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Lymph node metastases, sentinel lymph node biopsy, and lymphadenectomy in soft tissue sarcoma — when and why?

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ABSTRACT

The spread of soft tissue sarcomas (STS) through the lymphatic system occurs rarely, mainly in epithelioid sarcoma, angiosarcoma, rhabdomyosarcoma, and clear cell sarcoma (CARE). STS subtypes differ in terms of biological behavior. CARE histology and high-grade nodal disease are defined as risk factors in STS. The nodal involvement status in STS patients correlates with the subsequent development of distant metastases. Regional disease is considered clinically distinct from distant metastatic disease in case of recurrence, and it has a better prognosis and better outcomes in terms of long-term survival. Preoperative sentinel lymph node biopsy (SLNB) may be used to identify high-risk patients, as this technique also allows the determination of patients with occult microscopic lymph node disease. The positive result of SLNB may indicate regional lymphadenectomy (LND). Though data on LND in STS are limited, this tool may play a role in multimodal treatment. In the case of STS, a unified diagnosis protocol is needed but followed by an individual treatment approach depending on the results of nodal involvement.

Keywords: sarcoma, STS, lymph nodes, SLNB, lymphadenectomy, metastasis, prognosis, management

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Introduction

Soft tissue sarcomas (STS) are a heterogeneous group of malignant mesenchymal neoplasms that occur most frequently in the extremities. They constitute about 1% of all malignancies [1]. In general, sarcomas are characterized by locally aggressive, infiltrative, destructive growth, a high tendency to recur locally, and the ability to metastasize to the lungs and liver most commonly by the hematogenous route [2, 3]. In at least 10% of STS patients, metastases are present at the time of diagnosis [1]. Spread of STS through the lymphatic system occurs rarely. Lymph node metastases (LNM) are reported in 0.9% to 9% of all sarcoma cases [1, 3–5], mainly in epithelioid sarcoma, angiosarcoma, rhabdomyosarcoma, and clear cell sarcoma (CARE) [1].

Various studies show that the status of nodal involvement in STS patients and LMN treatment correlates with prognosis and long-term survival. Patients with regional lymph node metastases (RLNM) have a better prognosis than patients with systemic disease or combined LNM and systemic disease [5, 6]. According to Basile et al. [1], 5-year overall survival (OS) of patients with isolated LNM was 57.3%, while for those with stage IV disease was 14.6%, and for those with both LNM and systemic disease — 0%.

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Table 1. Frequency of lymph node metastases in selected sarcoma subtypes

Pathological type	Lymph node involvement	References
Rhabdomyosarcoma	6–37%	[3, 8, 13, 14, 15–19]
Epithelioid sarcoma	13–48%	[1, 8, 13, 14, 19, 20]
Clear cell sarcoma	4–50%	[8, 13, 14, 19–22]
Angiosarcoma	8–32.1%	[13, 14, 16, 19]
CIC–rearranged sarcomas	11–25%	[1, 13]
Leiomyosarcoma	1.4–8%	[3, 13, 14, 16]
Synovial sarcoma	0.6–19%	[3, 8, 13, 14, 17]
Osteosarcoma	3%	[13, 14]
Spindle cell sarcoma	5%	[18]

Currently, sarcoma treatment protocols differ depending on centers and their specialization. The results of a survey taken among members of the Musculoskeletal Tumors Society and the Society of Surgical Oncology in January 2022 on clear cell and epithelioid sarcoma show that surgical oncologists were in favor of performing LND while orthopedic oncologists preferred targeted lymph node excision with adjuvant radiotherapy. Among respondents, 79.9% have been practicing in academic settings, and 62.2% treated more than ten extremity sarcoma cases annually [7]. Considering the rarity of LNMs in STS, data on lymphadenectomy (LND) in patients with sarcoma are limited. Yet, lymphatic mapping and sentinel lymph node biopsy-guided LND are already confirmed as a prognostic tool in melanomas and breast cancers [8, 9]. In breast cancer, there is a tendency to limit radical LND even when the sentinel lymph node (SLN) is metastatic [10]. Considering the abovementioned factors, clinicians acknowledge the need for guidelines for individual treatment of STS subtypes and review of cancer staging [11, 12]. Therefore, this review aimed to assess the role of sentinel lymph node biopsy (SLNB) and LND in patients with sarcoma, especially STS of the extremities.

Lymph node metastases in sarcoma

Like other malignant neoplasms, sarcomas may spontaneously metastasize to the regional lymph nodes (RLN), starting first in the sentinel lymph node (SLN). The precise mechanisms by which neoplasms metastasize to LN have not yet been fully identified; however, the clinical importance of LNM is manifested in the staging and prognosis of all cancers. This pattern is affected by anatomy and runs as follows: tumor cells enter the initial lymphatics, assisted by increased pressure in the primary tumor and increased flow rates through the collecting lymphatics, and the lymphatic

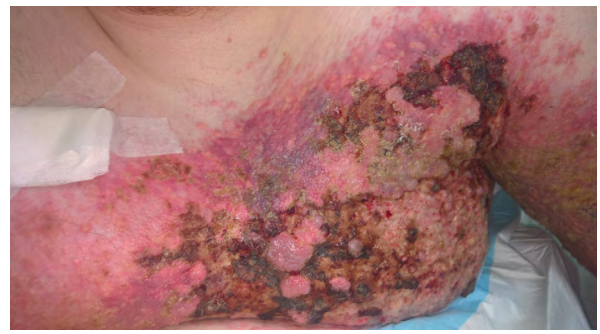

Figure 1. Photograph of the axillary region of a patient with visible lymph nodes rhabdomyosarcoma metastases

trunks allow more cancer cells to flow per unit of time into the afferent lymphatics and the subcapsular sinus of the SLN. Anatomy is not the only factor affecting the path of cancer cells to the SLN. Other complex biochemical, genetic, and molecular events facilitate this process [3, 10].

