarcomas.

There were no cases where the treatment of the first malignancy (i.e. radiation therapy or chemo therapy) could be linked to the development of the second malignancy. (Table 1).

The median age of STS patients with an OPN before the sarcoma was 60 (range 28-80) years and also 60 (range 33-73) years if the OPN was diagnosed after the STS, while the median age of STS in patients with only an STS was 52 (range 14-78) years. The median follow-up period in the group of patients with STS and OPN, calculated from the date of the STS-diagnosis, was 48 (range 4-162) months; median follow-up period post-sarcoma OPNs 83 (range 11-162) months, and median follow-up period pre-sarcoma OPNs 18 (range 4-113). Of the 17 patients with STS and an OPN, 7 patients (41%) are still alive with a median follow up of 113 (range 18-162) months. Two patients died of the OPN (colon carcinoma and malignant schwannoma located in the cervical spine) (12%) whereas six patients died of their STS (35%) and two patients died of metastases of either the STS or the OPN (one patient with rectal cancer and one patient with endometrial carcinoma and breast cancer). The 5-year overall survival rate in STS-only patients was $79 \pm 13\%$ compared to $50 \pm 27\%$ in patients with an STS and OPN (p = 0.049). In Figure 2 the overall survival of the non-metastasized STS-only patients is compared with the OPN-STS and STS-OPN groups. The OPN-STS group had a significantly shorter overall survival. The 5-year survival of the STS-only group ($79 \pm 13\%$) was not significantly different from the STS-OPN group ($83 \pm 17\%$) (p=0.46), whereas the 5-year survival rate of the OPN-STS group ($13 \pm 13\%$) was significantly decreased versus the STS-only group (P<0.0001) and the STS-OPN group (P= 0.009). The cause of death was the OPN in two cases (both in the STS-OPN group), the STS in 6 cases (five patients of the OPN-STS group and 1 patient whose STS and OPN were diagnosed simultaneously) and unknown in two cases.

Figure 2 Kaplan-Meier curve for overall survival in not-metastasized patients with only soft tissue sarcoma (STS-only) compared with not-metastasized patients with STS and another primary neoplasm (OPN). The group op patients with an OPN prior to STS are indicated as OPN-STS and the patients with an STS prior to an OPN are indicated as STS-OPN. The comparison STS-OPN versus STS-only was not significant (P=0.46). The comparison between OPN-STS versus STS-only was highly significant (P<0.0001) as well as the comparison between STS-OPN versus OPN-STS (P=0.009). (One patient with OPN and STS diagnosed simultaneously was classified as OPN-STS).
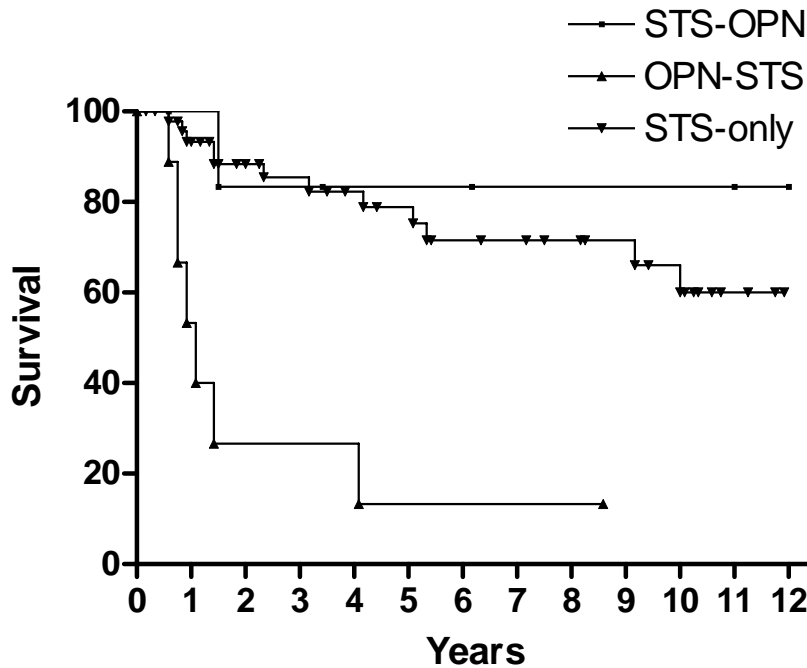
Discussion

Since the incidence of STS is low and the overall 5-years survival is 50-60%, data on the occurrence of OPN in patients with STS and its influence on survival are rare. The incidence of OPNs in patients with STS in this series was 23%, which is higher than the 16% incidence in 814 STS patients documented in the same period by the Comprehensive Cancer Center North Netherlands (CCCNN), the regional registry of cancer data in the northern part of The Netherlands. In the CCCNN series, 11% had an OPN prior to the STS and 5% had a OPN after STS (unpublished data). Our incidence figures are also significantly higher than those recently published by Merimsky et al. who found an OPN in 28 out of 375 STS cases (7.5%), half of which before and half which after diagnosis of STS (Table 3).[13] This might be due to selection criteria since we have included adult patients with large, merely high grade (88%) STS in the extremities. Another reason might be the fact that in this series no patients were

lost in follow-up and that we were able to question all survivors specifically about OPN's in their past medical history.

Table 3 Studies of STS and OPN in the literature

Study	Current study	Merimsky[13]
Number of pts	73	375
Definition of STS patients	High grade STS of the extremities	STS
Incidence of OPN in %	23	7.5
M:F ratio	2:3	Not available
% STS preceding OPN*	47	50
% OPN preceding STS	53	50
Most frequent OPN's	-adenoca breast -squamous cell ca head and neck -renal clear cell ca -colorectal adenoca	-renal clear cell ca -STS -adenoca ca -colon ca
Median age STS diagnosis	60 (range 28-80)	47 (range 16-72)
Median age OPN diagnosis	53 (range 18-80)	68 (range 35-87)
Median duration of follow-up (since STS diagnosis)	48 (range 4-162)	51 (range 0-258)
Overall survival if 1 st tumor is STS: median (range) in months	85 (11-162)	78 (5-258)
Interval between STS and OPN: median (range) in months	84 (0-145)	120 (0-252)
Overall survival if 1 st tumor is OPN: (range) in months**	76 (20-282)	102 (3-319)
Interval between OPN and STS: median (range) in years	68 (1-273)	84 (0-324)

Legend:
* = including patients whose STS and OPN were diagnosed simultaneously
** = from the time of diagnosis of the first tumor

Cohen et al. also report an incidence of OPN in STS patients.[19] These data can not be compared to our data in the same way as Merimsky's, due to the selection of patients: Cohen included exclusively OPN's *after* STS diagnosed in children and adolescents (< 18 years old) and documented an incidence rate of 1.8% (27/1499 patients) with a cumulative incidence of 2%. This incidence rate was 12 times the expected incidence rate during the first 5 year.

