Follow-up Strategies for Primary Extremity Soft-tissue Sarcoma in Adults: A Systematic Review of the Published Literature

DIETMAR DAMMERER¹, ANNELIES VAN BEECK², VIKTORIA SCHNEEWEISS¹ and ANTON SCHWABEGGER³

¹Department of Orthopaedics and Traumatology, Medical University of Innsbruck, Innsbruck, Austria; ²Antwerp University Hospital, Edegem, Belgium; ³Department of Plastic Surgery, Medical University of Innsbruck, Innsbruck, Austria

Abstract. Aim: Follow-up strategies for primary extremity soft-tissue sarcomas (eSTS) in adults were evaluated in a systematic review of the published literature. Material and Methods: The published literature was reviewed using PubMed. Of 136,646 studies published between 1985 and 2019, 78 original articles met the inclusion criteria. Articles were selected on the basis of the PRISMA guidelines. The selected articles were then cross-searched to identify further publications. August 1, 2019 was used as the concluding date of publication. Results: A variety of follow-up schedules have been reported in recently published literature. Two official guidelines have been approved by international societies. The guidelines distinguish between high- and low-grade STS, but mention a wide range of follow-up intervals. Established tools of follow-up include computed tomograph, X-rays of the chest, and magnetic resonance imaging of the primary tumor site in addition to clinical observation and physical examination. Conclusion: Further research will be needed to establish evidence-based guidelines and schedules for follow-up strategies in patients with eSTS.

Soft-tissue sarcomas (STS) of the extremities constitute less than 1% of all malignant tumors (1-4). Patients with high-grade STS are at risk of developing local recurrence (LR) and distant metastases (DM) after having undergone successful surgical resection of the primary tumor (5-10). Rates of STS differ in terms of size, grade, and subtype (5, 11). According to the published literature, 12,750 new cases of STS and 5,270 deaths occurred in the United States, resulting in a mortality rate of about 40% in 2019 (12-14). Recent published studies have revealed a yearly incidence of about 4-5/100,000 in Europe; liposarcoma and leiomyosarcoma are the most common histological subtypes (15-17). Nearly every third patient with primarily local STS will develop DM during the follow-up period, most likely in the lungs (18).

The large majority of STS are primarily located in the extremities: about 40% occur in the lower limbs (1, 2, 19-30). The second most frequent location is the abdomen (retroperitoneal or visceral); the lesions are usually very voluminous at the time of presentation (1, 19-23). More than 75% of malignant STS are located beneath the fascia (20, 22, 23, 27). The median age of patients at the initial diagnosis of primary STS is around 50 years and a slight preponderance of the male gender has been reported (1, 4, 21, 22, 25, 26, 28, 30, 31).

STS are divided into more than 50 histological subtypes, arising from mesodermal or neuroectodermal tissue (15, 19, 32). The histological classification is based on the differentiation of tumor cells, regardless of their origin (33). The European Society of Medical Oncology (ESMO) (21, 34), as well as Brennan and co-workers (21, 34) have identified more than 80 histological entities that may be further subdivided into even greater numbers of subsets. The National Comprehensive Cancer Network (NCCN) makes a rough division of STS into those of the extremity (eSTS), the superficial trunk or head and neck, the retroperitoneum, the abdomen, gastrointestinal stromal tumors, desmoid tumors (aggressive fibromatosis), and rhabdomyosarcoma (35). The most prevalent histological subtype has proven to be liposarcoma, followed by leiomyosarcoma (20-22, 27, 28, 36).

The treatment is primarily decided on the basis of tumor stage, grade, location, and the individual features of the
patient. Wide excision with negative margins is the gold standard for localized eSTS. According to the American Joint Committee on Cancer, adjuvant radiotherapy was shown to be beneficial in patients with high-grade lesions, lesions in deep location or large entities (>5 cm) (37). If negative margins are not achieved at the first attempt, the surgeon is well advised to perform revision surgery with wide excision if possible (34). Radical resection, which is defined as the excision of the entire anatomical compartment including the tumor, can also be performed in some cases. However, this approach impairs the patient’s quality of life and should be avoided if medically justified (38). The extent of treatment in advanced or metastatic disease is a more complex issue and must be decided on an individual basis. Surgery remains the standard approach for lung metastases without extrapulmonary spread, provided all lesions (local and metastatic) can be excised completely even if the patient has several metastases (24, 39). Chemotherapy might be added in selected cases, although its influence on survival remains to be proven, while for extrapulmonary disease it constitutes adjuvant treatment. For localized but clinically unresectable STS, the ESMO guidelines state that chemotherapy or radiotherapy should be administered either individually or in combination. The patient should be evaluated for surgery again after the treatment (34).

As regards imaging studies during follow-up, computed tomographic (CT) scans, X-rays of the chest, and magnetic resonance imaging (MRI) of tumor sites are established procedures for STS (34). According to the published literature, ultrasonography or CT scans of the abdomen are not performed consistently, although STS is associated with metastases in virtually any region of the body, including the brain, bones, the abdomen, and the retroperitoneum (34). As these metastases are reported to be rare occurrences, a diagnostic MRI of the brain or CT scans of the abdomen are only performed when the patients are symptomatic (40). Thus, there is a lack of any consensus on the reasons for, or frequency of, follow-up examinations in patients with STS (5, 34). In addition, the overall duration of follow-up and the most suitable imaging procedures are not conclusively established. The same applies to whether follow-up investigations should be conducted at specialized sarcoma centers.

Although diagnostic equipment and algorithms, interdisciplinary sarcoma boards (oncologists, radiologists, surgeons, pathologists etc.), and treatment modalities have improved markedly over time, the follow-up regimen for eSTS has not changed for decades (40). In the present report, we summarize the evidence on follow-up strategies after primary treatment of extremity STS in adult patients in terms of the frequency and duration of follow-up investigations, and the most suitable imaging procedures.