Research shows that lymph node involvement in STS is generally uncommon (0.9–6%) [1, 3, 13]. Regional lymph nodes metastases are also rare; the reported incidence ranges from 2 to 10% of sarcoma patients [4, 8, 13, 14]. Nevertheless, specific STS subtypes are associated with increased risk of LNMs. These are rhabdomyosarcoma, clear cell sarcoma, angiosarcoma, and epithelioid sarcoma, often referred to by CARE acronym [1, 3] (Tab. 1 [1, 3, 8, 13–22], Fig. 1).

Historically, synovial sarcoma was included in the group of STS with a higher risk of LNM, but analysis of the SEER database from 2004 to 2013 questioned previous findings. Jacobs et al. [5] reported 4.2 % of synovial sarcoma patients with LNM and Garcia-Ortega et al. [3] — 5.8%; both provided evidence that lymph node dissemination was not different than most STS subtypes. CIC-rearranged sarcomas (CRS) are distinct pathologic entities belonging to the subset of

Table 2. Histology-specific prognosis by lymph node metastases (LNM) status in selected sarcoma subtypes

	Five-year survival probability [%]		References
	No RLNM	RLNM present	
Epithelioid sarcoma	43.3–68	17	[3, 20, 33, 34]
Synovial sarcoma	26–67	17	[3, 20, 35]
Angiosarcoma	22–41	22	[3, 35, 36, 37, 38]
Clear cell sarcoma	47–82,4	44	[8, 33, 38–40]
Rhabdomyosarcoma	41–61,8	–	[3, 5, 35, 38]
Embryonal Rhabdomyosarcoma	73.4–91.8	75.8	[5, 38]
Alveolar Rhabdomyosarcoma	47.8	–	[5]
CIC-rearranged sarcomas	24	0	[1, 41]

RLNM — regional lymph node metastases

Table 3. Prognosis in patients depending on the type of metastasis

	Median overall survival [months]	Median recurrence-free survival [months]	Five-year survival probability [%]	Ten-year survival probability [%]	References
Localized disease	107–141	114	61–81	66	[1, 6, 8, 42, 43]
Regional lymph node metastasis	21–51	21	12–51	33	[1, 6, 8, 42, 43]
Distant metastases	18	20	21–22	14	[1, 6, 8, 42, 43]
Regional lymph node metastasis and distant metastases	14–15	20–21	11	9	[6, 8, 42]

undifferentiated small round cell sarcomas of bone and soft tissue, most closely related to Ewing sarcoma. They are characterized by genetic abnormalities, the most common of which is the CIC-DUX4 rearrangement used in diagnosis. These are extremely rare and relatively recently defined tumors. Still, recent research into their biology shows that in addition to their aggressive course and high rate of distant metastases [23], they may also have a high risk of lymph node metastasis [24]. Lymph node involvement in this sarcoma subtype is often the second most common site of metastasis [25]. Furthermore, the primary focus of CRS may be located in the lymph nodes [26, 27]. Also, histopathological analyses of CRS showed a high rate of lymphatic and vascular invasion [28–31]. The prevalence of lymph node involvement in this sarcoma is estimated to range from 11 to 25%, with the specific incidence varying depending on the study [23, 32].

The presence of RLNM and/or distant metastases (DM) significantly impacts prognosis; therefore, accurate evaluation of the RLN status is critical in the early phase to decide on possibly aggressive surgical resection of nodal metastases necessary for long-term survival [8]. The presence of LNM in STS is an adverse prognostic factor. The 5-year OS rate in patients with LNM varies from 12% to 29.3%, and for patients with DM, it is 25% to 40% [3] (Tab. 2 [1, 3, 5, 8, 33–42]). The shortest median OS rate was 14–15 months in patients with both N1M1 disease (RLN and DM present), longer for patients with LNM only (21–51 months), and most prolonged in N0M0 patients (107–141 months) (Tab. 3 [1, 6, 8, 42, 43]). In a retrospective study on 853 STS cases, Garcia-Ortega et al. [3] observed that more than half of LNM patients (52.1%) presented simultaneously with DM. Al-Refaie et al. [35] noted synchronous metastasis in 57% of patients. The existing theories assume that RLNs are disease incubators that spread remotely or are essential markers of the potential coexistence of occult micrometastatic disease, which forms DM [3, 44]. However, more research is needed to determine whether STS RLN promotes the development of DM. The presence of metachronous RLNM without DM and with multimodal treatment, including LND, results in better outcomes. Behranwala et al. [22] analyzed survival of different groups of STS patients: one with RLNM present during the primary diagnosis

and a second where the patients developed RLNM and DM after diagnosis. In this group, the median time was 13.5 months. Patients underwent LND as a part of multimodal treatment. Five-year survival in the group of patients with isolated RLNM was 23.9%, while all patients with DM died. The synchronous and metachronous RLNM survival in 1 year was 67.54% and 94.44%, respectively. Authors underlined the positive role of LND but could not assess its impact in the retrospective study [22].

Other confirmed factors that adversely affect the prognosis of STS patients are CARE subtypes, tumor grade, tumor size (> 5 cm), and patient age [36, 45]. The tumor size > 10 cm ($p = 0.025$) is more often connected with local recurrence [3, 36]. The other possible factors, such as the number of positive nodes identified or the effect of time from the first diagnosis to LNM detection, are still under research. Regarding the number of nodes identified, most STS patients had only one positive node (59%), and 40.6% had multiple positive lymph nodes (median 9, range 5–88). In terms of the number of nodes removed, Johannesmeyer et al. [13] observed no statistical difference ($p = 0.71$) when comparing the survival of STS patients with up to 4 excised nodes with patients with more than 10. Concerning the influence of time from the first diagnosis to LNM detection, Emori et al. [45] observed that the 5-year OS rate of patients differs significantly depending on the time of LNM detection. If it is less than eight months after primary diagnosis the survival rate is 19%; if more than eight months, OS is 71% [45]. However, other researchers have not confirmed such dependency [5, 19]. Understanding the impact of RLNM on STS prognosis may help guide treatment strategies, including using SLNB and/or lymphadenectomy in selected patients [13].

