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REVIEW ARTICLE

Primary leiomyosarcoma of the skin: a comprehensive review on diagnosis and treatment

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Abstract
Sarcomas are a heterogeneous group of mesenchymal tumors which can affect bone and soft tissue. Leiomyosarcoma (LMS) is a rare subtype localized to the skin or subcutaneous tissue. Due to the heterogeneity of sarcomas, reviews and guidelines with an in-depth focus specifically on primary LMS of the skin are sparse. This article is intended to provide an up to date and systematic overview on diagnosis, treatment, and surveillance of this rare entity to provide a framework for decision making and management for dermato-oncologists. We discuss novel treatment options for advanced disease such as targeted therapy with kinase inhibitors and immune checkpoint blockade which may improve the prognosis even in advanced stages of LMS.

Keywords Leiomyosarcoma · Soft tissue sarcoma · Skin · Platelet-derived growth factor · Immune checkpoint blockade

Epidemiology

The incidence of soft tissue sarcomas is approximately 10,000 cases per year in the United States with an overall mortality rate of about 4000 adults and children, underlining their aggressive behavior [1]. Sarcoma can become apparent on the skin either as primary tumor or metastatic spread. Leiomyosarcoma (LMS) represents a rare subtype entity that accounts for roughly 3% of all soft tissue sarcomas with an incidence rate of 0.04% [1–5]. The tumors' localisation ranges from superficial skin to involvement of the deep fascia [1–4]. Caucasian individuals are more often affected than other ethnic groups [6, 7]. Cutaneous LMS has a peak incidence in patients in the fifth to seventh decade of life [2, 8, 9]. Men are more often affected than women with a ratio of approximately 3:1. Subcutaneous LMS commonly arises on the extremitites (50–85%), equally affecting females and males in the fifth through eighth decade of life [2, 10, 11].

Etiology and pathogenesis

Data on the etiology of soft tissue tumors is limited. It is believed that not only environmental, but also genetic and immunologic factors, previous injuries, familial cancer syndromes, mechanical tissue affection, and infections are linked to the occurence of soft tissue tumors (47). It has been suggested that chemical carcinogens can significantly contribute to the genesis of soft tissue sarcoma, especially phenoxyacetic herbicides, chlorophenols as well as dioxin, which are used in forestry work. Several cases of angiosarcoma have been described after ionizing radiation in patients with breast cancer. The incidence of angiosarcoma seemed to correlate with the radiation dose with most patients receiving at least 50 Gray (gy) [12]. However, it is unclear whether these general risk factors for sarcomas also apply for LMS. In virtually all cases, LMS arises de novo and not from precancerous or preexisting lesions. Genetic disorders with predisposition for LMS include the Li-Fraumeni syndrome, a rare autosomal dominant disease with mutations in the TP53 tumour suppressor gene [13], as well as retinoblastoma with mutation of the RB1 locus [14].

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Two different subtypes of primary LMS exist, a superficial and a deep type differing in dermal and subcutaneous extension. Consequently, LMS can be divided into two different subgroups in association to skin affection. The first type is confined to the dermis of the skin and does not show deeper growth (cutaneous, superficial, or dermal LMS). This variant is thought to arise from the arrector pili muscle of the hair follicle. Subcutaneous extension into deeper tissue layers is also possible and observed in approximately 20–50% of the cases [15]. This type of LMS is then called subcutaneous LMS and believed to arise from smooth muscles of the small vessels of subcutaneous or fat tissue. This classification is of paramount importance because both subtypes show distinct clinical courses and differ considerably regarding the prognosis and the risk for metastatic spread [2, 8, 9, 16].

In very rare cases, LMS can occur in the skin or subcutaneous tissue as metastasis arising from remote, mostly visceral primaries such as uterus [17, 18] and retroperitoneum, and also from connective tissue [19] or spermatic cord [20]. Approximately 15 such cases have been recorded in the literature and were referred to as "secondary" LMS. They are found usually on the scalp or back and appear as multiple dermal or subcutaneous nodules [21].

