

# Management of soft tissue sarcomas of the chest wall: a comprehensive overview

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**Abstract:** Sarcomas of the chest wall are rare and their current treatment regimen is diverse and complex due to the heterogeneity of these tumors as well as the variations in tumor location and extent. They only account for 0.04% of newly diagnosed cancers of whom about 45% comprise soft tissue sarcomas. Larger cohort studies are scarce and often focus on one specific treatment item. We therefore aim to provide helicopter view for clinicians treating patients with sarcomas of the chest wall, focusing mainly on soft tissue sarcomas. This overview includes the value of neoadjuvant systemic or radiotherapy, surgical resection, approaches for thoracic wall reconstruction, and the need for follow-up. Provided the heterogeneity and relative rarity, we recommend that treatment decisions in soft tissue sarcoma of the chest wall are discussed in a multidisciplinary tumor board at a reference sarcoma center or within sarcoma networks to ensure personalized, rational decision making. A surgical oncologist specialized in sarcoma surgery is crucial, and for extensive resections involving the thoracic cavity we recommend involvement of a thoracic surgeon. In addition, a specialized medical- and radiation oncologist as well as a plastic surgeon is required to ensure the best multimodality treatment plan to optimize patient outcome.

**Keywords:** Sarcoma; chest wall; primary chest wall sarcoma; resection

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## Introduction

Sarcomas of the chest wall are a rare and heterogeneous group of mesenchymal neoplasms. The location, extent, and origin of these specific sarcomas result in diverse and complex treatment regimens that may consist of (neoadjuvant) systemic- and/or radiotherapy, resection and often chest wall reconstruction. Available (large) cohort studies and review articles are scarce and often focus on one specific treatment item. We therefore aim to provide a helicopter view for clinicians treating patients with sarcomas of the chest wall, focusing mainly on soft tissue sarcomas.

Primary sarcomas that are located in the chest wall account for only 0.04% of newly diagnosed cancers. They are estimated to represent less than 2–5% of thoracic neoplasms (1,2). Sarcomas are traditionally classified based on their origin in bony or soft tissue. Adhering to this classification, soft tissue sarcomas comprise of about 45% of sarcomas of the chest wall (see *Table 1*) (3–8). Chondrosarcoma (mainly in adults) and Ewing sarcoma (predominantly in children and adolescents) are the most common malignant bony chest wall sarcomas (8). Common soft tissue sarcomas of the chest wall include pleomorphic sarcoma not otherwise specified (NOS), liposarcomas, fibrosarcomas, and desmoid tumors. Given the relative rarity of thoracic sarcomas in conjunction with the expanded subdivision, there is no clear data known on the type-specific incidence and prevalence. However, over the past years, different groups have initiated studies aiming to provide more insight (9–11). These studies show that the most common histopathologic type differs between geographic regions, and that one of the risk factors for developing soft tissue sarcoma may be radiotherapy for previous cancer. For instance, angiosarcoma and pleomorphic sarcoma NOS are known to be radiotherapy-induced, and comprise about 3% of all soft tissue sarcomas (12). Radiotherapy-induced sarcoma typically occur after a median latency period of 10 years (range 6 months to 20 years), and in case of cutaneous angiosarcomas even earlier, around 4 years after radiotherapy (13).

Most patients with a soft tissue sarcoma of the chest wall present with an enlarging palpable mass. In less common cases, soft tissue sarcomas are observed as incidental findings on cross-sectional imaging such as computed tomography (CT) as symptoms are often lacking during the early stages of the disease. Patients with a sarcoma located in the chest wall may complain of pain and soreness due to increasing growth, mainly when cartilaginous or bony tumors damage

the periosteum. Larger tumors can result in impaired movement or muscle atrophy. Physical examination may demonstrate noticeable swelling, and careful palpation may reveal underlying asymmetry of the chest wall and describe the texture of the tumor (14).

An important step in imaging for a soft tissue mass suspicious for a sarcoma is magnetic resonance imaging (MRI), followed by a core needle biopsy. For distant staging either CT or positron emission tomography (PET)-CT can be used. The modality used for distant staging very much depends on the type of sarcoma found by the pathologist and its usual metastatic pattern. Accurate classification of the sarcoma type by histological biopsy reviewed by an experienced sarcoma pathologist is necessary to guide further therapeutic decisions. Lymph node dissemination is rare but can occur in soft tissue sarcoma subtypes such as synovial, clear cell, angiosarcoma, rhabdomyosarcoma, and epithelioid forms (15).