Materials and Methods

Studies published between January 1, 1985 and July 31, 2019 were included in a systematic review. In view of the fact that eSTS are rare malignancies, we considered eligible retrospective studies, case series, retrospective cohort studies, as well as individual case reports. The primary database used for the search was PubMed. As suggested in previous studies, further publications were identified by cross-searching the article references. Thus, a backward and forward citation search was performed. The concluding search date for the review was August 1, 2019. PubMed was searched using the following terms: STS OR soft tissue sarcoma* OR sarcoma* OR soft-tissue-sarcoma* AND follow-up OR follow up OR followup OR surveillance OR aftertreatment. The review was structured in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (41). Independently of each other, three Authors initially screened the published studies by their titles, and in a second step by the given abstract. Of these publications, all studies focusing on follow-up strategies after primary treatment of eSTS in adults were included. Publications with no mention of follow-up, those addressing pediatric STS, bone sarcoma, or STS at other locations than the limbs were excluded from the review. Studies comprising patients with eSTS, abdominal STS or gastrointestinal stromal tumors, leiomyosarcoma of the uterus or bone sarcoma were included when there was a clear distinction between eSTS and other STS or bone sarcoma. No publication was excluded on the basis of sample size or type of study because all of these were considered valuable for analysis. However, these factors were taken into account when interpreting the results.

Results

In all, 136,646 studies were identified. Based on the inclusion and exclusion criteria, 78 were deemed eligible for the analysis. Figure 1 shows a flow diagram of the study and the literature selection process according to the PRISMA checklist (41). Detailed study characteristics and the years of publication are presented in Table I and Figure 2.

The aim of follow-up after treatment for STS is early detection of LR and DM, because LR is observed in 40-60% of patients after therapy of eSTS (21, 42). The majority of recurrences occurred in high-grade eSTS within the first 2 to 3 years of surveillance and were classified as early recurrence (1, 32, 43-46). Late recurrence may occur especially in low-grade eSTS but was found to be significantly less common than early recurrence (21, 32, 45, 47). Since a recurrence may occur after 2 years (45) or more than 10 years of surveillance (21), the definition of a late recurrence is a crucial aspect. Risk factors influencing LR were found to be patient age (>50 years), deep location of the primary tumor (such as subfascial), primary tumor size (>5 cm), tumor grade (grade 2/3), and initial positive surgical margins (such as intralesional excision) (12, 22, 23, 25, 48-54).

The most common site (about 70%) of DM in eSTS was reported to be the lungs (14, 24, 42, 43). Distant metastases in patients with eSTS are more frequently seen in large and
deep high-grade STS (grade 2/3), independent of the histological subtype (24). Patients older than 50 years of age are at higher risk of developing DM (25, 49). Moreover, the likelihood of DM is higher once the patient has developed LR, although no study has been able to prove a causal association between the two entities (22, 36, 46, 49, 50, 55-57). According to some hypotheses, tumor persistence is a biological feature of sarcoma and occurs in conjunction with LR (46, 55).

Although STS is known to spread by the hematological route, an embryonal variant of rhabdomyosarcoma in adults which spreads to the lymph nodes has been discovered (56, 58, 59). The most common histological subtypes that develop abdominal or retroperitoneal metastases are (myxoid) liposarcoma (60-62) and leiomyosarcomas (63-65). The published literature also mentions the occurrence of abdominal or retroperitoneal metastases in conjunction with rare histological subtypes such as epithelioid sarcoma (64), synovial sarcoma (64), malignant peripheral nerve sheath tumor (66) and myxofibrosarcoma (66).

**Follow-up guidelines of Societies.** A variety of follow-up schedules have been reported in the published literature. A fixed follow-up schedule for patients with eSTS permits timely detection of LR and metastatic disease (34, 35). Two official guidelines have been approved by medical societies (34, 35). The guidelines issued by the ESMO make a distinction between low- and high-grade eSTS (34). For low-grade
Table I. Detailed study characteristics of the included publications.