Many possible explanations exist for the occurrence of multiple primary neoplasms in cancer patients such as genetic predisposition, exposure to carcinogens, treatment modalities that

increase the likelihood of developing a new malignancy (e.g. radiotherapy and chemotherapy), immune- compromised state, and increased age. [20-22] Four women out of 37 (11%) developed breastcancer at a median age of 58 (range 51-73). This percentage is higher than expected on the basis of their age and population incidence alone (9.7% by age 74 in the general female population).[25] In the literature female sex was found to be an independent risk factor for the presence of an OPN.[23,24] No obvious explanations were found to explain the high occurrence of OPNs in these sarcoma patients. The progress in preoperative staging by various imaging techniques, such as spiral computed tomography (CT), magnetic resonance imaging (MRI), ultrasound and positron emission tomography (PET), can increase the chance to find asymptomatic OPNs at the time of the sarcoma is diagnosed. On the other hand asymptomatic OPNs are not diagnosed during sarcoma follow up since extensive radiodiagnostic follow up of sarcoma patients is not indicated. An explanation of the high incidence of a second primary malignancy might be the improved survival due to better combined treatment strategies of the first tumor, thereby adding lifeyears in which a second primary neoplasm can develop. More epidemiologic data is emerging, indicating that the risk of a second malignancy is about twice as high for survivors of various types of cancer as compared to the general population.[26,27] Currently, in the Netherlands 10% of all registered invasive cancers are diagnosed in patients that had a previous OPN.[25] In our study 4 out of 37 women developed breast cancer, 3/73 cases had squamous cell carcinoma and 3/73 cases developed urinary tract carcinoma. This top three of most frequently diagnosed OPNs is the same as that in the CCCNN-data based on 814 STS patients and also comparable to the data of Merimsky et al. Other (case) reports also suggest that patients with STS are at increased risk of developing a second malignancy, most notably of the breast and kidney.[12,28,29]

Survival is significantly shortened if a OPN is diagnosed prior to the STS. The prognoses of OPNs that were diagnosed in the OPN-STS group did not significantly explain this difference in survival with the STS-OPN group. There were even more skin tumors, especially squamous cell carcinomas known for their favorable prognosis, diagnosed in the group with an OPN prior to STS. There was no significant difference in age at diagnosis in the STS-OPN group versus OPN-STS group. The presence of an OPN *before* an STS can either be an independent prognostic determinator that decreases survival due to it's own adverse effect on survival, possibly triggered by the combined treatment strategy in the subsequent STS. The occurrence of multiple tumours in one patient may also be due to un underlying genetic cause, i.e. an increased susceptibility to develop malignancies. The presence of as yet unknown cancer susceptibility genes in the population might explain the increased incidence of multiple

primary's in some cases and possibly also their reduced response to treatment and thereby their survival. Larger prospective studies are needed to verify these findings before further conclusions can be drawn for an individual patient with STS. Our data underline the need for thorough registration of follow-up data of cancer patients.

The complete information concerning demographic and treatment factors and the long follow-up period are the strengths of this retrospective cross-sectional study. Moreover, the fact that we only included locally advanced primary irresectable STS of the extremities makes our sample more homogeneous compared to most other studies.

In summary, the incidence of OPNs in patients with a locally advanced soft tissue sarcoma in the limb is higher in this series than reported to date. The data show that patients with an OPN before a locally advanced STS have a significant shorter survival than patients diagnosed with only a soft tissue sarcoma.

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Chapter 9

Future perspectives

Chapter 9

Study the past if you would define the future (Confucius 551 BC-479 BC)

Long-term research is important to gain genuine insights into the outcomes of cancer treatment. This is the case for sarcomas, as well as for other tumors, such as testicular cancer, breast cancer, colorectal tumors, tumors in children, and hematological malignancies. Long-term research has become an important component not just of clinical cancer research such as treatment induced morbidity but also of, for example, (genetic) epidemiological research.

Soft tissue sarcomas are a rare group of cancers accounting for circa 1% of all malignancies.[1] The heterogeneity of sarcoma types and the rarity of cases have hampered evidence-based randomized double-blind studies concerning optimal treatment. In the mid-seventies, several important observations reshaped the approach to sarcoma treatment. Firstly, due to more insight in the growth pattern of sarcomas, the local recurrence rate after limb salvage treatment decreased to 10-15%.[2] Secondly, histology, tumor type, grade, and size were defined as predictors of survival independent of the surgical therapy. Thirdly, local recurrence was not necessarily associated with poor outcome, as more than 30% of patients could be salvaged by additional surgery.[2] Finally, a major change is the shift from surgical resection alone as the treatment of sarcomas to the use of multimodality treatment: surgery, radiation and/or chemotherapy.[3]

This long-term research, into the value of regional perfusion as an induction treatment for primarily non-resectable soft-tissue sarcomas of the extremities, has also provided a lot of information that has already contributed to the improvement of this cancer treatment and will lead to further improvements in the future. The central issue should be the reduction of short-term and long-term complications caused by, on the one hand, extensive surgical resections and, on the other hand, the high radiation dosage. Tissue transposition and optimization of radiotherapy will be key elements in this endeavor. Years ago, we investigated the possibilities of intra-arterial chemotherapy in combination with radiotherapy.[4] Although this treatment was highly effective, the complications were severe.[5] Perfusion treatment in itself only causes minimal morbidity. Possibly, regional perfusion may be replaced by regional infusion, as is currently being developed for melanomas.[6,7] Using this technique, groin catheters are inserted percutaneously into the blood vessels. After isolation of the lower limb with a tourniquet, the intra-arterial infused chemotherapy will be manually flushed without using an oxygenation system. The major advantage of the minimally invasive infusion treatment is the possibility to be repeated and to evaluate it non-invasively with Positron

Emission Tomography (PET). If necessary, pre-operative radiation followed by surgery may be preferred to surgery followed by radiotherapy.

There have been several breakthroughs in diagnostic imaging and treatment, resulting in improved limb salvage and survival rate, as summarized previously in this thesis. New technologies of high interest for the surgical oncologist are already available or will become available.