Lymph node diagnostic evaluation in sarcomas

Several methods are recommended to evaluate lymph nodes. Clinical examination by palpation can determine whether the node is enlarged and firm. Ultrasound (USG) is often the first modality used for initial assessment to detect early LRs in STS, where a sensitivity of 92% and specificity of 94% have been reported [12, 46]. Guidelines recommend a magnetic resonance imaging (MRI) scan of the affected region for every patient with suspicious ultrasound or clinical features [11, 47]. Both modalities also detect lymph node recurrence after surgery and seem equally helpful. Retrospective analysis of STS of extremities shows that USG sensitivity was higher compared to MRI (100% *vs.* 93%), and specificity was lower 79% *vs.* 93 %, but the differences were not statistically significant. MRI is recommended during the early post-surgery period as it is easier to interpret [46]. However, Park et al. [48] showed that in postoperative surveillance of high-grade STS, short-term USG can enhance early detection of local recurrence and/or metastatic LN before routine MRI. The additional detection rate of local recurrence was 3.5% [95% confidence interval (CI) 1.7–7.1%], and LNM was 2.5% (95% CI 1.1–5.8%) [48].

Computed tomography (CT) is more specific but still has a high rate of false positives (23%) and is not sufficiently sensitive to detect micrometastases; therefore, it has a limited role in STS diagnosis. However, it is the modality of choice for DM and surveillance [10, 12]. Positron emission tomography (PET-CT) is increasingly used for staging sarcomas and is a less invasive alternative to SLNB (Fig. 2). Still, there is no standardized role for PET-CT in staging STS [12]. According to Burkhard-Meier et al. CT and MRI serve as standard tools in STS staging, while PET with 18-fluorodeoxyglucose (FDG-PET-CT) is used to exclude DM by including metabolic characteristics. Specificity and sensitivity of this modality in detecting LNM in STS and bone sarcoma is high, at a level of 90–100% [49]. Single-photon emission computed tomography/computed tomography (SPECT-CT) is used to facilitate identifying the target region for biopsy. Staging is incomplete without specifying the clinical and pathological status of RLN since, in the absence of DM diagnostic evaluation, RLN can identify patients with early biologically aggressive disease and help define the most appropriate medical treatment [10, 13]. Burkhard-Meier et al. [49] conducted research to identify predictive imaging criteria for LNM in STS. CT, PET-CT, and MRI images of suspicious LNs were analyzed. The results showed that growing LN size in terms of larger short axis diameter (SAD) and long axis diameter (LAD) correlate with the presence of LNM. Differences in median size for LNMs and benign LNs were 22.5 mm *vs.* 14 mm, $p < 0.001$ (SAD) and 29.5 mm *vs.* 21 mm, $p = 0.003$ (LAD) respectively. Analyses of receiver operating characteristic curves suggest cut-off values for SAD of 17 mm and LAD of 24 mm. Also, a high SAD/LAD ratio was found in metastatic patients, as malignant LN tends to be more circular. High maximal uptake of value (SUV_{max}), central necrosis, and high serum LDH were also associated with LNM and could have a predictive value [49].

Wagner et al. [50], reported that, in their group study, 17% of clinically normal nodes were positive for sarcoma cells when biopsied. As CT and MRI may not be efficient tools for examining pathologically non-enlarged nodes, nodal sampling is recommended for STS subtypes with a predilection for lymphatic spread [50]. The standard method is a core needle biopsy (CNB) performed under anesthesia and imaging guidance. Pavlidis et al. [51] observed in 530 cases that CNB had