Clinical presentation

The most common localization of LMS is on the hair-bearing extensor surfaces of the extremities, especially on the thighs. Another review proposed that the cutaneous variant most frequently affected the head and neck (48%), followed by extremities (31%) and trunk (21%) [22]. These data support early observations by Bernstein and Roenigk who first described a localization discrepancy between cutaneous LMS primarily located on head and neck and subcutaneous LMS primarily located on the lower extremities in a series of 34 patients [23]. Rare sites of dermal LMS were recorded in single case reports and included upper lips [24], penis and foreskin [25–27], scrotum [28], gingiva [29], orbit [30], face [31, 32], and nipple [33, 34].

The tumors usually present as skin-coloured, erythematous or blue papules, nodules or plaques, occasionally with irregular or ulcerative surface (Fig. 1). They are usually indolent, while pain has been reported in a subset of cases [8]. The mean diameter at first diagnosis is between 2 and 5 cm with a locally aggressive pattern of growth [2, 8, 35]. Although it is not reliably possible to distinguish clinically between cutaneous and subcutaneous LMS, the latter variant may be slightly larger at first presentation with a more circumscribed outline [8]. A recent analysis on 71 primary LMS cases revealed a mean diameter of 1.5 cm of dermal tumors compared to 3.8 cm of subcutaneous tumors [36]. Differential diagnosis for both variants comprises benign

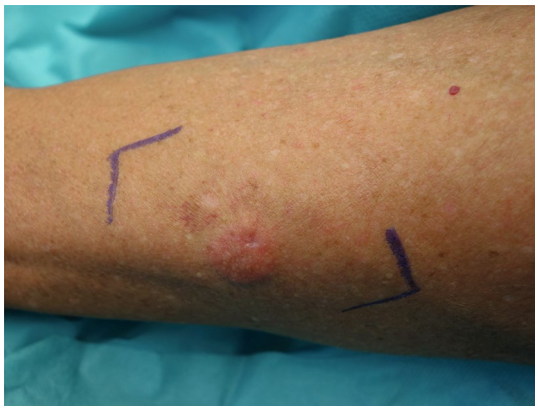

Fig. 1 Clinical presentation of LMS on the extensor surface of the arm in a female patient. Note the unspecific clinical appearance as erythematous nodule

dermatofibroma, dermatofibrosarcoma protuberans, pleomorphic dermal sarcoma, liposarcoma, or cutaneous B-cell lymphoma. One case has recently been described in which LMS was clinically confused with a keloidal scar [37]. Furthermore, metastases and epidermal cysts are relevant differential diagnoses [2, 3, 38].

Histopathology and grading

Most of the cutaneous LMS show atypical spindle cells with homogenous eosinophil cytoplasm and cigar-shaped nuclei. The tumoral cells arrange in fascicles or nodules, or undergo an infiltrative growth pattern (Fig. 2). Most frequently, cutaneous LMS are well-differentiated tumors without regressive or degenerative changes. However, necrosis, sclerosis, hemorrhage, hyalinization, and myxoid changes have been reported. Atypical mitotic figures, as well as mitotic "hot spots" are commonly identified in these tumors. Other spindle cell neoplasms in the skin with neural, vascular, melanocytic, fibrohistiocytic, or muscular differentiation need to be considered as differential diagnosis. Immunoperoxidase staining is routinely required to aid distinguishing them.

