

## RESEARCH ARTICLE

# Long-Term Treatment Results in Soft Tissue Sarcomas of the Thoracic Wall Treated with Pre-or-Postoperative Radiotherapy - a Single Institution Experience

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### Abstract

**Objective:** To evaluate the long term results among patients with soft tissue sarcoma of the thoracic wall. **Materials and Methods:** Twenty-six patients who were treated with pre-or postoperative radiotherapy between December 1980-December 2007, with a diagnosis of soft tissue sarcoma of the thoracic wall were retrospectively evaluated. **Results:** The median age was 44 years (14-85 years) and 15 of them were male. A total of 50% of patients were grade 3. The most common histologic type of tumor was undifferentiated pleomorphic sarcoma (26.9%). Tumor size varied between 2-25 cm (median 6.5 cm). Seventeen of the cases had marginal and 9 had wide local resection. Four cases received preoperative radiotherapy and 22 postoperative radiotherapy. Six of the patients with large and high grade tumors received chemotherapy. Median follow-up time was 82 months (9-309 months). Local recurrence and metastasis was detected in 34.6% and 42.3% of patients, respectively. Five-year local control (LC), disease-free survival (DFS), overall survival (OS), and disease-specific survival (DSS) were 62%, 38%, 69%, and 76% respectively. On univariate analysis, the patients with positive surgical margins had a markedly lower 5-year LC rate than patients with negative surgical margin, but the difference was not significant (43% vs 78%,  $p=0.1$ ). Five-year DFS (66% vs 17%) and DSS (92% vs 60%) rates were significantly worse for the patients who had high grade tumors ( $p=0.01$ ,  $p=0.008$  respectively). **Conclusions:** Tumor grade and surgical margin are essential parameters for determining the prognosis of thoracic wall soft tissue sarcoma both in our series and the literature.

**Keywords:** Thoracic wall soft tissue sarcoma - prognostic factors - radiotherapy

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### Introduction

Soft-tissue sarcomas (STS) comprise approximately 1-1,5% of all malignancies in adults and less than 10% of soft tissue sarcomas are located in the thoracic wall (Gross et al., 2005; Jamal et al., 2010). Clinical findings may vary from asymptomatic up to palpable mass, pain and ulceration. Some of these tumors can be found incidentally on imaging as part of screening or for investigation of an unrelated condition. Computerized tomography (CT) and magnetic resonance imaging (MRI) of primary site are required for radiological evaluation (Shah et al., 2010).

Thoracic wall STS were usually evaluated together with STS of other primary sites or bone and cartilaginous chest wall tumors due to their rarity (Pairolero et al., 1985; Athanassiadi et al., 2001; Coindre et al., 2001; Warzelhan.,

2001; Gross et al., 2005; Salas et al., 2009; Tsukushi et al., 2009; Jamal et al., 2010; Shah et al., 2010; Van Geel et al., 2011; Berna et al., 2012; Roger et al., 2013). While there are limited data about the prognostic factors for the patients with primary thoracic wall STS, they are generally treated like extremity sarcomas since the prognostic factors and the clinical behavior of thoracic wall sarcomas assumed to be similar to extremity STS (Greager et al., 1987; Gordon et al., 1991; Gross et al., 2005).

Surgery is the primary treatment modality in thoracic STS. Generally, wide local excision can be adequate for small superficial and low-grade lesions. But, a considerable proportion of the patients are presenting with locally advanced tumors not amenable to wide local excision with negative margins due to the bulk and extent of the tumor or proximity to critical tissues. Postoperative

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radiotherapy as an adjunct to surgical treatment is required for the patients with large and high grade tumors and with close or positive margins (Lindberg et al., 1981; Wouters et al., 2008; Burt et al., 2013). On the other hand preoperative radiotherapy, chemotherapy, or combined chemoradiotherapy can be applied to these patients in order to allow more conservative surgery with negative margins (Kraybill et al., 2010; Burt et al., 2013). Some authors recommended preoperative radiotherapy when close margins were anticipated in order to improve LC and DFS (Kachroo et al., 2012; Gronchi et al., 2013). However, regarding the uncertainty about the best treatment schedule in patients with large and high-grade STS, the institutes treat the most of the patients with their own protocols.

We aimed to evaluate the long term treatment results of the patients with STS of the thoracic wall who were treated with pre- or postoperative radiotherapy at our hospital.

## Materials and Methods

### *Patient and disease characteristics*

A total of 45 patients were admitted to our clinic between December 1980 and December 2007 with a diagnosis of STS of the thoracic wall. Nineteen of them were excluded from evaluation due to the absence of radiotherapy indication. Also, patients who received prior chemotherapy, radiotherapy, and specific histologic subgroups, including, rhabdomyosarcoma, extraosseous Ewing, primitive neuroectodermal tumor or dermatofibrosarcoma protuberans were not included in this study. While there is no common consensus on the terminology for STS of the thoracic wall, the patients who were analyzed in this series cover the chest wall tumors with a medial border of scapula, and tumors of the shoulder girdle-axilla.