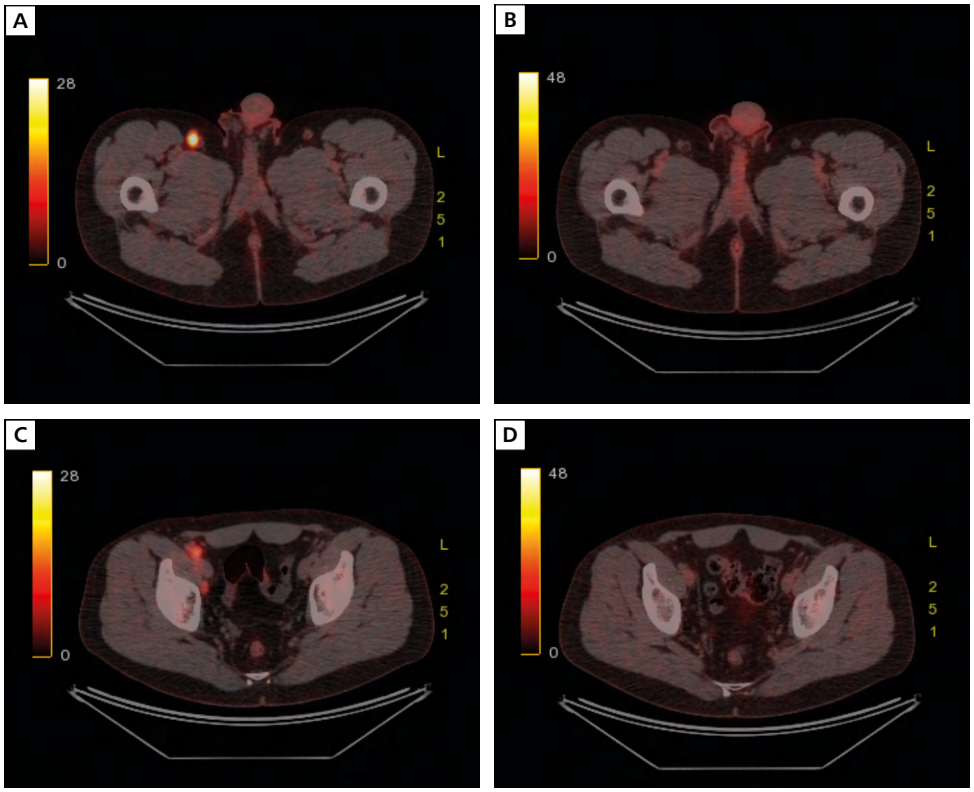

Figure 2. Positron emission tomography (PET-CT) evaluation of CIC-DUX4 sarcoma with metastatic inguinal (A, B) and iliac (C, D) lymph nodes before (A, C) and after (B, D) doxorubicin chemotherapy

a sensitivity rate of 96.3%, a specificity rate of 99.4%, and a diagnostic accuracy rate of 97.6%. A fine needle biopsy (FNAB) of an enlarged lymph node is rarely used to manage sarcoma, as it does not provide enough material for further analysis [51]. Fine needle aspiration cytology may be acceptable when the pathology team can compare the sample with the primary specimen.

Sentinel lymph node biopsy in sarcoma

Sentinel lymph node biopsy is a valuable diagnostic and prognostic tool. Identifying a positive SLN provides important prognostic information on more advanced diseases and identifies patients needing additional treatment, such as lymphadenectomy, adjuvant chemotherapy, or targeted radiation therapy [34]. Sentinel lymph node biopsy can identify patients with occult lymph node disease and significantly reduces the risk of acute and chronic complications, such as seroma, delayed wound healing, and chronic lymphedema, which are associated with complete dissections [8]. In addition, SLNB can be used in pediatric and adolescent and young adult (AYA) sarcoma patients to safely guide the rational selection of nodes for biopsy and identify therapy-changing nodal disease not identified with PET-CT [50].

The SLNB procedure attempts to mimic the natural migration of cells with the migration of known detectable tracers. The diagnostic advantage is time, as the tracers migrate to SLN in minutes or hours. In SLNB, only the first draining lymph node or lymph nodes, which are at high risk of developing metastasis, are biopsied [9]. The steps in the SLNB procedure are to find the node or nodes most likely to metastasize, remove it or them, and evaluate for metastases. Detectable particles are placed (injected) near the tumor mass, some in the nearby lymph channels, some along with the lymph fluid in the SLN. Sentinel lymph node biopsy is based on dual-mapping approaches, using a dye and a radiotracer. Studies show that using this dual technique generally results in a higher detection rate (95%) than using a radiotracer or a dye only [9]. The dye used is mainly isosulfan blue, methylene blue, or patent blue.

As for radiotracers, two types are used in SLNB: colloids labeled with Tc 99m and Tc 99m tilmanocept. The most used radiotracer is the colloid Tc 99m. In the United States, the radiotracer is usually a sulphur colloid (50–1000 nm), mainly a filtered sulphur colloid (30–50 nm). In Europe, a nano colloid of human serum albumin is mostly used (3–23 nm). Tc 99m tilmanocept is a colloid alternative approved by the Food and Drug Administration (FDA). It is used mainly in breast cancer,

Table 4. Results of sentinel lymph node biopsy (SLNB) in patients with sarcoma

Subtype	SLN-positive	False-negative	References
Rhabdomyosarcoma	0–21%	14%	[3, 22, 53, 54]
Clear cell	29–40%	13%	[3, 22, 53, 54]
Epithelioid	0–7%	8%	[3, 22, 53, 54]
Synovial	6–7%	3%	[3, 22, 53, 54]
Other*	0.4%	0%	[3]

* Liposarcoma, fibro myosarcoma, Ewing's sarcoma, alveolar soft part tumor; SNL — sentinel lymph node

melanoma, or squamous cell carcinoma of the oral cavity. The mechanism of Tc 99m is receptor-based. It specifically binds to CD206 receptors on the surface of macrophages and dendritic cells, enabling prolonged uptake in the first-level lymph nodes. The small size of this radiotracer allows for faster removal from the injection site than in the case of most colloids. Studies have shown that fewer nodes were removed with a tilmanocept than with a colloid filter. Moncayo et al. found that post-injection pain is lighter in the case of using Tc 99m tilmanocept [9]. In some circumstances, using SPECT or SPECT-CT may add value to SLNB and lymphoscintigraphic procedures.

Specimens from positive SLNB patients are analyzed by routine staining with H&E (the combination of two histological stains: hematoxylin and eosin) and when positive with the additional use of immunohistochemistry (IHC), enabling discovery of the occult micrometastases. This minimally invasive technique is used to identify patients with occult microscopic lymph node disease [52]. However, in the meta-analyses on 89,870 STS patients from the National Cancer Data Base (1998–2012), Wright et al. [52] showed that pathological LN evaluation in STS was performed inconsistently. In total, 3154 (3.5%) patients developed LN metastasis, 44.5% had pathologically confirmed LN metastasis, and 55.5% had clinically suspicious but not pathologically confirmed LN involvement [52]. Considering the confirmed importance of pathological evaluation of LN for staging and its impact on treatment and OS in STS patients, it is evident that a standardized pathological evaluation procedure needs to be developed. High-grade and CARE histology are associated with LNM in STS. Adult patients with both characteristics have an overall 11.9% risk of LNM and can be considered for pathologic assessment of LN [4]. Identification of a positive sentinel lymph node gives essential prognostic information on more advanced diseases and identifies those patients who will need further treatment, such as lymphadenectomy, adjuvant chemotherapy, or targeted radiation therapy, which should lead to better local control and might result in a survival benefit [21]. It is important in the case of STS, where the positive SLN rates reflect lymphatic involvement (presented in Tab. 1), except in cases of epithelioid sarcoma, as presented in Table 4 [3, 22, 53, 54]. Clear cell sarcoma results in the highest percentage of positive SLN, followed by rhabdomyosarcoma. In STS, the false negative rate associated with the procedure appears to be high, but in melanoma, the false negative rate of 7–18% is considered low, and the SLNB procedure is widely used [21].