Immunohistochemical detection of desmin, smooth muscle actin (SMA), and h-caldesmon as well as overexpression of receptor tyrosine kinases (IGFR, PDGFR etc.) is characteristic of LMS [8, 35, 36, 39–41]. SMA is present in virtually all tumors. However, it can also be found in other entities and lead to a diagnostic pitfall [42]. In contrast, desmin is not constantly and often only focally expressed in cutaneous LMS. In few cases, cytokeratins can be detected in LMS [11]. Of note, p53 immunoexpression in more than 1% of the cells in a cutaneous smooth muscle tumor was proposed as indicative of malignancy [43]. In 95% of LMS cases, strong expression of S100A6 was reported and proposed to be a

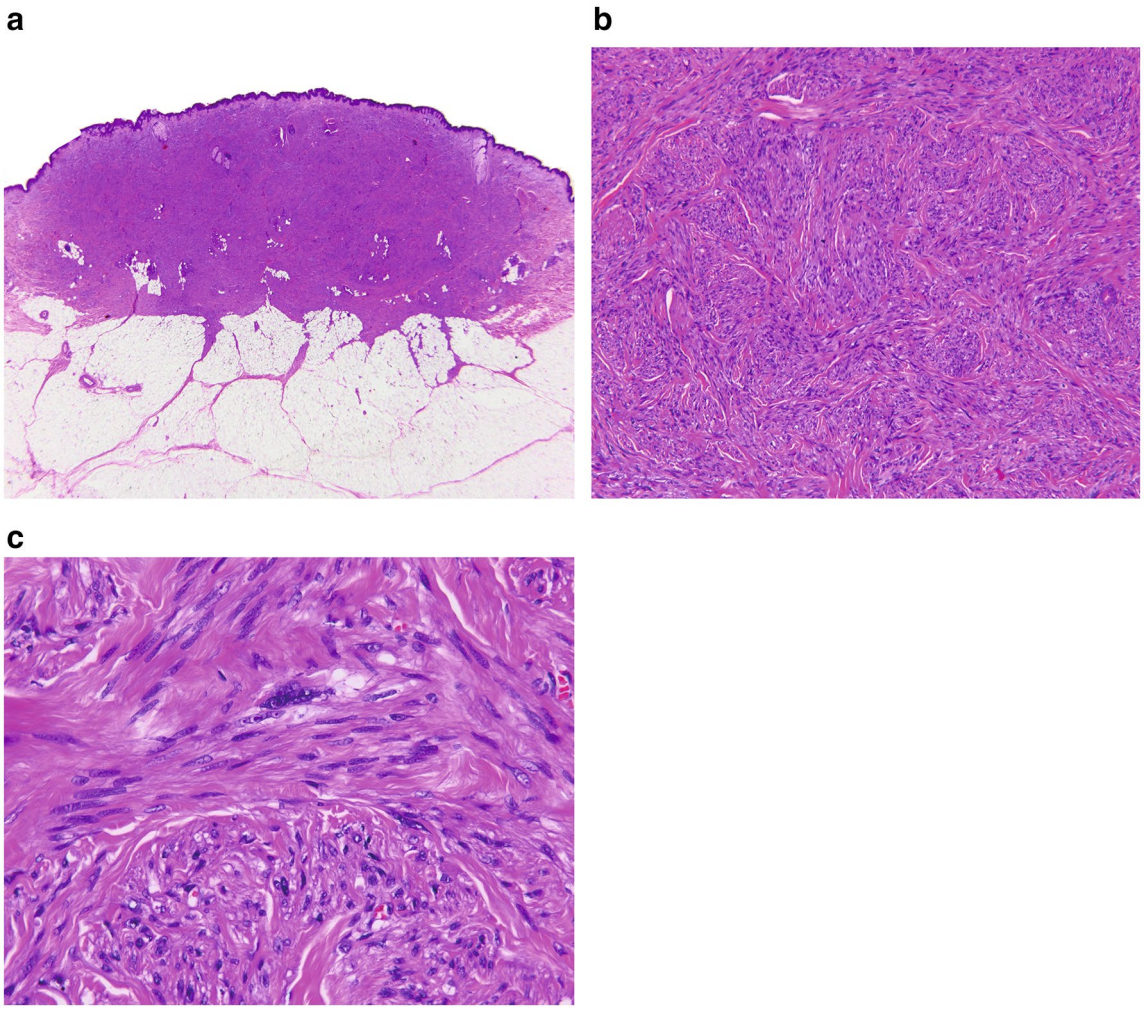

Fig. 2 Histopathology of dermal LMS. **a** Scanning magnification revealing a tumor of spindle cells located in the mid to deep dermis without signifcant involvement of the subcutaneous fat tissue. **b** The tumor cells arrange in fascicles or small nodules, in this case growing in a haphazard pattern. **c** Cytologically, the cells are highly differentiated with little mitotic activity (3 mitoses per high-power field, G1)