Recently, spiral computed tomography (CT) was introduced, providing the surgeon with optimal three-dimensional images (3D-images) and further facilitating preoperative treatment planning. Computer-assisted navigation systems have become available, which are extremely useful in the intra-operative treatment planning of sarcomas located in or near the pelvic girdle or vertebral column. Improvements in the radiodiagnostics of soft tissue sarcoma have had a major impact on the staging and planning of surgical treatment.[8] Imaging provides the clinician with crucial information in the diagnosis, staging, treatment planning, treatment evaluation, and post-treatment assessment of patients with soft tissue sarcoma. Magnetic Resonance Imaging (MRI), including contrast-enhanced sequences, is usually preferred for evaluating the primary site in extremity sarcomas and lesions of the head and neck. CT is generally preferred for imaging of the chest, abdomen, and pelvis, either in the evaluation of the primary site in those regions or for identifying metastatic disease. The experienced radiologist can often suggest a specific diagnosis or narrow the differential diagnosis from the imaging characteristics, particularly with MRI. It is imperative that imaging be performed in a manner specific for the evaluation of soft tissue masses, and before biopsy or surgery, to provide the most accurate preoperative assessment and treatment planning.

Although PET is not directly useful for diagnosing soft-tissue sarcomas, it may sometimes be helpful in the differential diagnosis of benign and malignant tumors. Its potential mainly lies in the area of therapy evaluation, and as such it is already being used with gastrointestinal stroma cell tumors.[9] Other areas of application might include Ewing's sarcoma and rhabdomyosarcoma and the evaluation of new induction chemotherapy treatments. PET-MRI provides a very good insight into local tumor growth processes, the presence of metastases and therapy evaluation. Figure 1. In patients with advanced solid tumors, phase I studies are being performed to measure the effect of oral angiogenesis inhibitors like AG-013736 with dynamic contrast-enhanced MRI as a pharmacodynamic measure of response.[10] Using the biologic activity of tumors will optimalize diagnostic as well as therapeutic options in the future.

Sentinel node biopsy has become a tool for the staging and treatment of breast cancer and will probably soon be used with melanoma also, while research is being conducted into its relevance with gastrointestinal tumors and lung cancer.[11] Sentinel node biopsy may also be used for staging sarcomas that have a slightly higher risk of developing lymphogenic metastases, such as synovial sarcoma, epitheloid sarcoma, rhabdomyosarcoma, and clear cell sarcoma.

The transition from conventional radiotherapy to three-dimensional conformal radiation therapy (3D-CRT) means a reduction in the volume of healthy tissue receiving a high dose in favour of the radiation target volume. The technique that is already being used with breast cancer, the simultaneous integrated boost, may in future also be applied to sarcomas. It involves applying more radiation to a small area, which reduces the overall treatment time. By contrast, the move from 3D-CRT to intensity modulated radiation therapy (IMRT) involves more fields, while the dose-volume histograms show that, as a consequence, a larger volume of normal tissue is exposed to lower doses. In addition, the number of monitor units is increased by a factor of 2 or 3, increasing the total body exposure, due to leakage radiation. Altogether, a disadvantage of IMRT is likely to be the almost double incidence of second malignancies compared with conventional radiotherapy from about 1% to 1.75% for patients surviving 10 years.[12]

The problem of radiotherapy has been, and will remain, a two-edged sword: although it is an important component of and for local tumor control, it may also induce secondary tumors and, in the long term, may also lead to fibrosis, with reduced limb function as the ultimate outcome.

What we have learnt by now is that reconstructive plastic surgery should be used on a much wider scale. Reconstructive plastic surgery procedures through tissue transfer and microvascular surgical techniques play a key role in coverage of major defects and prevention of wound-healing problems, and reduces the side effects of radiation treatment.

Sarcomas are an interesting tumor model. They give the word "radical" a new dimension. "Radical" from a purely surgical point of view, with "radical" excision of the root or source of a morbid process, appears to be highly important in the improvement of patient survival and the prevention of local recurrence. In the case of sarcomas, this has led to very extensive surgery, major amputations, and unique methods of reconstruction.

An example of one of the first successful "radical" operations, a hemipelvectomy, was reported by Charles Girard in 1895, for a recurrent sarcoma.[13] Pringle stated in 1916 that this procedure "entails the greatest mutilation for which surgery is responsible".[14] Nowadays these very extensive resections are preceded by more accurate preoperative assessment and followed by complex reconstructive procedures. This is shown in Figure 2.

Figure 1 PET-MRI provides a very good insight into local tumor growth processes and metastases as illustrated here in an upper leg with a locally advanced extremity sarcoma before and after isolated hyperthermic limb perfusion with TNFα and Melphalan.1"Radical" also becomes a more abstract term referring to a fundamental shift in our paradigms on cancer biology and the outcome of the patient, both oncologic and functional.
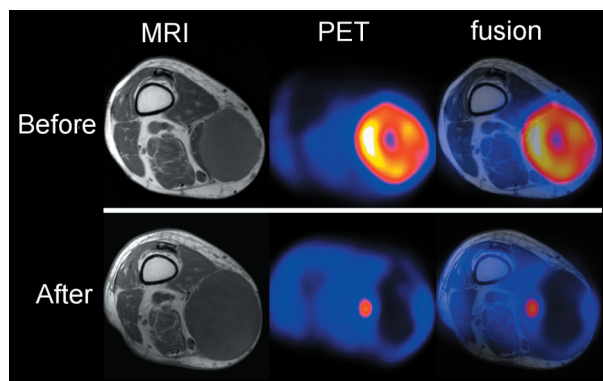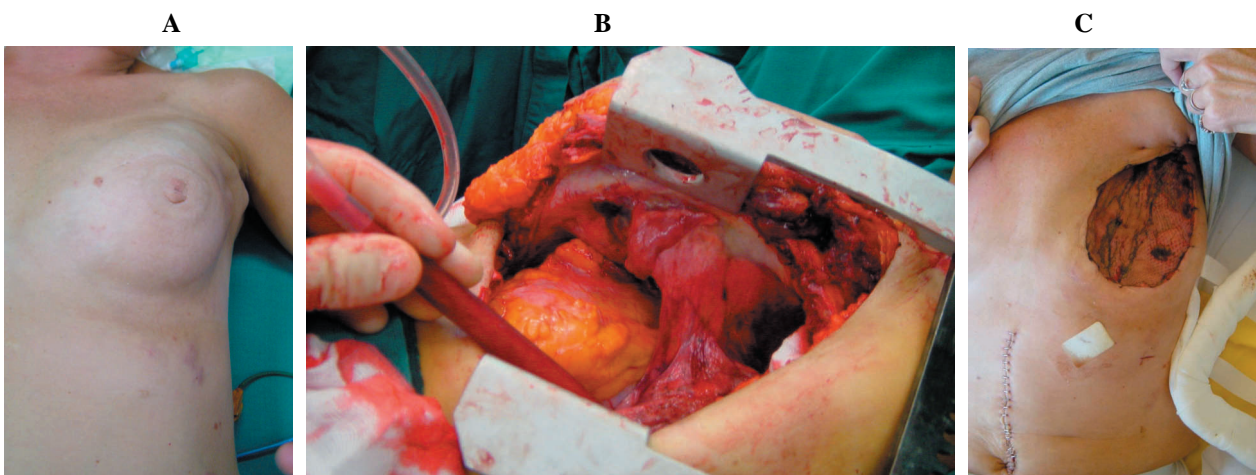

Figure 2 En bloc breast and chest wall resection for a high grade sarcoma.
(A)   Preoperative view of an angiosarcoma located in the left breast and thorax
(B)   The surgical defect, including a major portion of the chest wall
(C)   Reconstruction of the chest wall defect with polypropylene mesh, omental plasty and split skin graft.