Management schemes depending on the sentinel lymph node biopsy result in soft tissue sarcomas

Since standard screening procedures are missing, there is no unified procedure for STS treatment, which also depends on SLNB results. The guidelines, including the UK guidelines for the management of STS and SEOM Clinical Guideline of management of STS, recommend management based on staging and localization of primary tumors. Computed tomography and/or MRI should be contrast-enhanced, and then a preoperative core needle biopsy is recommended for diagnosis. Wide surgical resection is recommended, followed by radiotherapy for patients with high-grade tumors (Fig. 3). Chemotherapy is recommended in cases where it may contribute to local disease control. In terms of distant metastatic disease, surgery may have a palliative role, and radiotherapy or chemotherapy may be considered more appropriate. In the case of advanced disease, palliative-only therapy is implemented. A specialized management center should make the final decision on implementing a treatment procedure [11, 46].

However, Clinical Practice Guidelines in Oncology of the National Comprehensive Cancer Network (NCCN) recommend SNLB for high-risk STS patients. The risk factors are defined as high-grade nodal disease and CARE histology. In the case of a positive SNLB, those patients should be considered for regional LND [47]. To improve regional disease control, LND may also have a palliative role in selected patients, especially those with clinically positive lymph node disease [13].

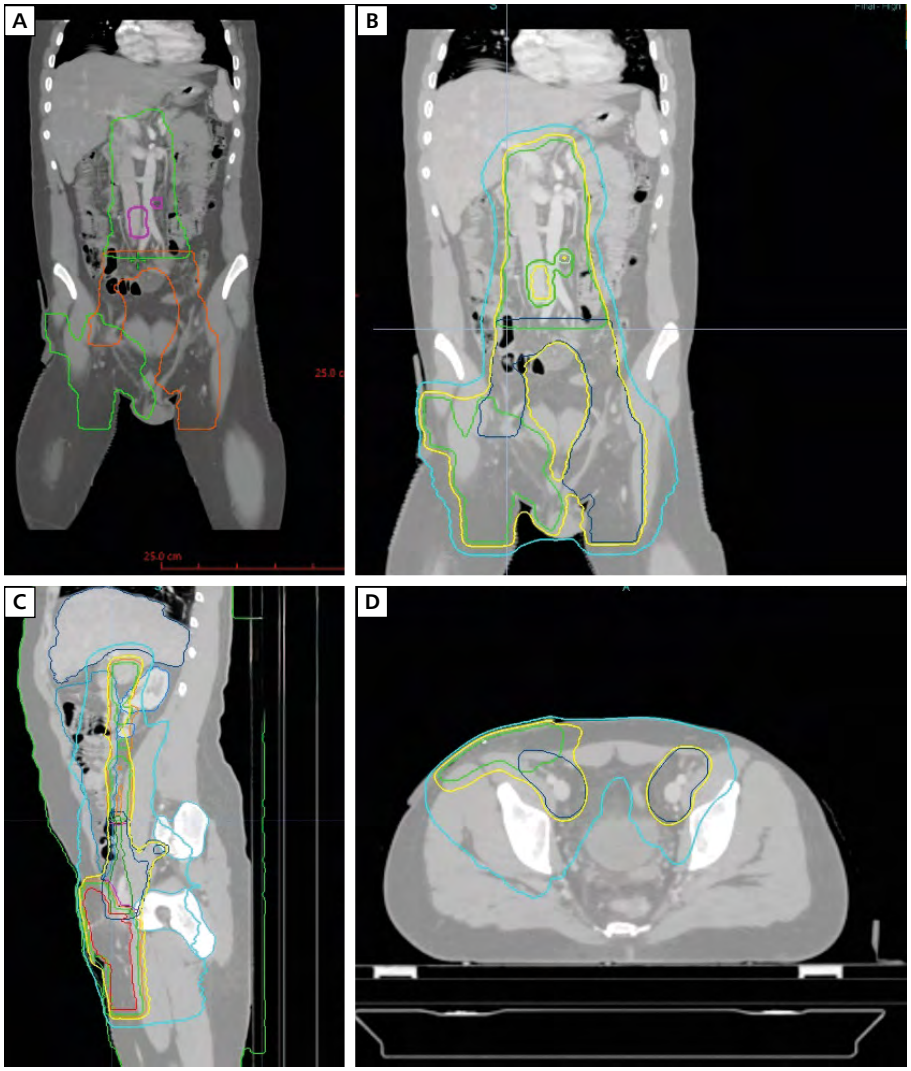

Figure 3. Definitive radiotherapy with simultaneous integrated boosts in an 18-year-old patient with para-testicular spindle cell rhabdomyosarcoma with paraaortic lymph node metastases after right orchidectomy. The figure shows the process of planning computed tomography (**A**) with delineated target volumes: CTV_51 (orange; left inguinal lymph nodes, bilateral iliac lymph nodes; 51 Gy in 30 fractions), CTV_54 (green; tumor bed, right inguinal lymph nodes and paraaortic lymph nodes; 54 Gy in 30 fractions), CTV_60 (magenta; metastatic paraaortic lymph nodes; 60 Gy in 30 fractions). Other scans (**B**–**D**) show different views of the dose distribution. In summary, the patient received 1.7/1.8/2 Gy up to 51/54/60 Gy with concurrent locoregional deep hyperthermia and chemotherapy. After radiotherapy, the patient continued chemotherapy until the end of 2022. After 14 months of follow-up, he remains disease-free