## (Neo)adjuvant therapy

Even though the keystone of the treatment of soft tissue sarcomas of the chest wall is surgical resection, (neo) adjuvant therapy may be of additional value, especially in high-grade tumors. In earlier times, postoperative radiotherapy after soft tissue sarcoma resection was introduced predominantly in extremity sarcomas to make limb-saving surgery possible. However, in some cases it also improved overall survival and local control (16). Preoperative radiotherapy can have several advantages, including more accurate target delineation, decrease of the dose as compared to postoperative radiotherapy (50–50.4 vs. 60–64 Gy), and no radiation delivered to a possible flap reconstruction. Because of these potential benefits, there has been a paradigm shift towards preoperative radiotherapy for those sarcoma subtypes that are known to be radiosensitive. Moreover, preoperative radiotherapy is specifically relevant in cases where only marginal surgical margins can be obtained, due to its anatomical relation to (vital) structures of which resection might result in serious impairment of function.

Neoadjuvant or adjuvant systemic therapy is not advised routinely in localized soft tissue chest wall sarcomas (17). However, there are certain subtypes (undifferentiated pleomorphic sarcoma, dedifferentiated or myxoid liposarcoma, and synovial sarcoma) that are more chemosensitive to conventional cytotoxic agents, i.e., doxorubicin and/or ifosfamide or the ‘newer’ histocyte

**Table 1** Sarcomas of the chest wall and their origin

Origin	Type of sarcoma of the chest wall
Bone	Ewing sarcoma, osteosarcoma
Cartilage	Chondrosarcoma
Vascular	Hemangiosarcoma
Adipose tissue	Liposarcoma
Fibrous tissue	Fibrosarcoma, MFH, solitary fibrous tumor, desmoid tumor
Muscle	Leiomyosarcoma, rhabdomyosarcoma, tendon sheath sarcoma
Nerve	Askin tumor (PNET), malignant schwannoma, neurofibrosarcoma, neuroblastoma

MFH, malignant fibrous histiocytoma; PNET, primitive neuroectodermal tumor.

specific cytotoxic trabectedin (leiomyosarcoma, liposarcoma). Overall, for soft tissue sarcomas, smaller trials and subgroup analyses indicate a benefit of adjuvant chemotherapy in fit patients with a high risk of death, and is therefore also advised in the European Society for Medical Oncology (ESMO) soft tissue sarcoma guideline (18). In specific cases with unresectable tumors or when surgery is likely to cause unacceptable morbidity, such as a desmoid tumor failing conservative therapy, patients are sometimes treated with systemic therapy such as chemotherapy or tyrosine kinase inhibitors, especially when they present with significant symptoms or rapid growth. Two frequently arising tumors of the chest wall are (radiotherapy induced) angiosarcoma, where in case of advanced disease paclitaxel is advised because these tumors are sensitive to taxanes; and solitary fibrous tumor which is refractory to doxorubicin, but may respond to dacarbazine and trabectedin or pazopanib (19-21).

Only a fraction of patients in prospective trials evaluating (neo)adjuvant chemotherapy in sarcomas represent chest wall sarcomas, though it is suggested that results should be extrapolated based on type of sarcoma rather than its primary anatomic location (18). On the other hand, it is suggested that local recurrence rate is higher in patients with chest wall sarcomas compared to, for instance, extremity localization. Especially in tumors involving the pleural cavity, the risk of local recurrence seems higher (22). Several cohort studies on treatment of primary sarcomas of the chest wall report on neoadjuvant chemo and radiotherapy, but without impact on survival or complete resection rate, even though the majority of patients presented with a high-grade sarcoma (22-24). However, it must be noted that the outcomes of these studies are influenced by the relatively small patient numbers and heterogeneity by several sarcoma types. Still, although

not specifically in soft tissue sarcomas of the chest wall, it has been shown that complete pathological response to neoadjuvant treatment is associated with better survival, analogous to bone sarcomas (25). Furthermore, it must be noted that sarcomas located in the chest wall are so rare that prognostic tools to such as ‘Sarculator’ or the ‘PERSONALISED SARcoma Care (PERSARC) model’ are not suitable to support shared decision making in patients suffering from sarcoma at these locations (26,27).