A patient with a sarcoma located in the chest underwent chest wall resection with subsequent reconstruction. Without doubt, the most radical of all potential sarcoma surgeries is translumbar amputation or hemicorporectomy, which was performed for the first time in 1962.[15]

This leads us to the other reason why "radical" is an interesting model. Sarcomas are an interesting tumor model because they also cause radical changes in other areas than surgery, due to their remarkably aggressive growth and metastasis pattern. In these cases, "radical" means "departing markedly from the usual or customary". The treatment of what used to be classified as leiomyosarcoma of the intestines but is now named gastrointestinal stroma tumor (GIST) in accordance with new insights into the condition, for example, made the cover of Time Magazine (volume 157, no 21, 2001). The selective tyrosine kinase inhibitor Imatinib, the new "target drug", heralded the "new war against cancer".

Angiogenesis inhibition remains a promising approach for new drug development in cancer therapy. In fact blocking vascular endothelial growth factor (VEGF) has already been shown to have potent antivascular effects and significant clinical activity as evidenced by an improvement in overall survival when combined with standard chemotherapy e.g. in colorectal cancer.[16,17] Beside that, there are also trials with Ecteinascidin-743 (ET-743; also known as trabectedin and Yondelis), an isolated, purified, and synthesized extract of the Caribbean marine tunicate *Ecteinascidia turbinata*. ET-743 would inhibit cell proliferation and be potent against a variety of soft tissue sarcoma cell lines, even those resistant to many other cytotoxic agents.[18]

With the improved treatment of aggressive cancers such as soft tissue sarcomas, the number of cancer survivors is increasing gradually and they reach a higher age. This has several implications which may also lead to further insight into (genetic) cancer epidemiology.

First, these patients often appear to be at increased risk of developing other malignancies later in life. This may either be due to chance occurrence thanks to increased life expectancy, or to environmental factors that also caused the first cancer or to long-term carcinogenicity of the therapy that was given for the first cancer. However, second malignancies might also occur due to the fact that the initial cancer arose as part of a genetic cancer predisposition. It can be expected that "new" hereditary cancer syndromes with only moderately increased cancer risks, will be delineated in the near future, if survivors of childhood cancer are monitored adequately. It will, however, need large datasets and long-term follow-up to establish these tentative cancer risk genes.

The second implication of improved cancer treatment and survival is that more patients will reach adulthood. Since in the treatment of cancer in children and young adults much attention is given to preserving fertility, these cancer survivors are now more often able to have children themselves. This may lead to a second way to recognize the possible genetic nature of their cancer (syndrome): if subsequently the same or related malignancies are diagnosed in their offspring. Long term follow-up data will be of great value here as well.

The fact that increased life expectancy due to improved treatment enables the occurrence of subsequent cancers in the same patient, is most clear in cases with 'early onset' cancers, e.g. retinoblastoma and soft tissue sarcoma. These types of cancer are however relatively rare in the general population. The same effect of improved prognosis can be expected in common cancers that are diagnosed at later age, such as colon cancer or breast cancer. Since these types of cancer are much more frequent, the contribution of second and third cancers in this population to general cancer incidence may become substantial. It is through longevity that we will be able to recognize underlying genetic predispositions to late-onset types of cancer in this population. These may be "high risk" genes that come to clinical expression at later age, but they may also be "moderate risk" genes with an gradually increasing age-related penetrance. In the view of increasing life expectancy in the general population, the contribution of such genes to the total cancer incidence and the implications in general practice and health care are hard to predict and deserve further research.

Since many high-grade tumors morphologically manifest themselves as undifferentiated tumors, the identification of chromosomal aberrations may be important for the final diagnosis and classification. With the help of micro-array analysis, which allows the simultaneous study of the expression of thousands of genes, it may be possible to realize a new classification, better diagnostics, and more effective therapies in the near future.

In essence, the new "radical" treatment for sarcomas involves radical resection, but also complex reconstruction and limb salvage techniques. Major contributions to this treatment approach include microvascular plastic surgery techniques, an increased emphasis on functionality, the development of prosthetic materials, neurovascular reconstruction, down-staging with isolated limb perfusion, and the concept of limb remodelling and replantation. The development of new kinase inhibitors and new angiogenese inhibitors might change in the near future the treatment approach and outcome of locally advanced and disseminated soft tissue sarcomas.

Chapter 9

"Radical" also becomes a more abstract term referring to a fundamental shift in our paradigms on cancer biology and the outcome of the patient, both oncologic and functional.

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Chapter 10

Summary / Samenvatting

Chapter 10

Summary

Chapter 1

The outline and aim of this thesis are described in this chapter. The following questions will be answered in the various chapters:

- Treatment options for radiation-induced sarcoma: what are the challenges in the treatment?
- What is the role of surgery in the multidisciplinary treatment of soft tissue sarcoma?
- During which periods, and through what causes, are patients at risk of losing an extremity with a locally advanced soft tissue sarcoma treated with isolated limb perfusion, surgery and radiotherapy?
- Is adjuvant radiotherapy indicated after isolated limb perfusion and resection for patients with a primarily irresectable soft tissue sarcoma in an extremity?
- What are the potentials of biological imaging in the prediction of long-term outcome of patients with a soft tissue sarcoma of the extremity treated with isolated limb perfusion?
- Do soft tissue sarcoma perfusion survivors differ from the general population in terms of quality of life and do post traumatic stress symptoms occur that should be taken into account in the longer term?
- Is the incidence of other primary tumors increased in patients with locally advanced soft tissue sarcoma of the extremities and does this affect long-term survival?

Chapter 2

Radiation-induced sarcomas are rare but extremely aggressive tumors that arise from a previous radiation site, often after a long period of time. The radiation was delivered to treat a either malignant or benign disease.

Between 1987 and 2003, 27 patients were diagnosed with radiation-induced sarcoma. The median post-radiation period was 8 (range 3-41) years. Median radiation dose was 50 (range 16-70) Gy. Five-year tumor-free survival rate and overall survival rate were 27 and 30%, respectively. Local recurrence rate after microscopic radical resection (=R0) was 54%. In the group as a whole, 41% of the patients developed distant metastases. Patients who had undergone R0 resection had a significantly better survival rate than patients who had undergone a microscopically positive resection (p=0.026).