In the meta-analysis of 16 independent studies, Wright et al. [52] observed the results of heterogeneous treatment after positive and negative SLNBs. In the case of positive SLNB results, patients were treated with adjuvant radiotherapy or adjuvant chemoradiation (in the case of rhabdomyosarcoma) or external beam radiation to the lymph node basin or radical LND (in the case of other STS). Recurrence and death rates in the SLN-positive group were higher than in the SLN-negative group [52]. The study on 64 sarcoma patients by Teterycz et al. [6] showed no significant differences in OS between SLNB-negative and SLNB-positive patients. However regarding therapeutic LND, patients with negative lymph nodes achieved median OS of 70 months in comparison to patients with positive LND, who had a median OS of 18 months. The difference was statistically significant with a hazard ratio of 4.6 (95% CI 2.1–9.7; $p < 0.001$) [6].

Lymphadenectomy in soft tissue sarcomas

Lymphadenectomy — lymph node dissection — is usually performed as an open surgery under anesthesia. Depending on the development of the disease, it may be

regional and cover only chosen LNs close to the initial tumor or radical when most of the LNs in the tumor area are removed. LND depends also on the location of the sarcoma. It may be axillary, where the nodes on all levels and their connective tissue capsules are removed; cervical, where the superficial and deep nodes are deleted; and inguinal, where the nodes from the femoral triangle and deep node are dissected. The presence of multiple, unresectable DMs confirmed beforehand by CT or MRI is a contraindication for LND. Other qualification factors are the patient's overall condition and the serum lactic dehydrogenase test result. The possible complications of LND may be pain, wound infection or necrosis, seroma, hemorrhage, lymphedema, fistula, nerve damage, or respiratory distress [33].

The precise role of lymphadenectomy (Fig. 4) in managing STS patients is unclear. Several studies show the potential impact of LND on OS and recurrence-free survival (RFS) in STS patients depending on the results of SLNB and the type of initial metastases and those developed after recurrence. The authors acknowledged the following limitations that could have potentially affected their results: 1. In the available studies, LND was included in multimodal treatment and evaluated retrospectively; 2. The rarity of LNMs in STS limited the number of patients and observations; 3. Several studies did not specify results for STS subtypes, so the general findings cannot be applied to subtypes due to their different biological behavior; 4. Nonrandomized patient selection and differences in applying adjuvant therapy protocols may have created a potential bias affecting OS outcomes; 5. Some studies were single-center studies or did not specify if DM patients had been included, which can result in a bias that impacted the results.

Radical LND could be suggested as a therapy for patients with isolated metastasis to regional nodes since it positively impacted median survival. Fong et al. [16] analyzed the clinical data of 1772 STS patients, and 46 (2.6%) developed LNM. One group received biopsy only and had median survival of 4.3 months. Another group of patients underwent therapeutic radical LND with curative intent and had median survival of 16.3 months [16]. LND may improve quality of life and avoid ulceration and should be considered part of multimodal STS treatment. Sawamura et al. [19] observed different groups of STS patients who received the multimodal treatment, including LND. Patients who underwent LND had a 1.5-year survival rate of 65% and 5-year survival rate of 30%. The other group of patients who were not treated with LND had a survival rate of 19% in both periods.

The type of recurrence after LND makes a significant difference in OS for patients with regional disease versus those with DM. Regional disease and regional recurrence have better prognosis than distant

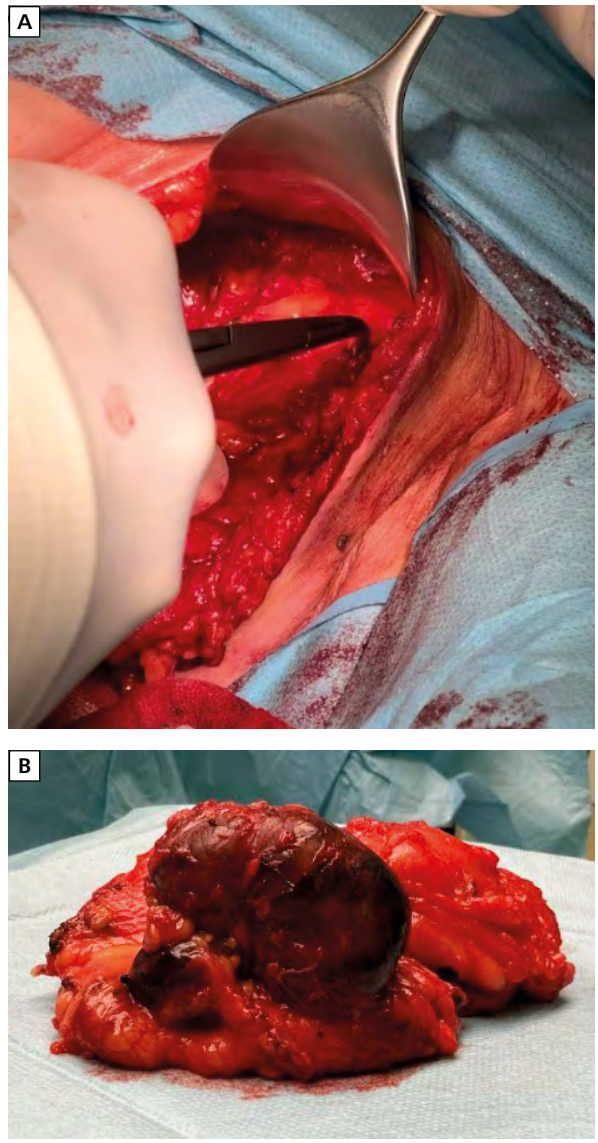

Figure 4. A. Axillary lymphadenectomy in a patient with the diagnosis of rhabdomyosarcoma; **B.** Contents of the left axillary fossa. Lymph node metastasis from a patient with the diagnosis of rhabdomyosarcoma