### Surgical management

Wide *en bloc* surgical resection with negative margins is the mainstay of treatment of chest wall sarcomas (28). An adequate preoperative surgical plan requires detailed information on the location of the tumor and involvement of surrounding tissue, especially in cases when a large resection (and subsequent reconstruction) is required. Only a small part of (mainly soft tissue) chest wall sarcomas are superficially located and do not require full-thickness chest wall resection (29). More commonly, the resection of chest wall sarcomas includes *en bloc* resection of bony structures (e.g., ribs, sternum, or vertebrae), and may even extend towards intrathoracic structures (e.g., lung, diaphragm, or pericardium). These factors may influence timing of surgery and the surgical team of choice. Based on available literature, the extent of margins of complete resection (wide *vs.* marginal) do not influence survival or local recurrence rates (29). As a result, expert consensus was obtained for negative margins in chest wall sarcoma resections (28). To increase the R0 rate, it is advised to perform a wide excision with a 2 cm macroscopic margin, unless vital organs or structures like heart, major vessels, trachea, and spine are adjacent. Even in locally advanced sarcomas or complex

cases involving multiple vital structures, surgery seems to provide acceptable perioperative morbidity and mortality, with similar 5-year overall survival compared to more superficial resections (22,23,30).

Studies on survival outcome after surgical resection of sarcomas of the chest wall are limited by small sample size due to the rarity of the disease and heterogeneity caused by, amongst others, tumor type. Despite this limitation, these studies suggest several factors influencing survival, including (in)complete resection, and tumor type and grade. In the single-center cohort study by Collaud and colleagues, a total of 23 patients were (surgically) treated for primary chest wall sarcoma between 2004 and 2018 (22). Most patients presented with high-grade sarcomas (61%), and bone subtype (52%). Furthermore, the majority of patients (65%) required chest wall reconstruction following resection, with an R0 resection achieved in 83% of patients. Five-year overall survival rate was low (35%), with a significant difference between patients with R0 compared to incomplete resection (i.e., R1 or R2) in favor of R0 resection ( $P=0.029$ ). This relatively low survival rate compared to other studies might be the result of inclusion of high-grade and large tumors that required extensive surgery beyond the chest wall (31).

In a cohort study by Shewale and colleagues, 121 patients with chest wall sarcomas who underwent surgical resection between 1998 and 2013 were included (23). Most patients (64%) had high-grade sarcoma, and 49% received neoadjuvant chemotherapy and 10% neoadjuvant radiotherapy. The 5-year overall survival rate was 60%. A high tumor grade was associated with worse outcome (5-year overall survival of 42%) and depended on histologic type. An R0 resection was achieved in 85% and resulted in a significantly higher 5-year overall survival (62%) compared to R1 resections (27%) and R2 resections (29%) ( $P=0.003$ ). No patient-, tumor-, or treatment-related factors such as (neo)adjuvant therapy were correlated to achieving negative resections margins. After multivariate analysis, high tumor grade and incomplete resection were associated with worse overall survival (23), which may be the result of higher risk of recurrence and distant metastases, as described by McMillan and colleagues (32). They concluded high-grade tumor as a main predictor of disease recurrence in their cohort of 192 patients with chest wall soft tissue sarcoma.

Similar results are described in a study by Harati and colleagues, which included 110 patients with chest wall soft tissue sarcomas that were surgically treated between 1999 and 2016 (29). Most patients had high grade tumors

(42%), the most common subtypes were pleomorphic sarcoma NOS (28%), angiosarcoma (19%) or liposarcoma (17%), and R0 resection was achieved in 87%. Adjuvant radiotherapy was administered in 17% and adjuvant chemotherapy in 8% of patients. Median follow-up was 5.4 years, and 5-year overall survival rate was 66%. Patients with R0 resections had significantly better overall survival compared to patients with microscopic or macroscopic incomplete margins (70% *vs.* 39%, respectively). However, this difference did not sustain in multivariate analysis. Factors like tumor grade, size and type were found to be independent predictors of overall survival.

Although primarily indicated for curative attempts, surgical resection also has a place in patients with disseminated disease to obtain local control (e.g., for bleeding or odor-intensive tumors). Especially in these cases, surgical resection should be carefully considered and aimed to minimize postoperative morbidity, weighing its potential benefits.