Radiation-induced sarcomas tend to recur locally and develop distant metastases. Radical resection is the only procedure for improving patient survival. Even in a palliative setting radical surgery may contribute to improve the quality of life.

Chapter 3

The current treatment options of soft tissue sarcomas are described in this chapter. Combined modality treatment strategies are used in which the extend of local resection and the role of adjuvant radiation treatment are well defined. The optimal sequence of radiation and surgery remains complex. The introduction of hyperthermic isolated limb perfusion with Tumor Necrosis Factor alpha (TNFα) and melphalan was a breakthrough in limb salvage fom primarily irresectable soft tissue sarcomas. In the combined modality treatment, surgery still is the cornerstone of successful soft tissue sarcoma treatment.

Chapter 4

The long term limb salvage rate and the three time periods at risk for amputation of a limb with locally advanced soft tissue sarcoma after hyperthermic isolated limb perfusion with Tumor Necrosis Factor alpha (TNFα) and melphalan are described. 73 patients (36 male, 37 female; median age 54 (range 14 – 80) years) with biopsy proven soft tissue sarcoma underwent 78 perfusions followed by delayed surgical resection, with or without adjuvant radiation. A total of 21 amputations (28%) were performed. Overall 1, 5 and 10 years limb salvage was 80.1 ± 4.8, $68.2 \pm 6.5\%$ and $60.6 \pm 9.2\%$ respectively. The first period was within 1½ year after perfusion due to massive necrosis or recurrent disease (n=17). The second time period was within five years with two amputations performed for late local recurrence. The third episode occurred ten years after perfusion, two amputations performed for critical leg ischemia. Another two patients developed a pathological fracture of the femur due to radiation osteonecrosis. All four patients received post-perfusion radiotherapy.

Chapter 5

Can radiotherapy be given in combination with regional perfusion treatment for primary non-resectable sarcomas of the extremities and is adjuvant radiotherapy indicated after isolated limb perfusion and resection of a soft tissue sarcoma?

Between 1991 and 2003, 73 patients with a median age of 54 (range 14-80) years with a primary non-resectable soft tissue sarcoma were treated with isolated limb perfusion with Tumor Necrosis Factor alpha (TNFα) and melphalan. After a median period of 8 (range 2-15) weeks, the residual tumor mass was resected. Adjuvant external beam radiotherapy (EBRT) was given when the resection margins were marginally radically free (R0) or microscopically positive (R1). The aim of the study was the evaluation of the value of adjuvant radiotherapy.

Local recurrence was scored and calculated with the Kaplan-Meier method and the Log-rank test. After resection of the residual tumor mass, 58% of the patients were given EBRT (EBRT+ group), while 42% did not receive EBRT (EBRT- group). The median follow-up was 28 (range 2-159) months. There was significantly less local recurrence in the EBRT+ group than in the EBRT- group (p<0.0001). When only R0 resections in the non-metastasized patients were factored in, the difference remained significant (p=0.0003). In the EBRT- group, R1 or R2 resections resulted in earlier local recurrence than R0 resections (p=0.0475). Twelve patients presented with distant metastases at the time of the isolated limb perfusion (16%). During the follow-up, 25 patients (41%) developed distant metastases after an interval of nine months. The overall one-, five-, and ten-year survival rates were $83.1 \pm 4.4\%$, $61.4 \pm 6.4\%$ and $47.5 \pm 7.5\%$, respectively. Adjuvant radiotherapy as part of the combined modality treatment of soft tissue sarcoma of the extremities with isolated limb perfusion improves local tumor control. It is indicated when the resection margins are marginally free or microscopically positive, and seems to be beneficial even after a so-called R0 resection.

Chapter 6

Little is known about the potentials of biological imaging with 18F-fluorodeoxyglucose (FDG) uptake in Positron Emission Tomography (PET) and its role in long-term predictions for patients with a primary non-resectable soft tissue sarcoma of the extremities. The patients in the study underwent isolated limb perfusion with Tumor Necrosis Factor alpha and melphalan, with 'tumor kill' as the objective: reduction of the tumor facilitating tumor resection. A group of 13 patients was given two FDG- PET scans: one before and one after islated limb perfusion, after which tumor resection followed. Univariate analysis showed that the overall survival in this selected group of 13 patients was longer for those whose maximum standardized uptake value (SUVmax) of FDG after perfusion was low than for those whose SUVmax was high (144 versus 33 months; p=0.0004). The multivariate analysis did not show a significant difference between the two groups, but there was a trend towards a difference in overall survival (p=0.08).

Biological imaging seems a valuable instrument to gain insight into the effects of the treatment on the tumor, although it is currently not an 'absolute predictor' of the treatment outcome.

Chapter 7

The study evaluates the quality of life and post traumatic stress symptoms (PTSS) in patients with a soft tissue sarcoma who were treated with isolated limb perfusion followed by resection and radiotherapy. The treatment objective was limb salvage, even though the tumor seemed primarily non-resectable. Surviving patients were asked to fill out questionnaires. The average period after perfusion was 7 (range 1-13) years. The response rate (39/41 patients) was 98%. The following validated questionnaires were used: the RAND 36 and the Impact of Event Scale (IES). No differences were found in mean scores between the sarcoma group and a group from the general population, except that the sarcoma patients reported poorer physical functioning. Patients who had undergone an amputation following ILP exhibited significantly worse physical and social functioning and more role limitations due to physical and emotional problems than sarcoma patients whose limbs had been saved.

Eleven patients (28%) had a PTSS-score of 0, while eight patients (20.5%) had a score of >26. With such a high score, psychological counselling is recommended. The limb had not been amputated in this group of eight patients. Patients who indicated that the treatment mode had been chosen by the physician instead of by themselves or in consultation with the physician exhibited significantly poorer social functioning and more role limitations and intrusion. Greater satisfaction with the treatment was related to better social functioning, more vitality, better health perception, less intrusion, less avoidance, and less stress response symptoms.

Chapter 8

The purpose was to investigate the incidence of other primary neoplasms in patients with a locally advanced soft tissue sarcoma of the extremities and their effect on survival. Therefore a retrospective cohort of 73 patients, median age 54 (range 14-80) years diagnosed with locally advanced soft tissue sarcoma, all treated by isolated limb perfusion and delayed surgical resection was studied. Medical records were examined for clinical characteristics of the soft tissue sarcoma and other primary neoplasms, therapeutic interventions, morbidity and survival.