| ID | Study                        | Year | Region    | Country  | Study type       | LoE |
|----|------------------------------|------|-----------|----------|------------------|-----|
| 1  | Trojani et al. (89)          | 1984 | Europe    | France   | Case series      | 4   |
| 2  | Potter et al. (90)           | 1985 | North America | USA    | Case series      | 4   |
| 3  | Lawrence et al. (26)         | 1987 | North America | USA    | Survey           | 5   |
| 4  | Huth et al. (91)             | 1988 | North America | USA    | Prospective study | 3   |
| 5  | Reuther et al. (73)          | 1990 | Europe    | Germany  | Prospective study | 3   |
| 6  | Gustafson et al. (55)        | 1991 | Europe    | Sweden   | Case series      | 4   |
| 7  | Choi et al. (92)             | 1991 | North America | USA    | Comparative study | 4   |
| 8  | Gadd et al. (93)             | 1993 | North America | USA    | Case series      | 4   |
| 9  | Fong et al. (59)             | 1993 | North America | USA    | Case series      | 4   |
| 10 | Huth et al. (91)             | 1988 | North America | USA    | Randomized trial | 2   |
| 11 | Pisters et al. (22)          | 1996 | North America | USA    | Prospective study | 3   |
| 12 | Clasby et al. (1)            | 1997 | Europe    | UK       | Case series      | 4   |
| 13 | Guillou et al. (94)          | 1997 | Europe    | France   | Comparative study | 4   |
| 14 | Lewis et al. (46)            | 1997 | North America | USA    | Cohort study     | 3   |
| 15 | Brennan (50)                 | 1997 | North America | USA    | Expert opinion   | 5   |
| 16 | Brooks et al. (25)           | 1998 | North America | USA    | Prospective study | 3   |
| 17 | Lucas et al. (80)            | 1998 | Europe    | Switzerland | Case series | 4   |
| 18 | Levi et al. (15)             | 1999 | Europe    | Switzerland | Case series | 4   |
| 19 | Billingsley et al. (14)      | 1999 | North America | USA    | Prospective study | 3   |
| 20 | Billingsley et al. (24)      | 1999 | North America | USA    | Prospective study | 3   |
| 21 | Lewis et al. (27)            | 1999 | North America | USA    | Prospective study | 3   |
| 22 | Whalley et al. (42)          | 1999 | North America | USA    | Review article   | 5   |
| 23 | Lebens et al. (59)           | 2000 | North America | USA    | Case series      | 4   |
| 24 | Beilke et al. (71)           | 2000 | North America | USA    | Survey           | 5   |
| 25 | Whalley et al. (57)          | 2000 | North America | USA    | Case series      | 4   |
| 26 | Fleming et al. (95)          | 2001 | North America | USA    | Cohort study     | 4   |
| 27 | Porter et al. (86)           | 2002 | North America | USA    | Experimental study | 3   |
| 28 | Weitz et al. (49)            | 2003 | North America | USA    | Prospective study | 3   |
| 29 | Patel et al. (58)            | 2003 | North America | USA    | Review article   | 4   |
| 30 | Johnson et al. (96)          | 2003 | North America | USA    | Case series      | 4   |
| 31 | Eilber et al. (54)           | 2003 | North America | USA    | Case series      | 4   |
| 32 | Brenner et al. (87)          | 2003 | North America | USA    | Review article   | 5   |
| 33 | Kane JM (78)                 | 2004 | North America | USA    | Review article   | 5   |
| 34 | Goel et al. (97)             | 2004 | North America | USA    | Review article   | 5   |
| 35 | Clark et al. (19)            | 2005 | UK         | UK       | Review article   | 4   |
| 36 | Cool et al. (36)             | 2005 | Europe     | UK       | Case series      | 4   |
| 37 | Kranz et al. (52)            | 2006 | North America | USA    | Review article   | 5   |
| 38 | Igaru et al. (81)            | 2006 | North America | USA    | Case series      | 4   |
| 39 | Gerrand et al. (51)          | 2007 | Europe     | UK       | Survey           | 5   |
| 40 | van der Zee et al. (98)      | 2007 | Europe     | Netherlands | Review article | 5   |
| 41 | Penel et al. (28)            | 2008 | Europe     | France   | Prognostic study | 3   |
| 42 | James et al. (56)            | 2008 | Europe     | UK       | Review article   | 5   |
| 43 | Watts et al. (74)            | 2008 | Europe     | UK       | Case series      | 4   |
| 44 | Lachenmayer et al. (12)      | 2009 | Europe     | Germany  | Case series      | 4   |
| 45 | Labarre et al. (30)          | 2009 | Europe     | France   | Cohort study     | 3   |
| 46 | Blackmon et al. (39)         | 2009 | North America | USA    | Comparative study | 3   |
| 47 | Garner et al. (53)           | 2009 | North America | USA    | Review article   | 5   |
| 48 | Grim et al. (47)             | 2010 | Europe     | UK       | Guideline        | n.a. |
| 49 | Johnson et al. (12)          | 2011 | North America | USA    | Survey           | 5   |
| 50 | Husain et al. (99)           | 2011 | Asia       | India    | Review article   | 5   |
| 51 | Cho et al. (67)              | 2011 | Asia       | South Korea | Cohort study | 4   |
| 52 | Biao et al. (23)             | 2012 | North America | Canada | Prognostic study | 3   |
| 53 | Chou et al. (100)            | 2012 | Asia       | Taiwan   | Cohort study     | 3   |
| 54 | Bradley WG. (101)            | 2012 | North America | USA    | Review article   | 5   |
| 55 | Puri et al. (3)              | 2014 | Asia       | India    | Randomized controlled trial | 1   |
| 56 | Rothermundt et al. (4)       | 2014 | Europe     | UK and Switzerland | Case series | 4   |
| 57 | Brennan et al. (21)          | 2014 | North America | USA    | Prospective study | 3   |
| 58 | Damery et al. (24)           | 2014 | Europe     | UK       | Survey           | 5   |

Table I. Continued
eSTS, the guidelines suggest radiological imaging and clinical investigation of the primary tumor site every 4 to 6 months for a period of 3 to 5 years, and annually thereafter (34). Chest imaging (X-ray or CT) may be performed less frequently but no precise recommendations are provided (34). For high-grade eSTS, the guidelines recommend follow-up intervals of 3 to 4 months for 2 to 3 years, and 6-month intervals until 5 years after treatment (34). Yearly investigations are advised after 5 years (34). The ESMO guidelines include clinical examination of the primary tumor site and chest imaging (not specified further) in any surveillance visit of patients with high-grade tumors (34). In general, the guidelines recommend an individual risk assessment in accordance with this directory (34).

The guidelines issued by the NCCN distinguish between follow-up strategies for American Joint Committee on Cancer stage IA/IB, stage II/III and stage IV lesions (35). For stage IA/IB, the guidelines recommend history-taking and physical examination every 3 to 6 months for a period of 2 to 3 years, and at yearly intervals thereafter (35). Distant (especially chest) and local imaging are advised with due consideration to the patient’s risks; an interval of 6 to 12 months is suggested (35). Stage II/III tumors should be monitored every 3 to 6 months for 2 to 3 years, every 6 months for another 2 years, and then annually; the follow-up investigation must include history-taking, physical examination, and chest imaging (35). Local imaging should be performed under consideration of the patient’s individual risk but is advised as a routine measure in those with unresectable disease (35). Follow-up investigations of high-stage eSTS should include history-taking, physical examination, chest imaging, and local imaging dependent on individual risk factors. These investigations should be conducted at 2- to 6-month intervals for 2 to 3 years, 6-month intervals for a further 2 years, and yearly intervals thereafter (35). However, neither the ESMO nor the NCCN guidelines mention a specific endpoint for follow-up (34, 35).

Follow-up regimens in the published literature. Notwithstanding the diverse intervals for surveillance after the treatment of eSTS, the authors of published studies recommend increasingly frequent follow-up investigations (23, 36, 44, 51, 58, 67-69). Follow-up investigations should be ideally performed at 3- to 4-month intervals for the first 2 years after surgery (23, 36, 44, 51, 58, 67-69), and at 6-month intervals until the fifth year (1, 23, 36, 44, 51, 58, 67-69). This should be followed by yearly surveillance visits for a further 5 years, although a number of research groups did not specify an endpoint (23, 36, 44, 51, 58, 67-69).

In a prospective study of eSTS follow-up, Puri et al. noted that less frequent follow-up does not result in higher recurrence rates (3, 70). They suggest 6-month intervals for the first 5 years of surveillance, and yearly intervals for a further 5 years (3, 70). However, more frequent visits might be indicated for certain high-grade eSTS. Therefore, the individual risk assessment remains important (70). Damery et al. examined patient preferences for follow-up and...
ascertained that an interval of 6 months over a total duration of 5 years is the most acceptable option for patients with sarcoma (29).

Imaging. In addition to the frequency of follow-up, the follow-up modality for local and metastatic disease is a debated issue. For local control, all reviewed studies agreed that history-taking and physical examination, or at least the latter, should be a part of every follow-up visit (14, 29, 31, 36, 44, 47, 51, 52, 57, 58, 67-69, 71).