Pretreatment evaluation included medical history and physical examination, complete blood count, serum chemistry panel, CT of the thorax and/or MRI of the chest wall tumor site. The maximum tumor diameter was measured on CT scans taken at the time of diagnosis. Pathologic diagnosis was established by open biopsy or CT-guided core biopsy at our institution or by excision at another center in the case of recurrent tumors. All pathology specimens were reviewed by the same pathologist at our hospital before the treatment.

### *Treatment*

Radiotherapy was delivered with Co60 or 4-6 MV linear accelerators. Eighteen of the patients were irradiated with 2D technique (with customized blocks) with 2-5cm margins around the soft tissue mass or surgery incision before 2000. Afterwards, 3D conformal planning was started to be used. The clinical target volume was created by giving a margin 2-3 cm from the gross tumor volume seen in the planning CT and also we took into account the extension of the tumor on pre-operative images. Postoperative RT was used to patients with positive or close surgical margins and patients with high grade tumors. Some of the patients with large and high grade tumors received 2-3 courses of neoadjuvant or 6 courses of adjuvant chemotherapy consisting of 75mg/

m<sup>2</sup> Doxorubicin on D1, 2 gr/m<sup>2</sup> Ifosfamide and 2gr/m<sup>2</sup> Holoxan on 3 consecutive days (D1-3) every 3 weeks.

### *Follow-up*

During radiotherapy, all patients were observed per weekly in order to evaluate the acute side effects. Following completion of all therapy, patients were fully evaluated in our institution at every 3 months for 2 years, every 6 months between 3 and 5 years and yearly thereafter. CT or MRI of the thorax, and serum chemistry panel were repeated every 6-12 months. Further studies were requested according to the patients' complaints. Acute and late toxicities were graded according to the Radiation Therapy Oncology Group (RTOG) scoring criteria.

### *Prognostic factors and statistical methods*

Overall survival (OS) was calculated from the initiation of therapy to the date of death (whatever the cause) or date of last known follow-up. Disease-free survival (DFS) time was calculated to the date of first metastasis/local recurrence or last follow-up. Local control (LC), DFS, OS and disease specific survival (DSS) rates were analyzed by Kaplan-Meier method and compared with long rank test. Possible prognostic variables including tumor size, grade, surgical margin status, chemotherapy were analyzed for prognostic purposes. Multivariate analysis of these variables was performed by the Cox proportional hazard model. A p value of <0.05 was defined as statistically significant. Since this is a retrospective analysis; our institutional board was informed before the analysis and the analysis was conducted in accordance with the principles of the Declaration of Helsinki and the rules of Good Clinical Practice. National rules do not require obtaining ethical committee approvals for retrospective studies.

## Results

Presenting symptoms included thoracic wall mass in 19 patients (73.1%), pain associated with a mass in 3 patients (11.5%) and pain alone in 3 patients (11.5%). One patient (3.8%) was asymptomatic. The median age was 44 years (range 14-85 years) and 15 of them were male and 11 were female. The site of tumor origin was the anterior-lateral chest wall in 8 patients, posterior chest wall in 7 patients, axilla in 6 patients and shoulder girdle in 5 patients. Tumors were classified as grade-3 in 13 patients and grade 1 in 7 patients. Tumor size varied between 2-25 cm (median 6.5 cm). Undifferentiated pleomorphic sarcoma was the most commonly seen histopathology (26.9%) followed by liposarcoma and synovial sarcoma (23.1%). Patient and tumor characteristics are shown in Table 1.

Five patients had been treated elsewhere previously and referred us after local recurrence. 21 of the 26 patients did not receive any treatment before. Seventeen of the cases underwent marginal and 9 underwent wide local resection. The surgical margin was close or positive in 11 of the patients. Pectoral muscle was removed in 2 patients and 2 cases had thoracotomy with 2-3 rib resections

**Table 1. The Characteristics of Tumor and Treatment**

	N	%
Tumor localization		
Anterior-lateral chest wall	8	30.7
Posterior chest wall	7	26.9
Axillary	6	23.0
Shoulder girdle-supraspinous fossa	5	19.2
Tumor size		
≤5cm	8	30.8
>5cm	18	69.2
Histopathologic subtype		
Undifferentiated pleomorphic sarcoma	7	26.9
Synovial sarcoma	6	23.1
Liposarcoma	6	23.1
Fibrosarcoma	2	7.7
Sarcoma, not otherwise specified (NOS)	2	7.7
Malignant peripheral nerve sheath tumor	1	3.8
Alveolar soft-part sarcoma	1	3.8
Hemangiopericytoma	1	3.8
Radiotherapy		
Preoperative	4	15.4
Postoperative	22	84.6

\*The characteristics of tumor and treatment

metastasis. Seventeen cases died of progressive disease, 2 patients died due to cardiac disorders. None of them were related with treatment complications.