Seventeen patients of the 73 treated with isolated limb perfusion (23%) had another primary neoplasm: 8 other primary neoplasms before soft tissue sarcoma-diagnosis (47%), 1 synchronously, 1 between two other primary neoplasms, and 7 patients had another primary neoplasms after soft tissue sarcoma-diagnosis (41%). The median follow-up period after soft tissue sarcoma-diagnosis was 48 (4-162) months. The 5-year survival of the group with only a

non-metastasized soft tissue sarcoma (79 ± 13%) was not significantly different from the group with a soft tissue sarcoma before another primary neoplasms-diagnosis group (83 ± 17%) (p=0.46). The 5-year survival rate of the group with another primary neoplasms before soft tissue sarcoma-diagnosis (13 ± 13%) was however significantly decreased versus the group with only a soft tissue sarcoma (P<0.0001). The most frequent types of other primary neoplasms were breast cancer, squamouscell carcinoma and urinary tract (kidney and bladder) cancer.

The conclusion is that patients with locally advanced soft tissue sarcoma have a high risk to be diagnosed with another primary neoplasm. The overall survival in non-metastasized soft tissue sarcoma patients is significantly decreased if patients had another primary neoplasm before a soft tissue sarcoma.

Chapter 9

Perspectives about future and recent breakthroughs in diagnostic imaging and treatment of soft tissue sarcomas are described in this chapter such as three-dimensional images, PET-MRI combination, sentinel node biopsy for sarcomas, regional infusion, computer-assisted navigation systems to perform surgery, microvascular surgical reconstructive techniques, intensity modulated radiation therapy (IMRT), angiogenese and kinase inhibitors and new insights in (genetic) cancer epidemiology.

Conclusion

In the combined modality treatment of soft tissue sarcomas is surgery the cornerstone of successful treatment. Hyperthermic isolated limb perfusion with Tumor Necrosis Factor alpha (TNFα) and melphalan was a breakthrough in limb salvage for primarily irresectable soft tissue sarcomas. After this treatment, there are still three periods at risk for amputation due to massive necrosis, recurrent disease and critical leg ischemia. Adjuvant radiotherapy is indicated when resection margins are marginally free or microscopically positive, and seems to be beneficial even after microscopically negative resections. Even though 'soft tissue sarcoma- survivors' quality of life (QoL) was only different from a reference group in physical functioning, one fifth of the patients suffered from post traumatic stress symptoms (PTSS). An amputation, the physicians' decision rather than the patients' decision for the perfusion treatment and a low satisfaction with the performed treatment negatively influenced QoL. Patients with locally advanced soft tissue sarcoma have a high risk to be diagnosed with

another primary neoplasm. The overall survival in non-metastasized soft tissue sarcoma patients is significantly decreased if patients had another primary neoplasm before an soft tissue sarcoma. Biological imaging seems a valuable instrument to gain insight into the effects of the treatment on the tumor. Other 'radical' shifts in paradigms on cancer biology and the outcome of the patient both oncologic and functional will be the future of sarcoma treatment. A 'radical' operation will nevertheless remain the first step in a successful cancer treatment, more and more in a 'combinded modality' setting with pre-or postoperative radiotherapy and/or (neo)adjuvant chemotherapy.

Chapter 10

Samenvatting

Hoofdstuk 1

De achtergronden en het doel van dit proefschrift worden in dit hoofdstuk beschreven. De volgende vraagstellingen in de achtereenvolgende hoofdstukken zullen worden samengevat:

- Behandelingsmogelijkheden van het radiatiesarcoom: waar ligt de uitdaging in de behandeling?
- Wat is de rol van chirurgie in de multidisciplinaire behandeling van het weke-delen sarcoom?
- Wat zijn de risicovolle tijdsperiodes en de oorzaken om een extremiteit met een uitgebreid lokaal weke-delen sarcoom te verliezen na geïsoleerde regionale perfusie, resectie en radiotherapie?
- Is er indicatie voor adjuvante radiotherapie na geïsoleerde regionale perfusie en resectie voor patiënten met een primair irresectabel weke-delen sarcoom van een extremiteit?
- Wat zijn de mogelijkheden van 'biological imaging' bij het voorspellen van resultaten op lange termijn voor patiënten met een weke-delen sarcoom in de extremiteiten die behandeld werden met geïsoleerde perfusie?
- Verschilt de kwaliteit van het leven van de 'soft tissue sarcoma perfusion survivors' van de algemene bevolking en is er sprake van posttraumatische stress responssymptomen, waar op langere termijn rekening mee moet worden gehouden?
- Is er een verhoogde incidentie van andere primaire tumoren bij patiënten met een uitgebreid lokaal sarcoom van de extremiteiten en heeft dit gevolgen op de langetermijnoverleving?

Hoofdstuk 2

Radiatiesarcomen zijn zeldzame, maar bijzonder agressieve tumoren die ontstaan in een eerder bestralingsveld, vaak na een lang tijdsinterval. Deze bestraling werd gegeven om een al dan niet kwaadaardige aandoening te behandelen.

Tussen 1987 en 2003 werd bij 27 patiënten de diagnose radiatiesarcoom gesteld. Dat was gemiddeld (mediaan) 8 (spreiding 3-41) jaar na de bestraling. De mediane bestralingsdosis bedroeg 50 (spreiding 16-70) Gy. De vijfjaars ziektevrije overleving en de algehele overleving bedroeg respectievelijk 27 en 30 %. De kans op lokaal recidief na een microscopisch radicale resectie (=R0 resectie) bedroeg 54 %. In de hele groep ontwikkelde 41 % van de patiënten afstandsmetastasen. Patiënten die een R0 resectie ondergingen, hadden

een significant betere overleving dan patiënten met een niet-microscopisch vrije resectie (p=0.026).

Radiatiesarcomen hebben een grote tendens om lokaal te recidiveren en metastasen op afstand te ontwikkelen. Een radicale resectie is de enige kans om de overleving van de patiënten te verbeteren. Zelfs in een palliatieve setting kan radicale chirurgie bijdragen tot een verbetering van de kwaliteit van leven.

Hoofdstuk 3

De huidige behandelingsopties van het weke-delen sarcoom worden in dit hoofdstuk beschreven. In de gecombineerde modaliteitbehandeling strategieën zijn het belang van de lokale resectie en adjuvante radiotherapie duidelijk aangetoond. De optimale volgorde van radiotherapie en chirurgie blijft nog steeds een complexe zaak. Het invoeren van geïsoleerde regionale perfusie met Tumor Necrosis Factor alpha (TNFα) en melphalan was een doorbraak voor het behoud van de extremiteit bij het primair irresectabele weke-delen sarcoom. In de gecombineerde behandeling blijft chirurgie nog steeds een hoeksteen voor succesvolle behandeling van kwaadaardige tumoren van de weke-delen.

