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Chest Wall Resection for Adult Soft Tissue Sarcomas and Chondrosarcomas: Analysis of Prognostic Factors

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Abstract
Background Wide resection with tumor-free margins is necessary in soft-tissue sarcomas to minimize local recurrence and to contribute to long-term survival. Information about treatment outcome and prognostic factors of adult sarcoma requiring chest wall resection (CWR) is limited.
Methods Sixty consecutive patients were retrospectively studied for overall survival (OS), local recurrence-free survival (LRFS), and disease-free survival (DFS). Twenty-one prognostic factors regarding survival were analyzed by univariate analysis using the Kaplan-Meier method and the log-rank test.
Results With a median survival of 2.5 years, the OS was 46% (33%) at 5 (10) years. The LRFS was 64% at 5 and 10 years, and the DFS was 30% and 25% at 5 and 10 years. At the end of the study period, 26 patients (43%) were alive, of which 20 patients (33%) had no evidence of disease and 40 patients (67%) had no chest wall recurrence. In the group of 9 patients with a radiation-induced soft-tissue sarcoma, the median survival was 8 months. Favorable outcome in univariate analysis in OS and LRFS applied for the low-grade sarcoma, bone invasion, and sternal resection. For OS only, age below 60 years and no radiotherapy were significant factors contributing to an improved survival. CWR was considered radical (R0) at the pathological examination in 43 patients. There were 52 patients with an uneventful recovery. There was one postoperative death.
Conclusions CWR for soft-tissue sarcoma is a safe surgical procedure with low morbidity and a mortality rate of less than 1%. With proper patient selection acceptable survival can be reached in a large group of patients. Care must be given to patients with radiation-induced soft-tissue sarcoma who have a significantly worse prognosis.

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Introduction

Soft-tissue sarcomas (STS) account for approximately 1% of all malignancies in adults. STS involving the chest wall, ribs, or sternum and overlying soft tissue are rare. In a large series of 437 STS patients without metastases, only 17 were located in the chest wall [1].

STS are best treated by wide local excision and radiotherapy [2], which means that most of the STS of the chest wall need a full-thickness chest wall resection (CWR), perhaps in combination with skeletal reconstruction and soft tissue coverage, to obtain negative margins. Surgical treatment may be preceded or followed by radiotherapy according to local protocols, especially when narrow margins are expected or confirmed in the pathological specimen. There is no indication for (neo-) adjuvant chemotherapy except in prospective randomized trials.

The etiology of a STS is unknown, except in those patients who were treated in the past with radiotherapy for breast cancer or Hodgkin's disease. The cumulative radiotherapy-induced STS (RISTS) incidence is reported to be 0.07% at 5 years, 0.27% at 10 years, and 0.48% at 15 years after radiotherapy treatment [3].

Information about treatment and prognosis of adult STS located in the chest wall is limited, especially in cases with a full-thickness CWR. Only a few series are published in which the patients were collected over decades. In some of these series a substantial number of patients are children or adolescents with so-called small-cell sarcomas for whom the preferred treatment is salvage surgery after chemotherapy.

The aim of this study was to describe the factors that influence prognosis in adult STS patients in whom a CWR was performed. A relatively large group of these patients have been treated at our institute and therefore our experience can contribute to the treatment of patients worldwide.

Methods

A retrospective study was performed using a database of 229 consecutive patients surgically treated at the Daniel den Hoed Cancer Center with a CWR for a tumor or a radiation ulcer of the chest wall between 1986 and 2006. Sixty-six patients were identified as having a soft-tissue tumor. Because of the standard primary treatment of chemotherapy, Ewing's and other so-called small-cell sarcomas were excluded from this study ($n = 6$). Two patients developed a local recurrence treated by a second CWR: only the first CWR is included in this study.

A CWR was defined as a resection of at least one costa and/or the sternum or a wide soft-tissue resection requiring reconstruction (Fig. 1). If necessary, several types of inlays were used for skeletal reconstruction during the 20 years of this study. The first few years homologous dura mater was used (Lyodura®), later replaced by polyurethane (Neuropatch®) as an artificial inlay. In some cases polyglactine (Vicryl®) was used. Patients operated on after 2004 received a double-layer polypropylene-PTFE mesh (Composix®). Standard soft-tissue reconstruction was performed with a pedicled omentoplasty, unless primary closure could be established.

