in vivo *34*: 3057-3068 (2020)
doi:10.21873/invivo.12140

Review

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

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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

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Key Words: Follow up, systematic review, malignant tumor, soft tissue sarcoma.

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

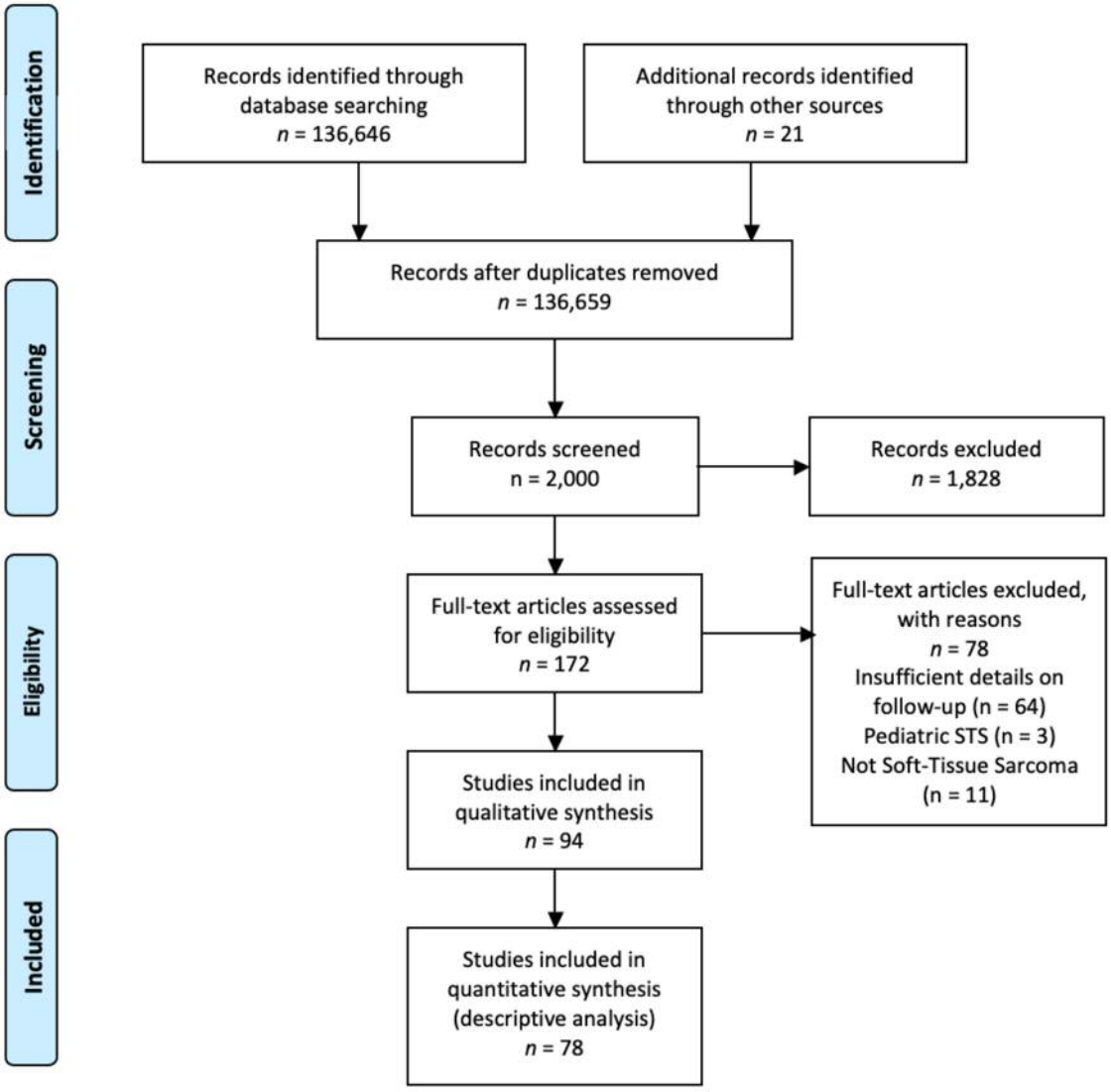

Figure 1. *Flow diagram according to PRISMA guidelines (41) showing study and literature selection process.*

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	Comperative 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	Pisters *et al*. (37)	1994	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	Comperative 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	USA	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	Whooley *et al*. (42)	1999	North America	USA	Review article	5
23	Gibbs *et al*. (32)	2000	North America	USA	Case series	4
24	Beitler *et al*. (71)	2000	North America	USA	Survey	5
25	Whooley *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	Europe	UK	Review article	
36	Cool *et al*. (36)	2005	Europe	UK	Case series	4
37	Kransdorf *et al*. (52)	2006	North America	USA	Review article	5
38	Iagaru *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	Grimer *et al*. (47)	2010	Europe	UK	Guideline	n.a.
49	Johnson *et al*. (2)	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	Biau *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*