On univariate analysis, 5-year DFS rate was better in patients with tumor ≤5cm than patients with tumor >5cm (68% vs 27%, p=0.06). The patients with positive surgical margins had a markedly lower 5-year LC rate than patients with negative surgical margin, but the difference was not significant (43% vs 78%, p=0.1). Five-year DFS (66% vs 17%) and DSS (92% vs 60%) rates were significantly worse for the patients who had high grade tumors (p=0.01, p=0.008 respectively) (Table 2). We did not find any significant prognostic factor for LC and survival rates on multivariate analysis.

Among 26 patients, acute radiation side effects were seen in 17 (65.3%) patients. The most common acute toxicity was grade 1 skin reaction (13 patients). One patient had Grade 2 and 1 patient had Grade 3 skin reactions. Grade 1 pneumonitis was observed in 2 patients. Fifteen (57.6%) patients had late side effects. Grade 1-2 subcutaneous fibrosis (38.4%) was the most common late

**Table 2. Univariate Analysis for Prognostic Factors in Local Control (LC), Disease-Free Survival (DFS) and Disease-Specific Survival (DSS)**

Prognostic factors	N	LC		DFS		DSS		
		5-yr (%)	P	5-yr (%)	P	5-yr (%)	P	
Tumor size	≤5cm	8	75	0.4	68	0.06	83	0.1
	>5cm	18	54		27		65	
Tumor grade	Grade 1-2	13	75	0.1	66	0.01	92	0.008
	Grade 3	13	47		17		60	
Surgical margin	Positive	11	43	0.1	35	0.9	73	0.8
	Negative	15	78		43		80	
Chemotherapy	Yes	6	66	0.9	16	0.07	66	0.09
	No	20	61		51		79	

and flap transfer was required. One patient underwent lobectomy due to the invasion of lung parenchyma with tumor and subclavian artery was ligated in another patient. Twenty two patients received postoperative radiotherapy with a median dose of 60 Gy (50-66 Gy) and 4 patients received preoperative radiotherapy with a median dose of 46 Gy (35-46 Gy) with conventional fractionation over 5-6 weeks. Three patients were treated with neoadjuvant chemotherapy. Adjuvant chemotherapy was given to 3 patients.

The median follow-up time was 82 months (9-309 months). Five-year LC, DFS, OS, and DSS rates were 62%, 38%, 69%, and 76% respectively. 7 patients have survived with no evidence of disease. Nine patients (34.6%) developed local recurrence with a median time of 20 months (2-53 months). Third relapse was observed in one patient and all other patients had second recurrence. All patients with recurrent disease underwent surgery. Afterwards, 4 of them were treated with chemotherapy, one of them received external radiotherapy, and one patient was treated with brachytherapy. Eleven (42.3%) patients developed distant metastasis after a median of 40 months (4-92 months). The most common metastatic sites were the lungs (38.5%) and the bones (3.8%). Three cases developed both local and distant metastasis. Chemotherapy was given to all cases developing distant

side effect. Grade 1-2 joint stiffness was seen in 2 patients and lung fibrosis was observed in 2 patients.

## Discussion

Primary STS of the thoracic wall are rarely seen. Thoracic wall sarcomas have worse prognosis compared to the extremity primaries and have better prognosis than pelvic, head and neck sarcomas (Singer et al., 1995; Coindre et al., 1996). The data about treatment outcome and prognostic factors for patients with primary STS of thoracic wall is limited while it is usually evaluated together with extremity or retroperitoneal sarcomas (Berna et al., 2012; Roger et al., 2013). Besides, in many studies patients with rhabdomyosarcoma, bone and cartilaginous chest wall tumors, borderline tumors like desmoids tumors, dermatofibrosarcoma protuberans and patients with tumors metastatic to the chest wall were included in the analysis (Pairolero et al., 1985; Coindre et al., 2001; Athanassiadi et al., 2001; Warzelhan et al., 2001; Salas et al., 2009; Tsukushi et al., 2009; Van Geel et al., 2011). Few studies focused exclusively on soft tissue tumors originally from chest wall alone are available (Greager et al., 1987; Gordon et al., 1991; Gross et al., 2005).