Patient demographics, pathology records, data on the surgical and (neo-) adjuvant treatment, postoperative morbidity, mortality, involvement of the resection margins, and length of follow-up were retrieved from the original patient files. Surgical aspects of the CWR technique performed in our hospital have been described earlier [4].

The end points of this study were overall survival (OS), disease-free survival (DFS), and local recurrence-free survival (LRFS). Univariate analysis was performed using the Kaplan-Meier method, the log-rank test, and the univariate Cox proportional hazards model. The outcome of patients who had postoperative radiotherapy in different subgroups was also studied: all patients excluding RISTS ($n = 9$), because in this group radiotherapy was no longer possible; all patients excluding borderline tumors ($n = 14$), because these patients potentially do not develop metastases; and patients with free (R0) and involved (R1 and R2) resection margins. Significance was set at $p \leq 0.05$. All the statistical analyses were performed using Stata version 9.2 (Stata Corporation, College Station, TX, USA).

Results

Sixty consecutive patients met the inclusion criteria of this study. There were 24 males and 36 females, ranging in age from 21 to 91 years. All but four patients underwent CWR with curative intent.

Two groups of patients were distinguished according to the grade of their tumor [5]. The low-grade group ($n = 22$) included grade I STS and patients with a borderline tumor like desmoid tumors and dermatofibrosarcoma protuberans. The high-grade group ($n = 38$) consisted of grade II and III STS, including 9 patients with a radiation-induced STS (RISTS).

In 11 patients the CWR consisted of an extended soft-tissue excision and reconstruction. In 27 patients three or more costae were removed. In 13 patients the CWR was performed including a (sub-) total sternectomy. In 13 patients the chest wall did not need to be reconstructed after the resection because the bony defect was too small. In some cases the defect was located under the scapula securing sufficient rigidity of the thorax. In 16 patients the

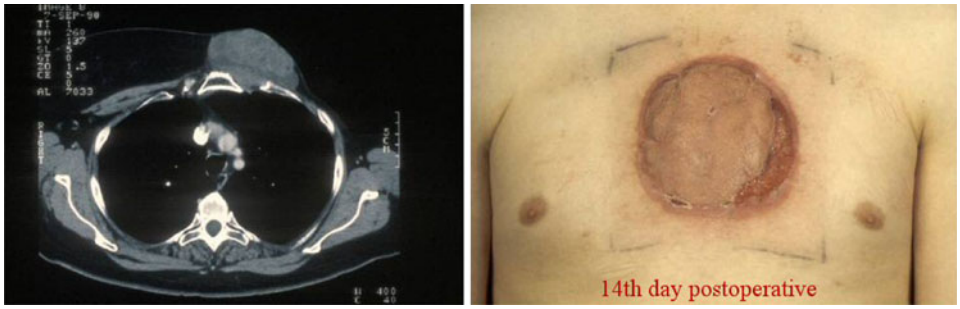

Fig. 1 High-grade sarcoma of the anterior chest wall treated by anterior chest wall resection and subtotal sternectomy followed by chest wall reconstruction (artificial inlay, pedicled omentoplasty, and meshed split skin graft)

overlying soft tissue needed reconstruction and/or skin transplantation.

At pathological examination bone invasion was seen in 23 patients. The CWR was considered radical with free resection margins (R0) in 43 patients. In 10 patients the CWR was microscopically irradical with involved resection margins (R1 resection), and in 7 patients a palliative resection was performed leading to gross involvement of tumor in the margins (R2 resection).

Sixteen patients, all in the high-grade STS group, had postoperative radiotherapy. None of the patients received chemotherapy.

There were 52 patients with an uneventful recovery or minor complications and 8 patients with serious postoperative complications. One patient with serious lung complications from ARDS required long-lasting artificial ventilation. Another patient developed pneumonia followed by cardiac failure with a fatal outcome. The artificial inlay for chest wall stabilization was removed in three of five patients after partial necrosis and subsequent infection of the wound.