differential factor to leiomyoma, in which S100A6 expression was much less common and of weaker intensity [44].

Different histological subtypes of cutaneous LMS have been reported. A case with intracytoplasmic eosinophilic granules in the neoplastic cells has been reported as a "granular form" of cutaneous LMS [45]. Epitheloid variants have also been described [46]. Desmoplasia (stromal sclerosis) can be observed in LMS, a phenomenon that might be a diagnostic challenge in some cases [47].

In a large series of LMS reported by Fields and Helwig, 80% of the tumors had more than two mitoses per ten high-power fields [8]. In general, cutaneous smooth muscle tumors showing cytologic atypia and more than two mitotic figures per ten high-power fields are diagnosed as LMS. Based on the good prognosis of dermal LMS, Fletcher et al. proposed and coined the term "atypical smooth muscle tumors" [48]. This terminology is currently not accepted by the WHO. However, it could offer an alternative to inappropriate diagnosis of sarcoma which bears psychological and social impact.

To estimate the prognosis of affected patients, grading of LMS should be performed. It is mainly based on histopathological parameters. One of the most commonly used classifications was proposed by Coindre et al. as the "French Federation of Cancer Centers Sarcoma Group" (FNCLCC) grading system. It is based on a score of three parameters (1) differentiation, (2) mitotic rate, and (3) amount of tumor necrosis [49], which sum up to three possible histologic gradings (Table 1).

Initial assessment and staging

As LMS is a rare tumor of the skin and the clincial presentation is not specific, usually a skin biopsy reveals the diagnosis. If a soft tissue sarcoma is suspected clinically,

Table 1 Grading system according to the French Federation of Cancer Centers Sarcoma Group (FNCLCC)

A: Tumor differentiation	
Score 1	Sarcoma closely resembling normal adult mesenchymal tissue (e.g., low-grade leiomyosarcoma)
Score 2	Sarcoma with low differentiated histological typing (e.g., myxoid liposarcoma)
Score3	Embryonal and undifferentiated sarcoma, (e.g., synovial sarcoma, doubtful type)
B: Mitotic count[a]	
Score 1	0–9/10 HPF
Score 2	10–19/10 HPF
Score 3	> 20/10 HPF
C: Tumour necrosis	
Score 0	No necrosis
Score 1	< 50% necrosis
Score 2	> 50% necrosis
Summary histological grade	
Grade 1	Total score 2–3
Grade 2	Total score 4–5
Grade 3	Total score 6–8

[a]HPF (high-power field) = 0.1734 mm^2

the initial evaluation should include a history of the growth dynamics of the tumor, a complete skin examination and palpation of the regional lymph nodes. Preoperative imaging is usually dispensable unless there is gross evidence for involvement of deeper anatomical structures like adjacent fascia, muscle tissue, or bones. Magnetic resonance imaging should then determine the extent of tumor involvement. As sarcomas do not primarily show a lymphogenic pattern of metastasis, ultrasonography of the regional lymph nodes has not been suggested in several guidelines. However, according to our experience, it should be considered and offered for high-risk cases or after local relapse. The European Society of Medical Oncology (ESMO) guidelines suggest performance of a spiral chest computed tomography (CT) when a soft tissue sarcoma is diagnosed to rule out pulmonary metastasis [50]. Due to the less aggressive course of LMS compared to other sarcomas, we recommend chest CT in case of high-risk disease (size ≥ 5 cm; subcutaneous localization; high-grade lesion). The role of positron emission tomography (PET) scanning has been matter of debate as the added value of this modality compared to CT is considered minimal [51, 52].