### Thoracic wall reconstruction

Surgical resection of soft tissue sarcomas of the chest wall results in defects of the thoracic wall, either full or partial thickness. The former should be reconstructed during the same surgical procedure depending on the size and location, to protect subjacent organs, without compromising chest wall integrity and associated biomechanics of breathing and providing adequate soft tissue coverage. Defects covering more than four ribs at the lateral thoracic wall are commonly in need for mesh repair as they are associated with increased risks of paradox breathing (i.e., reverse chest wall motion during breathing) and herniation. For defects of the lower anterior chest wall, it is important to reconstruct the diaphragm. In addition, a recent consensus paper states that rigid implants should be used to reconstruct the chest wall in defects that exceed 5 cm (28). Though, the closer the defect is to the apex, more support is provided by the surrounding structures and larger defects can be reconstructed without the use of meshes (33). In the case of retroscapular thoracic wall defects, reconstruction is of importance to prevent impingement and intrathoracic dislocation of the scapula and to restore the scapulothoracic rhythm.

Prior to providing a brief overview on the different reconstruction materials and methods it must be noted that all cases are unique due to the tumor's location, depth, and local tissue status (e.g., due to prior radiotherapy,

neoadjuvant treatment, and infection). Hence, individualized treatment and meticulous planning in reference sarcoma and thoracic surgery centers are specifically important (34,35). The arsenal to select and combine from includes synthetic meshes, osteosynthesis materials, composite implants, three-dimensional printed implants, pedicled and free flaps, where autologous skin grafting, negative pressure wound therapy, and direct closure are often only reserved for minor defects or as adjuncts.

Synthetic (often non-absorbable polypropylene) or biological meshes are used to avoid herniation of intrathoracic organs and improve chest wall stability. In general, meshes should be avoided in contaminated wounds or ulcerated tumors; if contaminated, pedicled or free flaps are preferred, which will be explained later on in this paper. Osteosynthesis material such as titanium rib or sternal fixation can maintain chest wall stability and improve postoperative functional outcome, especially after anterior and lateral resections (36). The incidence of (chronic) postoperative pain in patients with or without rib fixation is unknown. With the rapid development of three-dimensional printing techniques, even customized titanium implants can be produced for complex defects (37). Composite implants may consist of a combination of titanium implants and meshes; however, numerous other techniques have been described, including carbon fiber, rubber, and silicone (29). Although the previously mentioned methods and materials can make a significant contribution to the reconstruction, they always require additional efforts to reconstruct soft tissues. These constitute in most cases of pedicled or free flaps. Depending on the flap and its objective, flaps can be harvested as fasciocutaneous (i.e., flap that contains skin, subcutaneous tissue, and deep fascia), myocutaneous (i.e., a flap that also contains the underlying muscle), perforator or muscular flaps. The selection of pedicled flaps is usually based on the location of the defect. The pectoralis major flap can be used to cover cranial defects of the sternum (38). The vertical rectus abdominis musculocutaneous (VRAM) flap is especially suitable to cover anterior chest wall defects and can be extended to include a transverse rectus abdominis musculocutaneous (TRAM) flap that can cover defects up to 40 cm of the anterolateral chest wall. A pedicled latissimus dorsi flap is considered more versatile and can cover most defects of the chest wall due to its relatively large radius of rotation and may also be used to seal intrathoracic defects and obliterate dead space. Pedicled omentum majus flaps are generally considered a backup option, though well suited for obliteration of dead space (39).

When the use of pedicled flaps is not possible due to previous surgery, radiotherapy, or when larger volumes are needed to obliterate dead space, free flaps may be a solution, such as the perforator-based deep inferior epigastric artery perforator (DIEP) flap and the anterolateral thigh (ALT) flap (40). Depending on the flap and harvesting method used, adjuncts (e.g., autologous skin grafting, and negative pressure wound therapy) may be subsequently required to cover the donor or recipient site if primary closure is not possible. The advantage of for instance the DIEP flap is the possibility to harvest a large free flap without difficulties in primary closure of the donor site. In short, numerous reconstruction methods exist, each with its own advantages and disadvantages. Given the relatively low incidence of sarcomas of the chest wall and their uniqueness on a case-by-case basis, there is no universally accepted reconstruction method. The decision on which materials and methods to apply depends on the characteristics of the defect and the multidisciplinary surgical experience.