There is no data for the optimum treatment strategy for STS of thoracic wall. However, the general treatment principles of STS can be applied for them. Surgery is the

main treatment modality for all of the STS. Radiotherapy can be used as an adjuvant treatment modality as pre or postoperative schedule in order to improve LC rates. The literature on this subject mostly agreed on that radiotherapy has little or no role on DFS and OS rates. However, Burt et al. reported that DFS was significantly better for the patients who were treated by surgery plus radiotherapy for stage IIB-III chest wall sarcoma and there was a trend for OS as well (Burt et al., 2013). Although the role of chemotherapy is conflicting in STS, the use of adjuvant treatment for STS of thoracic wall has been extrapolated from the experience with extremity sarcomas since these tumors are rarely seen. The results of meta-analyses and randomized clinical trials showed that doxorubicin-based adjuvant chemotherapy improves relapse-free survival especially in patients with high grade extremity sarcomas (Pervaiz et al., 2008; Italiano et al., 2010).

In the treatment of STS wide resection is required to contribute to the long-term local control. Although the exact margin size is somewhat debated, 2 cm surgical margin for low-grade sarcomas, 4 cm margin for high-grade tumors is considered to be sufficient for wide local resection (Walsh et al., 2001). However, optimal margins may be hardly achievable in number of cases and sometimes close margins can be acceptable for thoracic STS since there are no clear anatomic boundaries and compartments. Thoracotomy with rib resection, excision of any involved structures, including parts of pleura, lung, and diaphragm may be required to get adequate resection, margins. Also, skeletal reconstructions, soft tissue coverage, flap transfer for extensive skin defect are often necessary for chest wall closure after large tumor excision. Type of surgical resection and surgical margin status have been reported to correlate with the local control (Pairolero et al., 1985; Sabaratnan et al., 1997; Pairolero et al., 2000; Athanassiadi et al., 2001). In our series, the LC rates were 43% and 78% for the patients with positive and negative margins respectively; although there is a distinct difference it was not statistically significant. Also, all of the patients treated with aggressive surgery were alive without local recurrence.

Large tumor size has been found to be another prognostic factor for STS of the thoracic wall. A study of 343 patients from the French Sarcoma Group database showed that tumor size is an important prognostic factor of metastasis-free survival and overall survival (Salas et al., 2006). Greager et al. analyzed 49 patients with STS of the thoracic wall and noted that all 10-year survivors had tumors with low grade or <5cm in diameter (Greager et al., 1987). Gross et al. also noted that tumor size less than 5 cm was determinants of a better DFS and OS (Gross et al., 2005). One of the largest series of patients who had soft-tissue sarcomas of the chest wall was reported by Gordon et al (1991). The authors reviewed 149 patients who had undergone surgical resection. Tumor size did not affect the survival in their analysis. However, their data comprised patients with desmoid tumors and rhabdomyosarcoma as well. In our series, there was a trend for DFS rates favoring the tumors less than 5 cm but it did not influence OS.

Histologic grade is an independent prognostic factor for DFS and OS in the thoracic wall sarcomas as in all

sarcomas at other sites (Greager et al., 1987; Gordon et al., 1991; Coindre et al., 2001; Gross et al., 2005; Salas et al., 2009;). Low-grade STS had a significantly better prognosis compared with high-grade tumors. Metastases develop in 10% of patients with low grade tumors compared with 50% in patients with high-grade STS despite optimal local treatment (Anderson et al., 1994). In this series, grade was found to be a significant prognostic factor both for DFS and DSS ( $p=0.01$  and  $p=0.008$  respectively). This difference cannot be extrapolated to multivariate analysis.

In our series, 5-year local recurrence free survival (LRFS) rate was lower than the literature; even all our patients received radiotherapy. This can be explained by the fact that the majority of our patients had more than 5 cm tumors and nearly half of them were located in the shoulder girdle-axilla area where it is difficult to get negative margins. The DFS rate is inferior in the current series than the others, that might be related with the large tumor size and the significant number of high grade tumors. The overall 5-year OS has been reported in range of 60 to 66% with LC exceeding 70% (Gordon et al., 1991; Wouters et al., 2008; Salas et al., 2009). In the Gross et al. study, the 5-year OS rate was 87.3% and DFS rate was 75.3% which was greater than those observed by our study and the others (Gross et al., 2005). It might be due to inclusion of more low-grade tumors in their series. So, it is difficult to compare the results of studies since inclusion criteria are different for all of them.

In conclusion, this study is an unplanned, retrospective analysis with small sample size, heterogenous patient-tumor characteristics extending over 3 decades. Besides these limitations, imaging, surgery and radiotherapy techniques and indications for chemotherapy have been evolved over the years. However, it appears that tumor size, grade and resection margins are essential parameters for determining the prognosis of thoracic wall STS both in our series and the literature. High grade has found to be the important factor affecting prognosis. It is not easy to perform well designed prospective studies due to the rarity of the STS of thoracic wall. Therefore regarding the similarity of the prognostic factors and the behaviors with extremity STS, thoracic wall STS should be assessed and treated in a multidisciplinary setting to optimize the patient outcome.

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