Soft tissue sarcomas are usually staged according to the TNM staging system developed by the International Union against Cancer (UICC) and the American Joint Committee on Cancer (AJCC). It integrates the histological grading with tumor size, involvement of regional lymph nodes, and distant metastasis (Table 2). However, the validity and applicability of this classification for primary LMS of the skin is questionable as a tumor size > 5 cm is rarely observed and most tumors will fall into the T1 category. Thus, a smaller cut-off value may be more applicable, particularly for cutaneous LMS. Poor differentiation (grade 3 or 4) results in up-staging to stages II or III irrespective of the tumor size.

Treatment of the primary tumor

The treatment of LMS should be managed in a multidisciplinary setting. Due to the risk of local recurrence, resection with wide margins is considered the gold standard. The most critical factor for recurrence-free survival are microscopically negative tumor margins. However, the exact width of safety margins is not entirely clear. Most studies recommend at least 1 cm, while others revealed lower rates of relapse after resection with 2–5 cm margins [53]. McKee et al. reported that surgical margins > 1 cm independently predicted longer local recurrence-free survival and are optimal in the resection of extremity soft tissue sarcomas [7, 53–55]. Deneve and co-workers reported that wide local excision with 1 cm was sufficient to achieve negative margins in 97% in a case series of 33 patients with LMS, suggesting that this approach may be sufficient to achieve diease control. However, the majority of tumors in this report were of low-risk and showed a low histological grade [7]. Due to the high risk for local relapse for subcutaneous LMS, excision with margins of at least 2–3 cm as well as complete resection of the subcutaneous tissue with the deep fascia is advisable if functionally and aesthetically acceptable. The maintainance of muscular function, aesthetic outcome, and quality of life must be taken into consideration while planning a treatment concept. For anatomic sites in which wide excision is not feasible, Moh's micrographic surgery is a valid

Table 2 Staging of LMS from the American Joint Commission on Cancer

T stage	
T0	No primary tumor
T1	Largest dimension 5 cm or less
	(a) superficial
	(b) deep tumor
T2	Largest dimension more than 5 cm
	(a) superficial
	(b) deep tumor
N stage	
N0	No nodal involvement
N1	Nodal involvement
M stage	
M0	No distant metastasis
M1	Distant metastasis

	G	T	N	M
Summary				
Stage I	1, 2	1a + b	0	0
	1,2	2a	0	0
Stage II	1, 2	2b	0	0
	3, 4	1a + b	0	0
	3, 4	2a	0	0
Stage III	3, 4	2b	0	0
Stage IV	Any	Any	1	0
	Any	Any	Any	1

alternative, although the evidence is limited to smaller case series. Recurrence rates varied from 0 to 13% in patients treated with Moh's surgery, predominantly for low-risk LMS [54, 56].

Adjuvant treatment

Adjuvant radiotherapy should be considered for patients with large lesions (> 5 cm), tumor-positive excision margins, high-grade LMS (G2, G3), and after local relapse. Radiation is performed with high energetic photons (6–18 MV) within 6 weeks after surgical intervention in a fractionated regimen (1, 8–2 gy/d) and a cumulative dosis of 40 gy to 50 gy [7, 57].

Adjuvant chemotherapy for resectable sarcoma is discussed controversially. In 2008, Pervaiz et al. published a meta-analysis with 1953 patients showing an increased overall survival (OS) after doxorubicin in combination with ifosfamid. The odds ratio (OR) for local recurrence was 0.73 (95% CI 0.56–0.94; $p = 0.02$) in favor of chemotherapy. For distant and overall recurrence, the OR was 0.67 (95% CI 0.56–0.82; $p = 0.0001$) in favor of chemotherapy. In terms of survival, doxorubicin alone had an OR of 0.84, yet without significance (95% CI 0.68–1.03; $p = 0.09$). Thus, the study presented only marginal efficacy of doxorubin in combination with ifosfamid in localized resectable soft tissue sarcoma [58]. As LMS tends to show a more indolent and favorable course compared to other soft tissue sarcomas, adjuvant chemotherapy is currently not recommended.