Hoofdstuk 4

De langetermijnresultaten van extremiteitsparende behandeling en de drie risicovolle tijdsperioden voor amputatie van een extremiteit met een uitgebreid lokaal weke-delen sarcoom die een hyperthermische geïsoleerde regionale perfusie met Tumor Necrosis Factor alpha (TNFα) en melphalan onderging, worden beschreven. 73 patiënten (36 mannen, 37 vrouwen; mediane leeftijd van 54 (spreiding 14-80) jaar) met een histologisch bewezen weke-delen sarcoom, ondergingen 78 perfusies, gevolgd door chirurgische resectie én al of niet aanvullende bestraling. In totaal werden 21 amputaties (28 %) verricht. De 1, 5 en 10 'limb salvage rate' was respectievelijk 80.1 ± 4.8, 68.2 ± 6.5 % en 60.6 ± 9.2 %. De eerste risicovolle periode voor amputatie viel binnen 1.5 jaar na de perfusie ten gevolge van uitgebreide necrose of lokaal recidief (n=17). De tweede periode viel binnen een tijdsperiode van vijf jaar, waarin twee amputaties werden verricht wegens laatijdig lokaal recidief. In de derde episode, tien jaar na perfusie, werden twee amputaties verricht wegens ernstige ischemische schade van de extremiteit. Twee andere patiënten ontwikkelden een pathologische fractuur ten gevolge van osteonecrose. Deze vier patiënten hadden allen radiotherapie gekregen na perfusie en resectie.

Hoofdstuk 5

Kan radiotherapie in de regionale perfusiebehandeling van patiënten met een primair irresectabel sarcoom van de extremiteiten worden gegeven en wat is de plaats van adjuvante radiotherapie na geïsoleerde regionale perfusie en resectie van een weke-delen sarcoom?

Van 1991 tot 2003 werden 73 patiënten met een mediane leeftijd van 54 (spreiding 14-80) jaar met een primair niet resectabel weke-delen sarcoom behandeld met geïsoleerde regionale perfusie met Tumor Necrosis Factor alpha (TNFα) en melphalan. Na een gemiddelde (mediane) periode van 8 (spreiding 2-15) weken werd de overgebleven tumor gereseceerd. Adjuvante radiotherapie (external beam radiotherapy, EBRT) werd in geval van krap radicaal vrije (R0) of microscopisch positieve (R1) resectiemarges gegeven. Het doel van de studie was de waarde van adjuvante radiotherapie te onderzoeken. Lokale recidieven werden gescoord en berekend met de Kaplan-Meier-methode en de Log-rank-test. Nadat de overgebleven tumor was gereseceerd, kregen 58 % van de patiënten bestraling (bestraling+ groep) en 42 % van de patiënten kregen geen bestraling (bestraling- groep). De gemiddelde (mediane) follow-up was 28 (spreiding 2-159) maanden. Er waren significant minder lokale recidieven in de bestraling+ groep vergeleken met de bestraling- groep (p<0.0001). Wanneer alleen R0-resecties in de niet-gemetastaseerde patiënten in beschouwing werden genomen bleef het verschil significant aanwezig (P=0.0003). In de bestraling- groep resulteerde een microscopisch niet radicale (R1) -resectie of macroscopisch niet radicale (R2) -resectie in een sneller optreden van lokaal recidief vergeleken met een resectie met vrije sneevlakken (R0-resectie) (p=0.0475). Twaalf patiënten presenteerden zich met metastasen op afstand ten tijde van de geïsoleerde regionale perfusie (16 %). Gedurende de follow-up ontwikkelden 25 patiënten (41 %) metastasen op afstand na een interval van negen maanden. De één, vijf- en tienjaars overleving was respectievelijk 83.1 ± 4.4 %, 61.4 ± 6.4 % and 47.5 ± 7.5 %. In de gecombineerde modaliteitsbehandeling van weke-delen sarcoom van de extremiteiten met geïsoleerde regionale perfusie verbetert adjuvante radiotherapie de lokale tumor controle. Adjuvante radiotherapie is geïndiceerd als de resectiemarges krap zijn of microscopisch niet vrij en lijkt eveneens een meerwaarde te hebben na een microscopisch vrije resectie.

Hoofdstuk 6

Er is weinig bekend over de mogelijkheden van 'biological imaging' met 18F-Fluorodeoxyglucose (FDG)-uptake met behulp van Positron Emissie Tomografie (PET) en de rol hiervan bij langetermijnvoorspellingen voor patiënten met een primair irresectabel weke-delen sarcoom van de extremiteiten. De patiënten ondergingen een geïsoleerde regionale

perfusie met Tumor Necrosis Factor alpha en melphalan met als doel 'tumor kill': verkleinen van de tumor en het vereenvoudigen van de resectie. Een groep van dertien patiënten kreeg twee FDG- PET scans: een vóór en een ná geïsoleerde regionale perfusie en voorafgaand aan de resectie van de tumor. De algehele overleving in deze geselecteerde groep van dertien patiënten was in de univariaat analyse langer indien de maximum gestandaardiseerde uptake waarde (=SUVmax) van de FDG-uptake na perfusie laag was in vergelijking met de groep waarbij de SUVmax hoog was (144 versus 33 maanden; p= 0.0004). Bij de multivariaatanalyse was er geen significant verschil tussen beide groepen, wel een trend voor een verschil in algehele overleving (p=0.08).

Biologische beeldvorming lijkt een waardevol instrument om inzichten te krijgen in de effecten van behandeling op de tumor zonder daarbij op dit moment een 'absolute voorspeller' te zijn van de uiteindelijke uitkomst van de behandeling.

Hoofdstuk 7

De kwaliteit van leven en de posttraumatische stress responssymptomen (PTSS) bij een groep patiënten die met een weke-delen sarcoom werden behandeld met geïsoleerde regionale perfusie, gevolgd door resectie en bestraling werden onderzocht. Het doel van de behandeling was de extremiteit te behouden, niettegenstaande de tumor primair irresectabel leek. Het behoud van de extremiteit slaagde bij het merendeel van de onderzochte patiënten (77 %). Negenendertig nog in leven zijnde patiënten werden gevraagd vragenlijsten in te vullen. De gemiddelde (mediane) tijd na perfusie bedroeg bij hen 7 (spreiding 1-13) jaar. De respons rate bedroeg 98 %. Er werd gebruik gemaakt van gevalideerde vragenlijsten: de RAND 36 en de Impact of Event Scale (IES). Er werden geen verschillen gevonden in de gemiddelde scores tussen de bestudeerde 'sarcoomgroep' en een referentiegroep, behalve dat de 'sarcoomgroep' fysiek slechter functioneerde. Patiënten die een amputatie ondergingen, functioneerden zowel fysiek als sociaal significant slechter en ze hadden meer fysieke en emotionele rolbeperkingen dan sarcoompatiënten waarbij de extremiteit gespaard kon blijven.