metastases. Witt et al. [53] presented results of a retrospective review where there was no difference in 5-year OS for patients with positive and negative SLNB (71.4% and 71.9%, respectively). For patients who underwent LND, the 5-year OS rate was 44.6%, and the RFS was 12 months. Regarding recurrence, 30% of patients after SLNB developed nodal recurrence, including DM, with five-year OS of 50%. Patients after LND with regional-only recurrence had an estimated 5-year OS rate of 66.7% compared with 29.1% for those who recurred distantly [53]. The patients with positive SLNB who underwent radical lymphadenectomy or who received adjuvant external beam radiation had high

rates of nodal disease control. Long-term follow-up data for 15 months analyzed by Wright et al. show that overall regional recurrence and distant recurrence rates in SLNB-negative patients were 10% and 14%, respectively. In SLNB-positive patients, overall regional and distant recurrence rates were 22% and 57%, respectively [52]. Developing local recurrences does not shorten OS if efficient treatment is offered. Ostafiichuk et al. [54] observed the 5-year survival rate and RFS of 429 patients with primary localized STS. All patients underwent surgical and chemoradiation treatment. Almost half of them (43.8%) developed local recurrences during the observation period and were treated with surgery and chemoradiation after. Five-year overall survival in the recurrence-free group was 43.1%, and in the second group, 43.6% with no statistical difference ($p = 0.9$). Median OS differed slightly: 35 months for patients without recurrences and 41 months for those with recurrences and additional treatment [54]. Patients at stage IV N1M0 (with RLNM) treated with radical therapy, including LND, have better outcomes than other patients of the same stage. Al-Refaie et al. [35] presented the study's results, in which all extremity STS patients were treated with LND for RLNM as a part of multimodal treatment. Some patients (28.5%) received doxorubicin-based systemic chemotherapy before LND and 34% after. Seventeen percent of patients were treated with external-beam radiation therapy to the ipsilateral nodal basic pre- or after LND. Five-year OS for patients who underwent LND with synchronous metastasis was 52% while for patients with metachronous disease was 66%, but these results were not statistically significant ($p = 0.35$). In regard to the post lymphadenectomy RFS was 45% and 29% with median survival to recurrence or death of 21.2 and 22.4 months, respectively, was also not statistically significant ($p = 0.9$) [35].

Treatment recommendations for high--risk soft tissue sarcomas subtypes

Clinicians consider regional disease clinically distinct from distant metastatic disease and think it has better outcomes. Also, STS subtypes differ in terms of biological behavior. The current TNM system has certain limitations in making individual prognostic or treatment recommendations, especially for STS. Therefore, different treatment procedures should be developed (3, 53). There are already such tools as the 'Sarculator' and Memorial Sloan Kettering Cancer Center (MSKCC) nomogram that provide prognostic information, and the Personalised Sarcoma Care (PERSARC) nomogram, which allows for dynamic modification of treatment and comparison of prognoses based on a change in treatment plans [55]. All models are based on clinical data, including, among others, site, age, tumor size, grade, histology, and surgical outcomes [3].

General treatment recommendations for STS subtypes with high levels of LN metastases are as follows:

— **clear cell sarcoma (CCS)** is STS with a poor prognosis. Treatment of CCS is challenging due to their different biological behavior and molecular pathogenesis. It has already been demonstrated that CCS is characterized by the translocation of t (12; 22), resulting in the rearrangement of the *EWSR1* gene and the overexpression of mesenchymal-epithelial transition factor (MET). Targeted therapies such as sunitinib and MET inhibitors, as well as immunotherapy, are under further investigation. Case studies showed that CCSs are usually resistant to conventional chemotherapy [56]. Sentinel lymph node biopsy is suggested, especially for patients with suspicion of lymph node involvement during staging. The possibility of occult LNM is high, although its impact on OS is still debatable. Multidisciplinary team (MDT) may consider therapeutic lymphadenectomy in controlling locoregional disease [8]. MDT may regard isolated limb perfusion (ILP) with high-dose tumor necrosis factor-alpha (TNF-a) and melphalan for local control in locally advanced unresectable tumors or in patients with concomitant metastatic disease. The benefit of ILP appears to be lower in patients with in-transit metastases. Adjuvant RT in this subtype may be recommended by MDT [20]. Still, the standard treatment for localized CCSs is surgical excision with negative margins;

— **epithelioid sarcoma (ES)** This aggressive sarcoma can be easily misdiagnosed initially as a benign process due to its frequently slow initial growth [57]. This results from a deficiency in SMARCB1/INI1. The recommended treatment is a wide surgical resection. Microscopically free margins are the most important prognostic factor for recurrence. Since distal sites are often affected, amputation is considered an option in selected patients, especially after the first local disease relapse. MDT may recommend sentinel lymph node biopsy/regional lymphadenectomy. Ultrasound scanning may be an effective postoperative tool after LND to seek for recurrence [44]. Perioperative RT is indicated to improve local control in primary and recurrent cases, with favorable results in local control compared to amputation, without impact on OS. MDT may recommend neoadjuvant chemotherapy in the localized setting, but there is no evidence of its impact on OS [20];