The median follow-up for all patients was 1.7 years (range = 2–247 months), and for the patients alive at the end of the study it was 2.7 years (range = 4–247 months). Median survival was 2.5 years. Overall survival (OS), local recurrence-free survival (LRFS), and disease-free survival (DFS) were 46, 64, and 30% at 5 years and 33, 64, and 25% at 10 years, respectively. At the end of the study period, 26 patients were alive, of which 20 patients had no evidence of disease and 40 patients had no local recurrence.

The outcome of the statistical analysis for factors with a positive influence on survival is presented in Table 1. In univariate analysis regarding OS and LRFS, a low-grade sarcoma, bone invasion, and sternal resection lead to a favorable prognosis (Fig. 2). Younger age (<60 years) and no postoperative radiotherapy are favorable prognostic factors for the OS. Although resection margin was not a significant factor, this margin could be difficult to confirm in some cases with very diffuse or multifocal tumors, like angiosarcomas. This so-called clinical radicality was a significant factor for LRFS. The difference in survival curves for curative and palliative CWR just did not reach a significant value ($p = 0.051$).

The effect of postoperative radiotherapy was studied separately in the following groups: (1) all patients without a RISTS, (2) all patients with a borderline tumor, (3) all R0 margins, and (4) all R1 and R2 resection margins. OS remained significantly improved for all 51 patients without RISTS and all patients without a borderline tumor receiving radiotherapy (Table 2).

Local recurrences were seen in 20/60 patients (33%); in 16/38 patients (42%) with a high-grade sarcoma and 6/22 patients (27%) with a low-grade sarcoma. All recurrences occurred within 12 months, except one patient with a high-grade STS (22 months). The median time to local recurrence for RISTS was 4 months. Two of the patients with a low-grade sarcoma underwent a second CWR for recurrent disease and remained free of disease until the end of the study period.

Distant metastases developed in 33 patients (48%). Of these patients only four had nonborderline low-grade STS.

Four patients underwent a CWR for palliative reasons. They survived 5, 11, 17, and 28 months, three of them with adequate local tumor control.

In the 9 patients with a RISTS (high-grade), the median survival was 8 months. Two patients who had a palliative CWR for RISTS lived 11 and 17 months and the second patient developed a local recurrence after 11 months.

Discussion

Our series of 60 patients with STS requiring CWR had a 5-year survival rate of 46%. High-grade tumors had a significantly worse prognosis (5-year OS = 23%) compared to low-grade STS (5-year OS = 85%). The morbidity rate was acceptably low, with one case of in-hospital mortality.

Most CWRs for sarcomas are performed in chondrosarcoma patients [6–9]. These chondrosarcomas are often low-grade tumors and therefore have a relatively good prognosis. In patients with low-grade STS, a 5-year OS of 67-80% has been described [6, 8–10]; in our study a 5-year OS of 85% was obtained. In the high-grade patient group, the OS is obviously worse, with the 5-year OS varying from 7 to 59% [7, 11–13]. Our study showed for all patients a 10-year OS of 33%, which is much lower than the 67-80% reported in literature [6, 14], with no 10-year survivors in the high-grade STS group. These different outcomes can be explained only by selection bias.

Current literature provides hardly any data for prognostic factors other than tumor grade; our study's analysis can provide surgeons with more data to make an evidence-based decision for their future patients (Table 3). Distinctly negative prognostic factors that reached significance in univariate analysis for overall, local recurrence-free, and disease-free survival were pathological grade II/III (for all $p < 0.0001$ and confirmed by others [13, 14]), no sternal resection, and no tumor invasion in bones confirmed by pathological examination. Since tumor grade is a well-accepted prognostic factor in sarcoma surgery, we could expect this outcome. In our opinion, there is no logical explanation for bone invasion and sternal resection as prognostic favorable factors. Perhaps some primary (non-osteo-) sarcomas of the bone have a better outcome than soft-tissue sarcomas. However, in this retrospective study we were unable to identify sarcomas as primary bone

Table 1 Prognostic factors for survival of 60 patients with chest wall resection for soft tissue sarcoma and chondrosarcoma