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ID	Study	Year	Region	Country	Study type	LoE
59	Rutkowski *et al*. (43)	2014	Europe	Poland	Review article	5
60	Cheney *et al*. (75)	2014	North America	USA	Cohort study	4
61	Bagaria *et al*. (20)	2015	North America	USA	Case series	4
62	Tseng *et al*. (102)	2015	North America	USA	Review article	4
63	Bhatt *et al*. (17)	2016	Europe	Ireland	Cohort study	4
64	Fujiki *et al*. (44)	2016	Asia	Japan	Case series	4
65	Richardson *et al*. (69)	2016	North America	USA	Case series	4
66	Park *et al*. (72)	2016	Asia	South Korea	Comperative study	3
67	Andritsch *et al*. (16)	2017	Euorpe	Austria	Review article	5
68	Trovik *et al*. (31)	2017	Europe	Scandinavian Multicenter	Cohort study	3
69	Smolle *et al*. (38)	2017	Europe	Austria	Review article	5
70	Sandrucci *et al*. (103)	2017	Europe	Italy	Survey	5
71	Patel *et al*. (77)	2017	North America	USA	Cohort study	3
72	Royce *et al*. (79)	2017	North America	USA	Experimental study	3
73	von Mehren *et al*. (35)	2018	North America	USA	Guideline	n.a.
74	Casali *et al*. (34)	2018	Europe	Italy	Guideline	n.a.
75	Ezuddin *et al*. (48)	2018	North America	USA	Review Article	5
76	Puri *et al*. (70)	2018	Asia	India	Randomized controlled trial	1
77	Siegel *et al*. (13)	2019	North America	USA	Statistics	n.a.
78	Park *et al*. (68)	2019	Asia	South Korea	Case series	4

LoE: Level of evidence; n.a.: not applicable.

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, 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

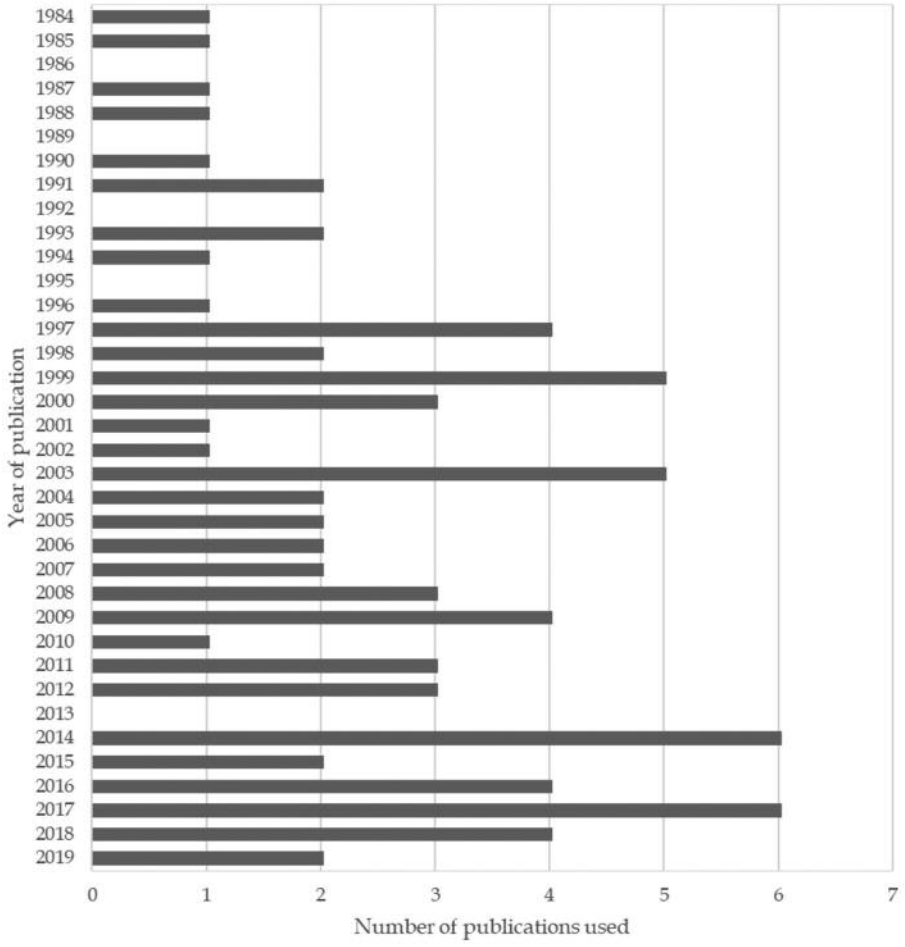

Figure 2. *Distribution of year of publication of included studies.*

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, 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 stategy 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. Schneeweiß 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.

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Received August 6, 2020
Revised September 14, 2020
Accepted September 21, 2020