In addition to local physical examination, MRI scans should be considered especially for non-palpable eSTS (44, 52, 53, 68, 72-74). Suspicious palpable lesions must be investigated by MRI (47, 75). With regard to distant metastasis, all authors suggest that some type of chest imaging must be conducted at every follow-up visit; the most accurate imaging modality is still a debated issue (3, 24, 31, 36, 44, 51, 57, 67, 69, 71, 76, 77). While the large majority of authors believe that a chest X-ray is sufficient for routine surveillance, some regard a chest CT as the appropriate modality for the detection of lung metastases (3, 24, 31, 36, 44, 51, 57, 67, 69, 71, 77). Puri et al. found no evidence of potential superiority of chest CT over plain chest radiographs in the detection of lung metastases (3). Four other research groups concluded that chest X-ray suffices as a routine imaging modality; a chest CT scan should be obtained in the event of suspicious findings on the chest X-ray (14, 36, 44, 57). After interviewing clinicians who treated patients with eSTS in the UK, Gerrand et al. concluded that a chest CT is rarely performed as a routine imaging modality for lung metastasis (51). Chest X-ray also appears to be given preference by patients, and is mentioned as the cost-effective option for primary eSTS and low-grade eSTS (29, 57, 58, 78, 79). According to the report published by Gerrand et al., it is current practice in the UK to perform routine imaging in high-risk patients (51).

Fluorodeoxyglucose positron-emission tomography (FDG-PET) has been discussed as an imaging modality for LR and metastatic spread to the lungs. However, it was proven inferior to MRI (for LR) and chest CT (for follow-up after resected
eSTS). FDG-PET is not recommended as the first choice for the detection of LR and pulmonary metastases (80, 81), but is a valuable tool for identifying extrapulmonary visceral spread (80).

**Discussion**

We analyzed original articles addressing follow-up strategies after the treatment of primary eSTS. The published literature revealed no clear consensus in regard to follow-up schedules. Although the diagnosis and treatment of these entities have improved markedly over the last few decades, the follow-up regimen has not changed over time (40). We aimed to summarize current approaches and provide an overview of existing follow-up regimens after primary treatment of eSTS. The strategies are analyzed in terms of the duration and frequency of follow-up as well as the most suitable imaging procedure.

**Follow-up frequency.** Postoperative follow-up after the treatment of primary eSTS, with or without curative intent, was shown to be important because it improves overall survival (71). A strict schedule contributes to early detection of LR and DM, and also helps to provide timely psychological support for the patient (19). However, the enforcement of strict follow-up regimens for all patients with eSTS has raised public, scientific, and economic concerns in recent years (5).

The risk of developing LR or DM is associated with numerous factors, such as histological STS subtype, tumor grade, tumor size, surgical margins, (neo-) adjuvant radiotherapy or chemotherapy, and patient-related factors (6-9, 82-84). Our literature search revealed no clear consensus as to when and how often follow-up investigations should be performed for these patients (5, 34, 35). A heuristic approach is pursued at many centers: the guidelines mention 3- to 4-month intervals during the first 3 years after surgery, every 6 months for the following 2 years, and at yearly intervals thereafter (5, 34, 35). Damery et al. examined patient preferences for follow-up and found that an interval of 6 months for a total duration of 5 years is most acceptable to patients with sarcoma (29). However, the current “one-follow-up-stategy-fits-all” approach may neglect the differing degrees of risk in the diverse eSTS population, and culminate in excessive surveillance for some patients. This might result in superfluous radiation exposure for patients and a significant workload for radiology departments (5, 34, 35).

By contrast, the absence of a regular follow-up strategy may result in a large number of patient visits to the Outpatient Department, significant costs of health care, and mental stress for the patient (5, 85). Recently Smolle et al. published a model to predict the individual patient’s risk of LR and DM during follow-up; the authors used a flexible parametric approach of competing risk regression (5). These models were incorporated in the PERSARC app for individualized sarcoma care and monitoring (5, 85). The limitations of the study performed by Smolle et al. include its retrospective nature, which may have resulted in a selection bias concerning diagnosis, treatment, and other aspects. However, it should be noted that their study was the first and the largest investigation of individualized follow-up strategies for high-grade eSTS with a flexible parametric model of competing risk regression (5). The study offers an evidence-based option of individual scheduling rather than adherence to calendar-based guidelines for follow-up investigations (5, 34, 35). The authors recommend much fewer radiological investigations for the assessment of disease status, especially after R0 resection, and take histological subtypes into account. Thus, the burden on the patient and the healthcare system is reduced (5). The use of flexible parametric models of competing risk regression to estimate the risk of LR and DM in eSTS patients is based on the fact that the risks do not increase or decrease consistently but vary markedly over time (5). However, a large-scale prospective investigation of eSTS is hindered by the rarity of this entity and the low percentage of resulting deaths (13). Furthermore, the issuance of guidelines is hindered by the diverse types of STS, and differences in their location, grade, size, and histology. Individualized follow-up might serve as a useful option for patients with eSTS.

**Imaging.** All of the reviewed studies agree that history-taking and physical examination, or at least the latter, should be a part of every follow-up visit (14, 29, 31, 36, 44, 47, 51, 52, 57, 58, 67-69, 71). Tumor characteristics (location, size, grade, etc.) have a strong impact on the LR rate (23, 36, 44, 51, 58, 67-69), and imply the need for follow-up imaging. In addition to the physical examination, MRI scans should be considered especially in cases of non-palpable eSTS (44, 52, 53, 68, 72-74). The published literature reveals that MRI is the best choice for local surveillance (44, 52, 53, 68, 72-74, 77). Patient factors, such as a non-compatible pacemaker, claustrophobia, metal, or prostheses reduce the suitability of MRI. CT or PET-CT may be used in these instances but is less specific than MRI (72, 73). Additionally, in a compliant patient with an eSTS in a superficial location, an assessment by the clinician or patient may reduce the need for local imaging because autodetection of LR has been reported in more than 50% of cases (3, 4, 43). Suspicious palpable lesions must be investigated further (47, 75).