Elf patiënten (28 %) hadden een PTSS-score van nul, acht patiënten (20.5 %) een score >26. Bij deze hoge score wordt psychologische ondersteuning geadviseerd. Bij geen van deze acht patiënten was een extremiteit geamputeerd. Patiënten die aangaven dat de keuze van behandeling gemaakt was door hun arts in plaats van door henzelf of in samenspraak, functioneerden achteraf sociaal significant slechter en hadden meer rolbeperkingen en intrusie. Een grotere tevredenheid met de behandeling was gerelateerd met beter sociaal

functioneren, meer vitaliteit, een betere gezondheidsperceptie, minder intrusie, minder vermijdingsgedrag en minder stress responssymptomen.

Hoofdstuk 8

Het opzet was de incidentie van andere primaire tumoren te onderzoeken bij patiënten met een uitgebreid lokaal weke-delen sarcoom van de extremiteiten en het effect van de andere primaire tumor op de overleving. Daarom werd een retrospectieve cohort van 73 patiënten, gediagnosticeerd met een uitgebreid lokaal weke-delen sarcoom op de gemiddelde (mediane) leeftijd van 54 (spreiding 14-80) jaar en behandeld met geïsoleerde regionale perfusie van de extremiteit gevolgd door chirurgische resectie, bestudeerd. Medische dossiers werden nagekeken op klinische karakteristieken van het weke-delen sarcoom en de andere primaire tumor, de uitgevoerde behandeling, morbiditeit en overleving.

Zeventien patiënten van de 73 die behandeld waren met geïsoleerde regionale perfusie (23 %) hadden een andere primaire tumor: 8 hadden een andere primaire tumor vóór de diagnose van het weke-delen sarcoom (47 %), 1 synchroon, 1 had een weke-delen sarcoom tussen twee andere primaire tumoren in, en 7 hadden een andere primaire tumor na de diagnose van het weke-delen sarcoom (41 %). De mediane follow-up periode na de diagnose van het weke-delen sarcoom was 48 (4-162) maanden. De 5-jaars overleving van groep met een niet-gemetastaseerd weke-delen sarcoom zonder een andere primaire tumor (79 ± 13 %) was niet significant verschillend van de groep die een weke-delen sarcoom vóór de andere primaire tumor hadden (83 ± 17 %) (p=0.46). De 5-jaarsoverleving van de groep met een andere primaire tumor vóór de weke-delen sarcoom (13 ± 13 %) daarentegen was significant minder versus de groep met alleen een weke-delen sarcoom (P<0.0001). De frequentst voorkomende vormen andere primaire tumor waren borstkanker, plaveiselcelcarcinoom en tumoren van de urinewegen (nier en blaas).

De conclusie is dat patiënten met een uitgebreid lokaal weke-delen sarcoom een hoog risico hebben om gediagnosticeerd te worden met een andere primaire tumor. De overleving in niet-gemetastaseerde weke-delen sarcoom-patiënten was significant minder als patiënten al een andere primaire tumor hadden vóór de diagnose van het weke-delen sarcoom.

Hoofdstuk 9

Perspectieven over toekomstige en recente doorbraken in beeldvorming en behandeling van het weke-delen sarcoom worden in dit hoofdstuk beschreven zoals driedimensionele

beeldvorming, PET-MRI combinatie, schildwachtklierbiopsie voor weke-delen sarcomen, regionale infusie, computer geassisteerde navigatie systemen tijdens chirurgische ingrepen, microvasculaire reconstructieve chirurgische technieken, 'intensity modulated radiation therapy' (IMRT), angiogenese en kinase inhibitoren en nieuwe inzichten in (genetische) kankerepidemiologie.

Conclusie

In de gecombineerde behandeling van weke-delen sarcomen is chirurgie de hoeksteen van een succesvolle behandeling. Hyperthermische geïsoleerde perfusie van een extremiteit met Tumor Necrosis Factor alpha (TNFα) en melphalan was een doorbraak voor het behoud van de extremiteit bij primair irresectabele weke-delen sarcomen. Na deze behandeling zijn er nog drie risicovolle tijdsperioden voor amputatie ten gevolge van uitgebreide necrose, lokaal recidief en ernstige ischemische schade van een extremiteit. Adjuvante radiotherapie is aangewezen wanneer de resectiemarges krap zijn of microscopisch niet vrij en lijkt zelfs een meerwaarde te hebben na een microscopisch vrije resectie. Alhoewel de levenskwaliteit van de in leven zijnde patiënten die een weke-delen sarcoom hebben gehad alleen in fysiek functioneren verschilt van een referentiegroep, lijdt een vijfde van hen aan posttraumatische stress responssymptomen (PTSS). Een amputatie, de behandelingskeuze voor de perfusie door de arts eerder dan door de patiënt en lage tevredenheid over de uitgevoerde behandeling beïnvloedden de kwaliteit van leven negatief. Patiënten met een uitgebreid lokaal weke-delen sarcoom lopen een hoog risico om gediagnosticeerd te worden met een andere primaire tumor. De overleving van patiënten met een niet-gemetastaseerd weke-delen sarcoom was significant minder als patiënten al een andere primaire tumor vóór de diagnose van het weke-delen sarcoom hadden.

Biologische beeldvorming lijkt een waardevol instrument om inzicht te krijgen in de effecten van de tumorbehandeling. Andere 'radicale' verschuivingen in paradigma's van de kankerbiologie en de gevolgen voor de patiënt, zowel op oncologisch als functioneel gebied, zullen in de toekomst de behandeling van weke-delen sarcomen bepalen. Een 'radicale' operatie zal niettemin de eerste stap in een succesvolle kankerbehandeling blijven, meer en meer in een 'combined modality' setting met pre- of postoperatieve radiotherapie en/of (neo)adjuvante chemotherapie.

Dankwoord

Dankwoord

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Curriculum vitae

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Katja Maria Jozef Thijssens was born on the 4th of December 1970 in Antwerp, Belgium. She finished high school (majoring in Latin-mathematics) at the Royal Lyceum in Antwerp. In 1988 she started Medical School in Antwerp. During the medical study, she did internships at Harvard Medical School in Boston and in Candy, Sri Lanka. She graduated cum laude (in Belgium it was a 7-year program) in 1995. That same year she started her surgical training with residencies in Onze-Lieve-Vrouw Middelaresziekenhuis (Deurne-Antwerpen), the University Hospital Antwerp (UZA) and Leiden University Medical Centre (LUMC). She became a surgeon in 2001. Till the end off 2002 she continued with a gastro-enterology/laparascopic fellowship in the Medical Centre Leeuwarden. In January 2003 she started a fellowship (as 'chivo') in Surgical Oncology at the University Medical Center Groningen. She is an active member of the Society of Surgical Oncology. Currently, she is working as the first female surgeon in Twente in the regional hospital (Streekziekenhuis Midden Twente) located in Hengelo, The Netherlands.