Management of advanced disease

In most cases, chemotherapy is an important mainstay of the management of advanced disease which may be combined with radiation of skin masses to achieve local control. Common regimens are based on anthracyclines (doxorubicine, epirubicine) and on gemcitabine.

First-line treatment of choice usually is polychemotherapy with doxorubicine, e.g., doxorubicine plus ifosfamide or doxorubicine plus dacarbazine as LMS is considered an anthracycline-sensitive entity (Table 3). Pegylated liposomal doxorubince or epirubcine may be used instead of unencapsulated doxorubicine because of better tolerability, although a trend for lower response rates were reported decades ago [59]. Tap et al. recently performed an open-label phase 1 and randomized phase 2 trial with doxorubicine plus olaratumab in patients with advanced soft tissue sarcomas with LMS being the most common

Table 3 First-line treatments for metastatic LMS

Study	Scheme	Dosage (cumulative)	ORR (%)	PFS	OS
LeCesne et al. [61]	Doxorubicin	75 mg/m^2 Q3W	23.3	29 weeks (median)	Not reported
	Ifosfamide	5 g/m^2 Q3W			
Worden et al. [70]	Doxorubicin	60 mg/m^2 Q3W	23	55% (after 1 year)	73% (after 2 years)
	Ifosfamide	6 g/m^2 Q3W			
Antman et al. [71]	Doxorubicin	60 mg/m^2 Q3W	17	Not reported	12.5 months (median)
	Dacarbazine	1000 mg/m^2 Q3W			
Leu et al. [72]	Gemcitabine	1350 mg/m^2 Q3W	43	6.7 months (median)	13 months (median)
	Docetaxel	100 mg/m^2 Q3W			
Hensley et al. [73]	Gemcitabine	1800 mg/m^2 Q3W	53	5.6 months (median)	17.9 months (median)
	Docetaxel	100 mg/m^2 Q3W			
Tap et al. [60]	Doxorubicin	75 mg/m^2 Q3W	18.2	6.6 months (median)	26.5 (median)
	Olaratumab	15 mg/kg (d1 + d8) Q3W			

ORR objective response rate; *PFS* progression-free survival; *OS* overall survival; *Q3W* tri-weekly; *d* day

histologic type (38%). Olaratumab is a monoclonal antibody targeting the platelet-derived growth factor receptor α (PDGFRα) which prevents its ligands from binding and thereby inhibits the signaling pathway. The study population was randomized to doxorubicine alone or in combination with olaratumab (15 mg/kg body weigth). The combination cohort showed better progression-free survival (PFS) and OS which was consistent across all subgroups [60]. Adverse events of olaratumab include neutropenia, diarrhea, vomiting, nausea, and mucositis. Nevertheless, it may be better tolerable than polychemotherapy although comparative trials are lacking and a major phase III trial (ANNOUNCE trial; NCT02451943) is currently ongoing. Further combinations for LMS are gemcitabine plus docetaxel and monochemotherapy with gemcitabine which is usually well tolerated but little efficient.

After failure of an anthracycline-based therapy, second-line treatment with trabectedin (ecteinascidin) showed some efficacy in LMS in several phase II trials and was approved by the EMA in 2007 [61, 62]. The recommended dosage is 1.5 mg/m^2 body surface area applied three-weekly as slow infusion over 24 h until disease progression or development of unacceptable toxicity. Targeted agents such as multikinase inhibitors and immune checkpoint blockers are currently under investigation. Sorafenib was assessed in 37 patients ($n = 19$ with LMS) in a phase II trial, but failed to show radiologic responses and was accompanied by a poor PFS of 2–3 months in the LMS subgroup [63]. Regorafenib, an orally active multikinase inhibitor with proven activity in gastrointestinal stromal tumor (GIST), was investigated in a recent phase II trial with refractory soft tissue sarcomas. In the LMS cohort ($n = 28$), patients treated with regorafenib showed a median PFS of 3.7 months (95% CI 2.5–5.0) which was signifcnantly longer than in the placebo group. However, no difference in OS was observed.