A comprehensive follow-up strategy should include local control as well as systemic surveillance (14, 24, 42, 43). Concerning DM, all publications recommended chest imaging at every visit, although the authors were not unanimous about whether a chest X-ray (79, 86) or a chest CT (3, 24, 31, 36,
44, 51, 57, 67, 69, 71, 77) is the most accurate modality. The latter modalities are the main tools of surveillance for potential metastases in the lung (79, 86). Chest X-rays are considered equivalent to chest CT (3, 70). Radiation exposure during a CT scan is 100-fold higher than the effective dose of an X-ray, thus raising the likelihood of carcinogenesis (87, 88). CT scans or X-rays of the chest and MRI scans of the primary tumor site are well accepted. Ultrasound or CT scans of the abdomen are not obtained on a routine basis (34). eSTS is known to spread to any region of the body, including the abdomen, brain, bones and the retroperitoneum (40). However, these metastases are considered rare (40). Therefore, further diagnostic investigations such as an MRI of the brain or a CT scan of the abdomen are usually obtained when a patient has corresponding symptoms (40). Computed tomographic scans or ultrasonography of the abdomen, and even whole-body MRI should be used for early detection of metastases in the abdomen or the retroperitoneum, when the disease is still amenable to surgical resection (40). Additional FDG-PET is a valuable tool for the detection of extrapulmonary visceral metastatic spread (80).

We conclude that patients with eSTS must be followed-up at specialized sarcoma centers, although this may signify a challenge for the patient in terms of distance and accessibility.

The primary limitation of this systematic literature review is that the minimized exclusion criteria might have led to unjustified conclusions. However, we did take sample size and the hierarchy of evidence into account. The main strengths of the review are its novelty, broad basis, and the heterogeneity of the database.

Conclusion

Further research on follow-up strategies for eSTS is an urgent necessity. A small number of the numerous aspects of follow-up have been adequately researched and can be recommended without hesitation. These include the intervals of follow-up examinations. A 6-month interval between clinic visits appears to suffice, and was not inferior to shorter intervals. Furthermore, routine chest X-rays may be recommended for the detection of lung metastases. A CT of the chest should be considered as a secondary imaging modality when the chest X-ray reveals suspicious findings. An individualized follow-up strategy using a standardized flow chart for typical tumor or patient characteristics is currently being developed but calls for further improvement. The additional value of follow-up flow charts is yet to be proven. Further investigation and standardization are undoubtedly needed in this field.

Conflicts of Interest

The Authors declare that there are no conflicts of interest.

Authors’ Contributions

D. Dammerer: Study protocol, study design, literature research, data analysis, editing and writing of the article. A. Van Beeck: Data analysis, co-editing, writing and proofreading of the article. V. Schneeweß performed the literature research, data analysis and proofreading of the article. A. Schwabegger supervised the study results and proofread the article. All Authors made pertinent contributions to the article, and proofread and approved the final article before submission.