Covariate (n =)		Overall survival			Local recurrence-free survival		
		HR	95% CI HR	p	HR	95% CI HR	p
Gender	Female (36)	1	0.32–1.32	0.23	1	0.17–1.36	0.16
	Male (24)	0.65			0.48		
Age	<60 years (40)	1	1.19–4.68	0.01	1	0.34–2.70	0.93
	≥60 years (20)	2.36			0.96		
Indication	Curative (56)	1	0.95–7.93	0.051	1	0.46–8.71	0.35
	Palliative (4)	2.75			2.00		
Diameter[a]	≤5 cm (27)	1	0.71–2.91	0.32	1	0.35–2.37	0.86
	>5 cm (30)	1.43			0.91		
Resection	Soft tissue (11)	1	0.21–1.10	0.08	1	0.14–1.14	0.08
	Bone/soft tissue (49)	0.48			0.40		
Number of costae	1, 2 (33)	1	0.35–1.42	0.33	1	0.22–1.55	0.27
	3, 4, 5 (27)	0.71			0.58		
Sternum resection	No (47)	1	0.046–0.54	0.001	1	0.02–1.18	0.04
	Yes (13)	0.16			0.16		
Lung resection	No (55)	1	0.36–3.90	0.79	1	0.28–5.26	0.81
	Yes (5)	1.18			1.20		
Reconstruction bone	No (13)	1	0.28–1.30	0.19	1	0.22–1.72	0.35
	Yes (47)	0.60			0.62		
Reconstruction soft tissue	No (44)	1	0.86–3.88	0.11	1	0.57–4.52	0.37
	Yes (16)	1.83			1.60		
Grade	I (22)	1	4.57–82.03	<0.0001	1	1.62–31.19	0.003
	II/III (38)	19.36			7.10		
Bone invasion (pathol)	No (37)	1	0.21–0.95	0.03	1	0.06–0.78	0.01
	Yes (23)	0.45			0.22		
Radical (pathol)	No (17)	1	0.80–3.30	0.18	1	0.55–3.97	0.43
	Yes (43)	1.62			1.48		
Radical (clinical)	No (20)	1	0.27–1.09	0.08	1	0.12–0.80	0.01
	Yes (40)	0.54			0.31		
Radiotherapy[b]	No (44)	1	0.12–4.58	0.02	1	0.73–4.94	0.18
	Yes (16)	2.26			1.90		
Complication	No (47)	1	0.51–2.52	0.75	1	0.21–2.48	0.60
	Yes (13)	1.14			0.72		
Complication serious	No (52)	1	0.30–2.44	0.77	1	0.22–4.22	0.97
	Yes (8)	0.85			0.97		

[a] Data of three patients missing

[b] See also Table 2

sarcomas or not. Other factors that might influence prognosis are radical resection [10, 12, 14] (confirmed in our series only for LRFS in the clinical radical group), tumor size less than 5 cm [14], age [10] (in our series for OS), synchronous metastases [10], and local recurrence [10], although the latter prognostic factor could not be confirmed in another study [12].

The best results in STS surgery in the extremities are seen in patients with a R0 resection. The margin for sarcoma resection is the subject of current discussion and at present 2 cm is considered to be sufficient [2].Nevertheless, when the tumor invades the bony chest wall, this margin will not be reached at the inner side. Therefore, a minor margin is accepted as radical here, even when tumor is seen at the level of the pleura. If the resection margin is not free in its tangential way, the need of re-resection is questionable, since no statistical difference in outcome was found between pathological radical (R0) and irradical (R1 and R2) CWR (5-year OS of 25 and 20%, respectively, in the high-grade group).