— **rhabdomyosarcoma (RMS)** is the most common STS in children and adolescents aged < 20 years — about 70% of patients are diagnosed before the age of 10 years, and it is still relatively rare among other childhood cancers [38]. Rhabdomyosarcoma can also

develop in adults. This cancer arises from immature cells that can differentiate into skeletal muscle cells in the future. Rhabdomyosarcoma can arise from soft tissues, such as the skeletal muscle, connective tissue, bone, bladder, prostate, testis, nose, orbit, and anus [50, 58, 59]. The Children's Oncology Group recommends SLNB for direct treatment in patients with extremity rhabdomyosarcoma due to the high positive rate (17%) [9, 60]. In addition, RLN sampling has a positive effect on 10-year disease-specific survival (DSS) (64% *vs.* 49%; p = 0.005) [2]. The current standard therapeutic approach, following the recommendation of the European Rhabdoid Registry (EU-RHAB), is lymphadenectomy, multidrug conventional CT (including anthracyclines and alkylating agents, combining DOX-ICE-VCA cycles), intrathecal methotrexate and permissive use of myeloablative chemotherapy (CARBO-TT) with stem cell rescue and RT. The most commonly used chemotherapeutics for adult patients are doxorubicin, vincristine, actinomycin *D*, and ifosfamide. Cyclophosphamide (VAC) based chemotherapy is also the current standard. Despite aggressive intensive multidrug therapy and surgery with LND, long-term survival remains unsatisfactory (15–50%), and the conventional treatment is insufficient, especially in refractory tumors and in patients with an initially poor prognosis [20] (Fig. 1, 4);

— **synovial sarcoma** represents 5–10% of all STS. It affects young adults; the mean age of diagnosis is 39 years, and both sexes are equally affected. Synovial sarcoma is located in the extremities, often in feet and below the knees. The standard treatment is surgery after neoadjuvant therapy [61]. Sentinel lymph node biopsy is still under discussion in this diagnosis and some clinicians considers it not very relevant due to the relatively low rate of LNM [5, 8, 61]. In contrast, others suggest that it can be successfully and safely applied, but further studies are required on false negative rates, prognostic importance, and treatment procedures [43]. The recent Surveillance, Epidemiology, and End Results (SEER) database findings suggest that the rates of LNM are in line with other STS, so SLNB is not recommended [5, 61];

— **angiosarcoma (AS)** accounts for 1–4% of STS cases [17]. The neoplastic transformation of endothelial cells of blood or lymphatic vessels is related to their appearance. The primary sites of angiosarcoma include the skin, soft tissue, and viscera [33, 62]. The recommended treatment is surgery with complete resection, but wide margins are difficult to obtain because of the multifocal character of angiosarcoma. LND may be controversial in AS. Different studies show that multimodal treatment surgery combined with chemotherapy and radiotherapy results in a better prognosis [33, 62, 63]. Cutaneous angiosarcoma (CAS) represents 60% of all angiosarcomas and affects neck and head regions, mainly in patients over 70 years old, white (85%), and men (68.3%) [64, 65]. Clinically, two subtypes of CAS were described: one arising in chronically sun-damaged skin and the second because of chronic lymphedema, previous radiotherapy, and chemical exposure (Steward-Treves Syndrome). Its prognosis is described as poor. There is no standardized treatment, and LND may be performed if needed. The recommended procedures are surgery, which positively impacts OS, and chemotherapy and radiotherapy, which do not increase OS. Surgery, however, in some cases, is disputable due to the patient's age or anatomical location of the disease. There are no large reports on SNLB or LND procedures in angiosarcomas [64–66].

Conclusions

This study demonstrated that the role of sentinel lymph node biopsy and lymphadenectomy in STS remains to be defined. However, several important conclusions and recommendations can be drawn based on current research. There is a group of extremity STS: rhabdomyosarcoma, clear cell sarcoma, angiosarcoma, and epithelioid sarcoma (CARE) that has been associated with significantly increased risk of RLNM in comparison with other histological STS subtypes. Some adult CARE patients (11.9%) with high-grade tumors are likely to develop LNM. The involvement of lymph nodes in STS is an adverse prognostic factor for OS and DFS. Overall survival and recurrence-free survival in patients with LNM and metastatic disease are similar. However, the prognosis is much worse when both LNM and DM are present. Although the short duration from primary diagnosis to LNM detection (< 8 months) is questionable OS risk factor, it is essential to identify patients at high risk of developing lymph node disease as early as possible. Therefore, a unified procedure for diagnosis should be agreed upon. Preoperative SNLB has a significant role in identifying high-risk factors in STS patients, as this technique also allows the determination of patients with occult microscopic lymph node disease. Positive results of SNLB may indicate regional lymphadenectomy, as not-treated patients with LNM tend to develop DM ultimately. There are no significant differences in OS in patients with regional and radical lymphadenectomy. OS depends rather on the type of recurrence they developed after surgery. Clinicians usually consider regional disease as clinically distinct from distant metastatic disease and with better outcomes. Therefore, different

adjuvant treatment procedures for regional and distant recurrences should be developed, such as chemotherapy or targeted radiation therapy after lymphadenectomy. Lymphadenectomy itself should be part of multimodal STS treatment. LND should lead to better local control and benefit survival. In the case of STS, the standard TNM system has some limitations regarding prognosis and treatment recommendations. Therefore, it is necessary to use nomograms that allow for more of an individual approach to each patient and perhaps the creation of a subclassification of clinical stage IV sarcomas. Current treatment recommendations for STS should probably be reviewed and adjusted for each pathological subtype.

Article Information and Declarations

Author contributions

A.M.C.: conceptualization and methodology, data curation, writing, supervision, project administration, funding acquisition; A.N., P.C.: writing; M.K., M.S., T.Ś., P.Rogala: visualization; P.Rutkowski: conceptualization and methodology, supervision.
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Conflict of interest

The authors declare that they have no conflict of interest.

Supplementary material

None.

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