References

1 Clasby R, Tilling K, Smith MA and Fletcher CD: Variable management of soft tissue sarcoma: Regional audit with implications for specialist care. Br J Surg 84(12): 1692-1696, 1997. PMID: 9448617.
2 Johnson FE, Sakata K, Sarkar S, Audisio RA, Kraybill WG, Gibbs JF, Beiter AL and Virgo KS: Patient surveillance after treatment for soft-tissue sarcoma. Int J Oncol 38(1): 233-239, 2011. PMID: 21109945. DOI: 10.3892/ijo_00000843
3 Puri A, Gulia A, Hawaldar R, Ranganathan P and Badwe RA: Does intensity of surveillance affect survival after surgery for sarcomas? Results of a randomized noninferiority trial. Clin Orthop Relat Res 472(5): 1568-1575, 2014. PMID: 24249538. DOI: 10.1007/s11999-013-3385-9
4 Rothermundt C, Whelan JS, Dileo P, Strauss SJ, Coleman J, Briggs TW, Haile SR and Seddon BM: What is the role of routine follow-up for localised limb soft tissue sarcomas? A retrospective analysis of 174 patients. Br J Cancer 110(10): 2420-2426, 2014. PMID: 24736584. DOI: 10.1038/bjc.2014.200
5 Smolle MA, Sande MV, Callegaro D, Wunder J, Hayes A, Leitner L, Bergovec M, Tunn PU, van Praag V, Fiocco M, Panotopoulos J, Willegger M, Windhager R, Dijkstra SPD, van Houdt WJ, Riedl JM, Stotz M, Gerger A, Pichler M, Stüger H, Liegl-Atzwanger B, Smolle J, Andreou D, Leitner A, Gronchi A, Haas RL and Szkandera J: Individualizing follow-up strategies in high-grade soft-tissue sarcoma with flexible parametric competing risk regression models. Cancers (Basel) 12(1), 2019. PMID: 31877801. DOI: 10.3390/cancers12010047
6 Italiano A, Le Cesne A, Mendiboure J, Blay JY, Piperno-Neumann S, Chevreau C, Delcambre C, Penel N, Terrier P, Ranchere-Vince D, Lae M, Le Guelllec S, Michels JJ, Robin YM, Bellera C and Bonvalot S: Prognostic factors and impact of adjuvant treatments on local and metastatic relapse of soft-tissue sarcoma patients in the competing risks setting. Cancer 120(21): 3361-3369, 2014. PMID: 25042799. DOI: 10.1002/cncr.28885
7 Mareatty-Nielsen K, Aggerholm-Pedersen N, Safwat A, Jørgensen PH, Hansen BH, Baarentzen S, Pedersen AB and Keller J: Prognostic factors for local recurrence and mortality in adult soft tissue sarcoma of the extremities and trunk wall: A cohort study of 922 consecutive patients. Acta Orthop 85(3): 323-332, 2014. PMID: 24694277. DOI: 10.3109/17453674.2014.90834
8 Novais EN, Demiralp B, Alderete J, Larson MC, Rose PS and Sim FH: Do surgical margin and local recurrence influence survival in soft tissue sarcomas? Clin Orthop Relat Res 468(11): 3003-3011, 2010. PMID: 20645035. DOI: 10.1007/s11999-010-1471-9
9 Willeumier J, Fiocco M, Nout R, Dijkstra S, Asthon W, Pollock R, Hartgrink H, Bovée J and van de Sande M: High-grade soft tissue sarcomas of the extremities: Surgical margins influence only local recurrence not overall survival. Int Orthop 39(5): 935-941, 2015. PMID: 25743028. DOI: 10.1007/s00264-015-2694-x
10 Singer S, Demetri GD, Baldini EH and Fletcher CD: Management of soft-tissue sarcomas: An overview and update. Lancet Oncol 15: 75-85, 2000. PMID: 11905672. DOI: 10.1016/s1470-2045(00)00016-4
11 Classification of Tumours of Soft Tissue and Bone. Fourth Edition. Fletcher C.D., Hogendoorn PCW, Mertens F. (eds.). Geneva: IARC Press; pp. 83-84, 2013.
12 Lachenmayer A, Yang Q, Eisenberger CF, Boeckle E, Poremba C, Heinecke A, Ohmann C, Knoeefl WT and Peiper M: Superficial soft tissue sarcomas of the extremities and trunk. World J Surg 33(8): 1641-1649, 2009. PMID: 19430830. DOI: 10.1007/s00268-009-0051-1
13 Siegel RL, Miller KD and Jemal A: Cancer statistics, 2019. CA Cancer J Clin 69(1): 7-34, 2019. PMID: 30620402. DOI: 10.3322/caac.21551
14 Andritsch E, Beishon M, Bielack S, Bonvalot S, Casali P, Crul, Bhatt N, Deady S, Gillis A, Bertuzzi A, Fabre A, Heffernan E, Hogendoorn P, Kozhaeva O, Lavender V, Lovey J, Negrouk A, Pereira P, Roca P, de Lempdes GR, Sarcoma. Ann Surg Oncol 35(5): 1427-1435, 2017. PMID: 28266233. DOI: 10.1008/00264-015-2694-x
15 Billingsley KG, Lewis JJ, Leung DH, Casper ES, Woodruff JM and Brennan MF: Multifactorial analysis of the survival of patients with distant metastasis arising from primary extremity sarcoma. Cancer 85(2): 389-395, 1999. PMID: 10023707.
16 Levi F, La Vecchia C, Randimbison L and Te VC: Descriptive epidemiology of soft tissue sarcomas in vaud, switzerland. Eur J Cancer 35(12): 1711-1716, 1999. PMID: 2402324. DOI: 10.1159/000101763
17 Andritsch E, Beishon M, Bielack S, Bonvalot S, Casali P, Crul M, Delgado Bolton R, Donati DM, Douis H, Haas R, Hogendoorn P, Kozhaeva O, Lavender V, Lovey J, Negrouk A, Pereira P, Roca P, de Lempdes GR, Sarcoma. Ann Surg Oncol 35(5): 1427-1435, 2017. PMID: 28266233. DOI: 10.1008/00264-015-2694-x
18 Posch F, Leitner L, Bergovec M, Bezan A, Stotz M, Gerger A, Superficial soft tissue sarcomas of the extremities and trunk. Acta Orthop 72(1): 129-135, 2011. PMID: 26589778. DOI: 10.1002/caac.21551
19 Penel N, Brosge J, Robin YM, Vanseymortier L, Clisant S and Adenis A: Frequency of certain established risk factors in soft tissue sarcomas in adults: A prospective descriptive study of 658 cases. Sarcoma 2008: 459386, 2008. PMID: 18497869. DOI: 10.1155/2008/459386
20 Trovik C, Bjerkehagen B, Billingham L, Barton P, Al-Janabi H and Grimer R: Patient preferences for clinical follow-up after primary treatment for soft tissue sarcoma: A cross-sectional survey and discrete choice experiment. Eur J Surg Oncol 40(12): 1655-1661, 2014. PMID: 25108811. DOI: 10.1016/j.ejso.2014.04.020.
21 Damery S, Biswas M, Billingham L, Barton P, Al-Janabi H and Grimer R: Patient preferences for clinical follow-up after primary treatment for soft tissue sarcoma: A cross-sectional survey and discrete choice experiment. Eur J Surg Oncol 40(12): 1655-1661, 2014. PMID: 25108811. DOI: 10.1016/j.ejso.2014.04.020.
22 Trovik C, Bjerkehagen B, Billingham L, Barton P, Al-Janabi H and Grimer R: Patient preferences for clinical follow-up after primary treatment for soft tissue sarcoma: A cross-sectional survey and discrete choice experiment. Eur J Surg Oncol 40(12): 1655-1661, 2014. PMID: 25108811. DOI: 10.1016/j.ejso.2014.04.020.
23 Damery S, Biswas M, Billingham L, Barton P, Al-Janabi H and Grimer R: Patient preferences for clinical follow-up after primary treatment for soft tissue sarcoma: A cross-sectional survey and discrete choice experiment. Eur J Surg Oncol 40(12): 1655-1661, 2014. PMID: 25108811. DOI: 10.1016/j.ejso.2014.04.020.
in vivo 34: 3057-3068 (2020)
Puri A, Ranganathan P, Gulia A, Crasto S, Hawaldar R and Badwe RA: Does a less intensive surveillance protocol affect the survival of patients after treatment of a sarcoma of the limb? Updated results of the randomized toss study. Bone Joint J 100-B(2): 262-268, 2018. PMID: 29437071. DOI: 10.1302/0301-620X.100B2.BJJ-2017-0789.R1

Beitler AL, Virgo KS, Johnson FE, Gibbs JF and Kraybill WG: Current follow-up strategies after potentially curative resection of extremity sarcomas: Results of a survey of the members of the Society of Surgical Oncology. Cancer 88(4): 777-785, 2000. PMID: 10679646. DOI: 10.1002/SC1197-0142(20000215)88:4<777::AID-CNCR7>3.0.CO;2-R

Park SY, Chung HW, Chae SY and Lee JS: Comparison of MRI and PET-CT in detecting the loco-regional recurrence of soft tissue sarcomas during surveillance. Skeletal Radiol 45(10): 1375-1384, 2016. PMID: 27488833. DOI: 10.1007/s00256-016-2440-5

Reuther G and Mutschler W: Detection of local recurrent disease in musculoskeletal tumors: Magnetic resonance imaging versus computed tomography. Skeletal Radiol 19(2): 85-90, 1990. PMID: 2321049. DOI: 10.1007/BF00197611

Watts AC, Teoh K, Evans T, Beggs I, Robb J and Porter D: MRI surveillance after resection for primary musculoskeletal sarcoma. J Bone Joint Surg Br 90(4): 484-487, 2008. PMID: 18378924. DOI: 10.1302/0301-620X.90B4.20089