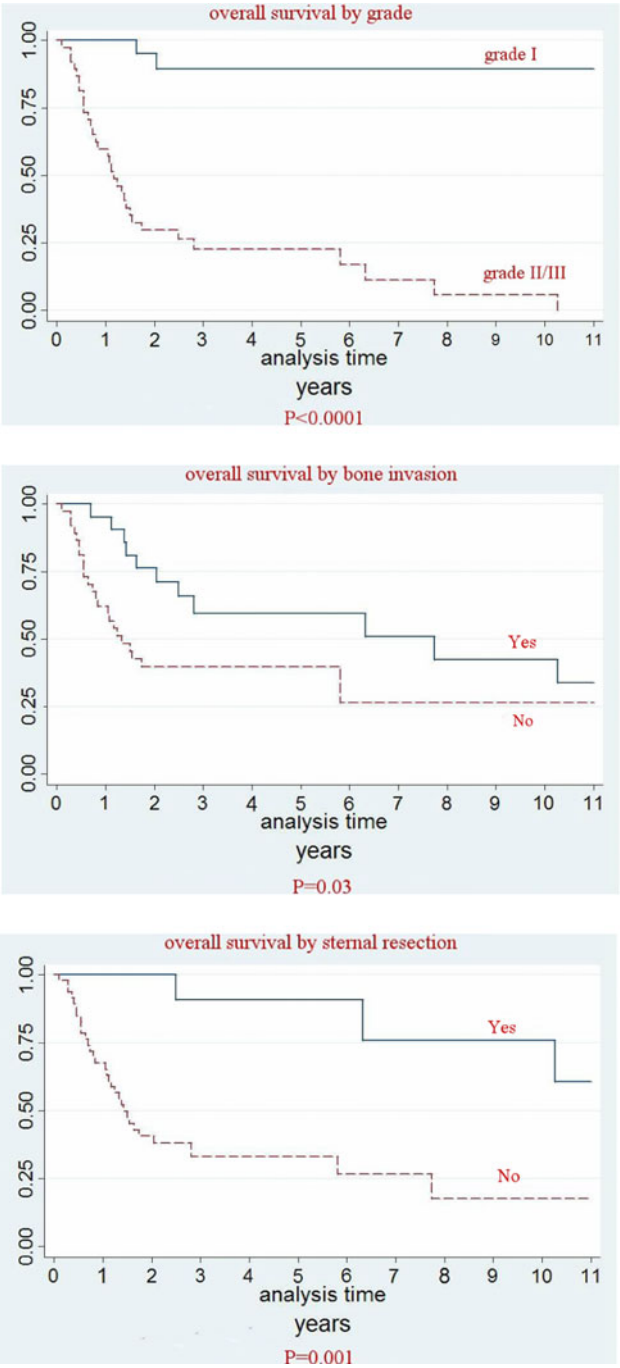

Fig. 2 Overall survival of chest wall resection for soft tissue sarcoma and chondrosarcoma by grade, bone invasion, and sternal resection

OS in all patients with postoperative radiotherapy is significantly worse ($p = 0.02$), but LRFS is not ($p = 0.18$). This finding is in contrast with the results for extremity sarcomas, in which radiotherapy improves local control but not the overall survival [15, 16]. It has also been found that prognosis of chest wall sarcomas is similar to that of extremity sarcomas [11]. These different outcomes are explained probably by selection bias. The 60 selected patients in our study may be an unfavorable group. This remarkable result was further studied in subgroups of patients who did or did not have radiotherapy. Table 2 shows that there was no difference between the R0 and R1/2 groups. The OS remained significant for all 51 patients without RISTS and for all patients without borderline tumors. These findings are an important contribution to the existing literature concerning the role of radiotherapy in CWR.

A radical resection is advised only for chondrosarcomas: the 5-year survival rate was 100% for R0 resections compared to 50% for irradical resections [8].

In the literature, complication rates after CWR for STS are very low and comparable with our complication rate of 12%, including one postoperative death. A postoperative death was also reported in another series of 16 patients [9, 13]. The risk for adverse events is lower than that for CWR for recurrent breast cancer [9]. The reason for this is probably the higher number of ulcerating tumors in breast cancer patients, leading to an increased risk for infectious complications [17].

In our series the prognosis for CWR in radiation-induced STS was poor compared to other series. The overall survival of 9 patients in our study (8 patients after breast cancer and 1 patient after Hodgkin's disease) ranged between 2 and 26 (median = 8) months. Other reports show an actuarial 5-year survival of 36%, and after a median follow-up of 30 months, a 5-year survival of 48% [3, 18]. A possible explanation for our relatively poor outcome could be the extensive tumor growth in our group of patients and the fact that they did not receive radiotherapy after CWR. Based on the results of our series, one could argue that a CWR is indicated in this group of patients only as a palliative procedure.