To induce better regeneration of tissue in reconstructive surgery, other applications can be used such as (bio) materials containing biodegradable poly lactide-co-glycolide (PLGA) and  $\beta$ -tricalcium phosphate ( $\beta$ -TCP) (41,42). This material can be used alone, or in combination with other biomaterials or autogenous bone. PLGA and  $\beta$ -TCP might provide better regeneration of tissue by neutralizing pH, thereby reducing the inflammatory response. The specific scaffolds formed from  $\beta$ -TCP can facilitate all fundamental requirements for rapid biomaterial integration, resorption and subsequent bone replacement. This material is available in plates of different sizes, and when immersed in saline solution at a high temperature, the material becomes moldable and can be easily cut to the ideal size for the chest wall defect to be covered using monofilament threads for its support. Together with any type of absorbable or non-absorbable mesh it may improve implantation at the edges of the surgical wound. In larger chest wall defects, it is recommended to cover the entire material with an adjacent muscle flap and use a drain to avoid the formation of localized seroma. These techniques and materials together are key elements to help re-establish the continuity, rigidity, and physiology of the chest wall.

### Quality of life after thoracic wall resection and reconstruction

In general, the health-related quality of life after oncological resection and reconstruction of the chest wall

is considered fair and comparable to that of the general population. Though, moderate impairments have also been described because of limitations in breathing and usual activities (43,44).

### Functional results after thoracic wall resection and reconstruction

When the integrity of the thoracic wall is restored after resection, the effect on pulmonary function is relatively marginal. The study by Daigeler and colleagues, only found a considerable decrease of 18% in the forced expiratory volume in 1 second (FEV1) while all other pulmonary function parameters remained approximately at preoperative levels (45). This decrease was not found to be correlated with the extent of chest wall resection but rather the pain during respiration that in turn was neither associated with the extent of resection. Similar results were found by Klesius and colleagues, in a different population of patients with deep mediastinal wound infection and sternum necrosis treated by complete sternal resection with plastic reconstruction by bilateral pectoralis major flaps (46). Nevertheless, although often considered as marginal, it is hard to generalize the effects of resection on pulmonary function as the affected location differs per patient. For example, diaphragm resection has much more impact than resection of the cranial ribs as they relatively contribute less to the process of ventilation.

### Follow-up

The histological type of the soft tissue sarcomas of the chest wall is considered the most important determining factor for the risk of metastases during follow up. Imaging must be oriented to detect local recurrence and pulmonary and/or intra-abdominal metastases. The chance of other intra-abdominal metastases depends on the histological subtype, with a higher risk for myxoid liposarcoma and leiomyosarcoma. Although other sites of metastases are also described, these locations are extremely rare, and follow-up regimens should therefore not focus on these sites (47). The follow-up regimen for the individual patient can be based on a combination of tumor size, histological type, and tumor grade. A practical approach is suggested in guidelines such as the ESMO guideline; i.e., intermediate-/high-grade patients may be followed every 3–4 months in the first 2–3 years, then twice a year up to the fifth year, and once

a year thereafter (18). Low-grade sarcoma patients may be followed every 6 months for the first 5 years, then annually. The diagnostic modality which is used differs per sarcoma, but MRI (and/or CT) can be used to assess local recurrence and is therefore recommended to perform at least once 3–4 months after resection of soft tissue sarcomas of the chest wall, and after that annually. Conventional radiology or CT scans can be used to assess signs of pulmonary metastases, where the latter is more likely to detect abnormalities at an early stage. For each patient with a soft tissue sarcoma of the chest wall, the decision on follow-up should be made after multidisciplinary consultation in a specialized sarcoma center and extrapolated from follow-up regimens of similar subtypes at different sites of the body.

### Conclusions

In conclusion, chest wall sarcomas are a very rare type of malignant tumors and comprise a wide variety of histological subtypes and locations affected. Therefore, treatment of these tumors is highly individualized. Treatment decisions in soft tissue sarcoma of the chest wall are guided by size, relation to vital structures and the subsequent possible difficulties in resection and reconstruction, histological subtype, grade, and responsiveness to radio- and chemotherapy. All (soft tissue) sarcomas of the chest wall should be discussed in a multidisciplinary tumor board at a reference sarcoma center or within sarcoma networks to ensure personalized, rational decision making. A surgical oncologist specialized in sarcoma surgery is crucial, and for extensive resections involving the thoracic cavity we recommend involvement of a thoracic surgeon. In addition, a specialized medical- and radiation oncologist as well as a plastic surgeon is required to ensure the best multimodality treatment plan to optimize patient outcome. Lastly, given the considerable heterogeneity and rapid evolution in reconstruction methods, we recommend future selection of broadly applicable reconstruction methods that can be universally applied for most defects to define their value.

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