Cheney MD, Giraud C, Goldberg SI, Rosenthal DI, Hornick FJ, Choy E, Mullen JT, Chen YL and Delaney TF: MRI surveillance following treatment of extremity soft tissue sarcoma. J Surg Oncol 109(6): 593-596, 2014. PMID: 24374823. DOI: 10.1002/jso.23541

Tsagopoulos P, Bauer HC, Styrcen E, Trovik CS, Zaikova O and Brosjö O: Prognostic factors and follow-up strategy for superficial soft-tissue sarcomas: Analysis of 622 surgically treated patients from the Scandinavian Sarcoma Group register. J Surg Oncol 111(8): 951-956, 2015. PMID: 26040651. DOI: 10.1002/jso.23927

Patel SA, Royce TJ, Baryskauskas CM, Thornton KA, Raut CP and Baldini EH: Surveillance imaging patterns and outcomes following radiation therapy and radical resection for localized extremity and trunk soft tissue sarcoma. Ann Surg Oncol 24(6): 1588-1595, 2017. PMID: 28058559. DOI: 10.1245/s10434-016-5755-5

Kane JM: Surveillance strategies for patients following surgical resection of soft tissue sarcomas. Curr Opin Oncol 16(4): 328-332, 2004. PMID: 15187887. DOI: 10.1097/01.cco.0000127879.62254.d3

Royce TJ, Punglia RS, Chen AB, Patel SA, Thornton KA, Raut CP and Baldini EH: Cost-effectiveness of surveillance for distant recurrence in extremity soft tissue sarcoma. Ann Surg Oncol 24(11): 3264-3270, 2017. PMID: 28718037. DOI: 10.1245/s10434-017-5996-y

Lucas JD, O’Doherty MJ, Wong JC, Bingham JB, McKee PH, Fletcher CD and Smith MA: Evaluation of fluorodeoxyglucose positron emission tomography in the management of soft-tissue sarcomas. J Bone Joint Surg Br 80(3): 441-447, 1998. PMID: 9619933. DOI: 10.1002/(SICI)1097-0142(199802)80:3<441::AID-BJS1>3.0.CO;2-4

Iagaru A, Chawla S, Menendez L and Conti PS: 18F-FDG PET and PET-CT for detection of pulmonary metastases from musculoskeletal sarcomas. Nucl Med Commun 37(3): 375-383, 2016. PMID: 27369810. DOI: 10.1097/MD.0000000000013008

Gingerich AA, Bateni SB, Monjeazem AM, Darrow MA, Thorpe SW, Kirane AR, Bold RJ and Canter RJ: Neoadjuvant radiotherapy is associated with r0 resection and improved survival for patients with extremity soft tissue sarcoma undergoing surgery: A national systematic literature review. J Surg Oncol 113(10): 1885-1893, 2016. PMID: 27259022. DOI: 10.1002/jso.24482

Katsuyama Y, Hayashi D, Konishi E and Kubo T: Hepatic metastases from primary extremity leiomyosarcomas: Two case reports. Medicine 97(18): e5958, 2018. PMID: 29718861. DOI: 10.1097/MD.0000000000010598

King DM, Hackbart DA, Kilian CM and Carrera GF: Soft-tissue sarcoma metastases identified on abdomen and pelvis CT imaging. Clin Orthop Relat Res 467(11): 2838-2844, 2009. PMID: 19636646. DOI: 10.1007/s11999-009-0989-1

Spence D, Seifert B, Gillanders C, Smith MA: MRI surveillance for local recurrence in extremity soft tissue sarcoma. Eur J Surg Oncol 36(6): 479-486, 2019. PMID: 30253419. DOI: 10.1159/000493389

Thompson MJ, Ross J, Domson G and Foster W: Screening CT abdomen/pelvis for metastases in patients with soft-tissue sarcoma of the extremity. Bone Joint J 93-B(1): 45-49, 2015. PMID: 25792705. DOI: 10.1302/0301-620X.93B1.BJ-2014-0801

Mizoshiri N, Shirai T, Terauchi R, Tsuchida S, Mori Y, Katsuyama Y, Hayashi D, Konishi E and Kubo T: Hepatic metastases from primary extremity leiomyosarcomas: Two case reports. Medicine 97(18): e5958, 2018. PMID: 29718861. DOI: 10.1097/MD.0000000000010598

King DM, Hackbart DA, Kilian CM and Carrera GF: Soft-tissue sarcoma metastases identified on abdomen and pelvis CT imaging. Clin Orthop Relat Res 467(11): 2838-2844, 2009. PMID: 19636646. DOI: 10.1007/s11999-009-0989-1

Cho HS, Park IH, Jeong WJ, Han I and Kim HS: Prognostic value of computed tomography for monitoring pulmonary metastases in soft tissue sarcoma patients after surgical management: A retrospective cohort study. Ann Surg Oncol 18(12): 3392-3398, 2011. PMID: 21537873. DOI: 10.1245/s10434-011-1705-4

Park JW, Yoo HJ, Kim HS, Choi JY, Cho HS, Hong SH and Han I: MRI surveillance for local recurrence in extremity soft tissue sarcoma. Eur J Surg Oncol 45(2): 268-274, 2019. PMID: 30352764. DOI: 10.1016/j.ejso.2018.08.032

Richardson K, Potter M and Damron TA: Image intensive soft tissue sarcoma surveillance uncovers pathology earlier than patient complaints but with frequent initially indeterminate lesions. J Surg Oncol 113(7): 818-822, 2016. PMID: 27060189. DOI: 10.1002/jso.24230

Puri A, Ranganathan P, Gulia A, Crasto S, Hawaldar R and Badwe RA: Does a less intensive surveillance protocol affect the survival of patients after treatment of a sarcoma of the limb? Updated results of the randomized toss study. Bone Joint J 100-B(2): 262-268, 2018. PMID: 29437071. DOI: 10.1302/0301-620X.100B2.BJJ-2017-0789.R1
cancer database analysis. Ann Surg Oncol 24(11): 3252-3263, 2017. PMID: 28741123. DOI: 10.1245/s10434-017-6019-8