Soft tissue sarcomas are a heterogeneous group of tumors of mesenchymal origin. Expression of the immune checkpoint PD-L1 was observed in 15–65%, depending on tumor type and tissue of origin [64, 65]. LMS shows a microenvironment where the exploration of checkpoint blockade seems promising, although expression patterns have not been reported specifically for cutaneous or subcutaneous LMS to date. Monotherapy with ipilimumab or nivolumab had limited efficacy in several trials revealing response rates of 0–5% [64, 66]. Pembrolizumab was recently evaluated in an all-comer phase II trial with soft tissue and bone sarcoma in 86 patients with ten suffering from LMS. Althoug the overall response rate for soft tissue tumors was 18%, none of the patients with LMS showed a response [67]. A combination blockade with nivolumab plus ipilimuab revealed more favourable anti-tumor efficacy in a phase II trial with a response rate of 18% and a median OS of 14.3 months [64]. These data are encouraging, but definite conclusions on a significant role for checkpoint blockade in LMS are premature and further trials warranted.

Prognosis and surveillance

The overall prognosis of LMS is good with an overall five-year survival rate of 95% and development of distant metastases in less than 15% of all cases. However, local recurrence is seen in up to 30%. After 5 years, the risk for local relapse was 18% and 22% for cutaneous and subcutaneous LMS, respectively. The median time to recurrence was 4.0 years for dermal and 2.2 years for subcutaneous LMS, underlining that surveillance should be performed for at least 5 years after diagnosis [36]. The propensity of dermal LMS to metastasize has been evaluated differently. While some authors proposed that the dermal variant does

Table 4 Recommended follow-up guidelines for LMS

Year	1–3	3–5	5–10
Whole skin examination	Every 3 months	Every 6 months	Once a year
Sonography of primary tumor site	Every 3 months	Every 6 months	Once a year
Sonography of regional lymph nodes[a]	Every 3 months	Every 6 months	Once a year
spiral CT (chest)[a]	Every 3 months	Every 6 months	Once a year
Sonography abdomen[a]	Every 6 months	Every 6 months	Once a year
MRT of primary tumor site	Every 6 months	Every 12 months	Optional

[a]In high-risk cases only (> 5 cm tumor size, subcutaneous LMS, local relapse, high-grade LMS)

not metastasize at all [48], recent retrospective analyses report on distant metastases in approximately 10–12% of cases [36]. Subcutaneous LMS is associated with a higher metastatic potential of up to 50% after 5 years [36]. The median time to metastasis formation was 3.0 years for both, cutaneous and subcutaneous LMS. Most distant metastases are in the lungs, followed by lymph node and skin metastases in 25% [2, 15].

The risk of recurrence and metastasis underlines the need for regular surveillance. Follow-up guideline for LMS are little standardized and adopted from the soft tissue sarcomas in general. A complete skin examination should be performed every 3 months for 3 years after resection, then every 6 months for the next 2 years and then yearly for up to 10 years [68]. Due to the high risk for distant metastases, chest CT should be performed every 3–6 months for subcutaneous LMS together with MRT of the primary tumor site (Table 4).

Conclusion

A systematic approach to the diagnosis and management of LMS is important to achieve appropriate management of this rare entity. Dermal LMS is a low-risk tumor with little metastatic potential and a good prognosis. In contrast, subcutaneous LMS should be treated and surveilled as a high-risk soft tissue sarcoma due to its propensity for local recurrence and distant metastasis formation.

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