Reconstruction of the chest wall for stabilization is carried out for defects of more than one rib, although even larger defects on the posterior side do not require reconstruction. For reconstruction of the rigid chest wall several biologic (absorbable; Lyodura®,) and synthetic materials (absorbable such as Vicryl® and Dexon®, and nonabsorbable such as Prolene®, Marlex®, Gore-Tex®) and even combinations are available. Even a rigid reconstruction can be used (metal, methylmethacrylate). The best method is still being debated but the general thought is that absorbable materials do not pose wound problems in case of infection and the reconstruction is easier and faster. Nonrigid reconstruction is sufficient to temporarily stabilize the chest wall, enhance the respiratory function, and help the recovery of the patient. After CWR, lung function is reduced by about 10% [9].

The result of this study (and the experience in the entire series of 229 patients [17]) is that our method of reconstruction is safe and that a time-consuming skeletal reconstruction with rigid materials like steel or bone cement in combination with Marlex ® is not necessary [6, 9].

Table 2 Radiotherapy as a prognostic factor in subgroups of patients with chest wall resection for soft tissue sarcoma and chondrosarcoma

Covariate	Radiotherapy	Overall survival			Local recurrence-free survival		
		HR	95% CI HR	*p*	HR	95% CI HR	*p*
Exc RISTS[a] ($n = 51$)	No	1	0.13–5.32	0.02	1	0.84–7.11	0.09
	Yes	2.45			2.44		
Exc Borderline[b] ($n = 46$)	No	1	1.17–5.28	0.01	1	0.74–5.22	0.17
	Yes	2.49			1.96		
RO3 ($n = 43$)	No	1	0.59–5.90	0.28	1	0.23–5.77	0.86
	Yes	1.86			1.16		
R1 and R2[c] ($n = 17$)	No	1	0.92–6.62	0.06	1	0.69–7.71	0.16
	Yes	2.46			2.30		

[a] All patients excluding radiation-induced soft tissue sarcoma

[b] All patients excluding borderline tumors

[c] Resection margin is free (R0), microscopically involved (R1), grossly involved (R2)

Table 3 Review of the literature of chest wall resection for soft tissue sarcoma and chondrosarcoma

Author (year) [Ref]	*n*	% Overall survival and (disease-free survival)		Remarks
		5-year	10-year	
Perry (1990) [12]	28	59 (40)		Only high-grade sarcomas, including recurrent sarcomas
Gordon (1991) [11]	149	90 low-grade		
		49 high-grade		
Burt (1992) [10]	88	64		Chondrosarcomas
Martini (1996) [7]		80		Median follow-up 17 years
		64 Curative low-grade		
		7 Curative high-grade		
Chapelier (1997) [18]	15	48 (27)		Including radiation-induced sarcomas
				Median follow-up 30 months
Sabanathan (1997) [6]	22		67	Chondrosarcomas
Athenassiadi (2001) [19]	8	33		
Bricolli (2002) [9]	16	86		Chondrosarcomas
				Median follow-up 54 months
Fong (2004) [8]	24	92		Chondrosarcomas
		100 radical		
		50 irradical		
Kirova (2005) [3]	8	Median 40 m		Radiation-induced (osteo) sarcomas
Gross (2005) [14]	55	87 (75)	80 (64)	28 primary and 27 recurrent sarcomas
Pfannschmidt (2006) [13]	25	57		Median survival all patients 100 months
		42 high-grade		Median survival high-grade 36 months
van Geel (this series)	60	46 (28)	30 (25)	Median follow-up 1.7 years and survival 2.5 years
		85 (72) low-grade	85 (72)	
		23 (10) high-grade	6 (–)	

Conclusion

Despite the fact that most sarcomas of the chest wall are voluminous tumors, a chest wall resection is a safe surgical procedure with low morbidity and a mortality rate of less than 1%. After diagnosing a patient with a tumor of the chest wall, the patient's case should be discussed by a multidisciplinary group, including a surgeon, pathologist, radiologist, radiotherapist, medical oncologist, and plastic surgeon, to confirm optimal treatment planning and reconstructive possibilities. Even in isolated local recurrences, a second CWR can be considered. In patients with

systemic disease, a CWR can be considered for palliative reasons, for example, to maintain local tumor control in case of substantial tumor burden in the chest wall.

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