83 Gronchi A, Ferrari S, Quagliuolo V, Broto JM, Poussa AL, Grignani G, Basso U, Blay JY, Tendero O, Beveridge RD, Ferraresi V, Lugwosa I, Merlo DF, Fontana V, Marchesi E, Donati DM, Palassini E, Palmerini E, De Sanctis R, Morosi C, Stacchiotti S, Bagut S, Coindre JM, Dei Tos AP, Picci P, Bruzzi P and Casali PG: Histotype-tailored neoadjuvant chemotherapy versus standard chemotherapy in patients with high-risk soft-tissue sarcomas (ISG-STS 1001): An international, open-label, randomised, controlled, phase 3, multicentre trial. Lancet Oncol 18(6): 812-822, 2017. PMID: 28499583. DOI: 10.1016/S1470-2045(17)30334-0

84 Posch F, Partl R, Döller C, Riedl JM, Smolle M, Leitner L, Bergovec M, Liegl-Atzwanger B, Stotz M, Bezan A, Gerger A, Pichler M, Kapp KS, Stöger H, Leitner A and Szakadat J: Benefit of adjuvant radiotherapy for local control, distant metastasis, and survival outcomes in patients with localized soft-tissue sarcoma: Comparative effectiveness analysis of an observational cohort study. Ann Surg Oncol 25(3): 776-783, 2018. PMID: 28895087. DOI: 10.1245/s10434-017-6080-3

85 van Prag VM, Rueuten-Budde AJ, Jeys LM, Laitinen MK, Pollock R, Aston W, van der Hage JA, Dijkstra PDS, Ferguson PC, Griffin AM, Willeumier JJ, Wunder JS, van de Sande MAJ and Fiocco M: A prediction model for treatment decisions in high-grade extremity soft-tissue sarcomas: Personalised sarcoma care (PERSARC). Eur J Cancer 63: 313-323, 2017. PMID: 28797949. DOI: 10.1016/j.ejca.2016.07.032

86 Porter GA, Cantor SB, Ahmad SA, Lenert JT, Ballo MT, Hunt KK, Feig BW, Patel SR, Benjamin RS, Pollock RE and Pisters PW: Cost-effectiveness of staging computed tomography of the chest in patients with T2 soft tissue sarcomas. Cancer 104(1): 197-204, 2002. PMID: 11815977. DOI: 10.1002/cncr.10184

87 Brenner DJ, Doll R, Goodhead DT, Hall EJ, Land CE, Little Porter GA, Cantor SB, Ahmad SA, Lenert JT, Ballo MT, Hunt KK, Patel SR, Benjamin RS, Pollock RE and Pisters PW: Utility of chest computed tomography for staging in patients with T1 extremity soft tissue sarcomas. Cancer 92(4): 863-868, 2001. PMID: 11550159. DOI: 10.1002/jco.1997.157.2

88 Johnson GR, Zhuang H, Khan J, Chiang SB and Alavi A: Roles of positron emission tomography with fluorine-18-deoxyglucose in the detection of local recurrent and distant metastatic sarcoma. Clin Nucl Med 28(10): 815-820, 2003. PMID: 14508272. DOI: 10.1097/01.rnu.0000089523.00672.2b

89 Goel A, Christy MEL, Virgo KS, Kraybill WG and Johnson FE: Costs of follow-up after potentially curative treatment for extremity soft-tissue sarcoma. Int J Oncol 25(2): 429-435, 2004. PMID: 15254741.

90 van der Zeel J and Kroneman MW: Bismarck or Beveridge: a beauty contest between dinosaurs. BMC Health Serv Res 7: 94, 2007. PMID: 17594476. DOI: 10.1186/1472-6963-7-94

91 Husain N and Verma N: Curent concepts in pathology of soft tissue sarcoma. Indian J Surg Oncol 2(4): 302-308, 2011. PMID: 23204786. DOI: 10.1007/s13193-012-0134-6

92 Chou Y-S, Liu C-Y, Chou Y-C, Lin C-H, Chen T-H, Chiou H-J, Shiau C-Y, Wu Y-C, Liu C-L, Chao T-C, Tzeng C-H and Yen C-C: Follow-up after primary treatment of soft tissue sarcoma of extremities: impact of frequency of follow-up imaging on disease-specific survival. J Surg Oncol 106(2): 155-161, 2012. PMID: 22297812. DOI: 10.1002/jso.23060

93 Bradley Jr WG: Teleradiology. Neuroimaging Clin N Am 20: 637-644, 2012. PMID: 18573675. DOI: 10.1016/j.nic.2012.05.001

94 Rutkowski P and Ługowska I: Follow-up in soft tissue sarcoma: an overview. Eur J Cancer 87: 27-33, 2018. PMID: 28974986. DOI: 10.1002/ijc.29103

95 Fleming JB, Cantor SB, Varma DG, Holst D, Feig BW, Hunt KK, Patel SR, Benjamin RS, Pollock RE and Pisters PW: Utility of chest computed tomography for staging in patients with T1 extremity soft tissue sarcomas. Cancer 92(4): 863-868, 2001. PMID: 11550159. DOI: 10.1002/jco.1997.157.2

96 Johnson GR, Zhuang H, Khan J, Chiang SB and Alavi A: Roles of positron emission tomography with fluorine-18-deoxyglucose in the detection of local recurrent and distant metastatic sarcoma. Clin Nucl Med 28(10): 815-820, 2003. PMID: 14508272. DOI: 10.1097/01.rnu.0000089523.00672.2b

97 Goel A, Christy MEL, Virgo KS, Kraybill WG and Johnson FE: Costs of follow-up after potentially curative treatment for extremity soft-tissue sarcoma. Int J Oncol 25(2): 429-435, 2004. PMID: 15254741.

98 Reiser M, Kuhn F-P and Debus J: Radiologie. Georg Thieme Verlag KG: Stuttgart, 2011.

99 Trojan J, Sestak J and Gvozdenko S: Diagnostic accuracy of FDG-PET/CT in the evaluation of local recurrence after surgery for soft tissue sarcoma. Eur J Surg Oncol 39(1): 96-100, 2013. PMID: 23467634. DOI: 10.1016/j.ejso.2012.09.010

100 Johnson GR, Zhuang H, Khan J, Chiang SB and Alavi A: Roles of positron emission tomography with fluorine-18-deoxyglucose in the detection of local recurrent and distant metastatic sarcoma. Clin Nucl Med 28(10): 815-820, 2003. PMID: 14508272. DOI: 10.1097/01.rnu.0000089523.00672.2b

101 Reiser M, Kuhn F-P and Debus J: Radiologie. Georg Thieme Verlag KG: Stuttgart, 2011.

102 Revised September 14, 2020

103 Accepted September 21, 2020

3608