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Cutaneous Leiomyosarcoma: A Single Institution Experience of Treatment and Outcomes with a Standardized Margin of Resection

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Abstract

Introduction—Cutaneous leiomyosarcoma (LMS) is a rare dermal-based tumor for which treatment algorithms have been poorly defined. We report our single institution experience treating cutaneous LMS using a median of a 1 cm margin for resection.

Methods—An IRB approved review of patients with cutaneous LMS from 2005-2010 was performed with outcomes reported.

Results—33 patients with cutaneous LMS were treated, 76% were male, 97% were Caucasian with a median age of 63.5 years. 67% of tumors were located on the extremities. Pre-operative staging was negative for distant metastasis in all patients. 88% of tumors were low grade with a median tumor size of 1.3 cm. 100% of tumors tested for smooth muscle actin were positive. A majority (94%) of patients underwent primary surgical resection with a median margin of 1 cm. Final resection margin was negative in 32/33 (97%). Adjuvant radiotherapy was used in 15%. There were no recurrences or metastatic spread and 100% were alive at last follow up, median of 15.5 months.

Conclusions—Cutaneous LMS is primarily a low-grade malignancy affecting elderly male Caucasians. Good oncologic control and an excellent outcome are possible with a 1 cm resection margin in the vast majority of cases.

Keywords

Cutaneous leiomyosarcoma; leiomyosarcoma; LMS; recurrence; actin; margin; low grade

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Introduction

Cutaneous leiomyosarcoma (LMS) is a rare soft tissue tumor believed to arise from the arrector pili muscle of hair follicles and accounts for 1-3% of all soft tissue sarcomas.[1, 2] Although cutaneous LMS originates within the dermis of the skin, occasional extension into the subcutaneous tissue is seen. Histologically, LMS is characterized by a dermal-based proliferation of spindle cells with blunt-ended, “cigar-shaped” nuclei and increased mitotic figures.[3] Immunohistochemical staining, using vimentin, smooth muscle actin, and desmin, is often utilized to aid in the diagnosis of cutaneous LMS and exclude other cutaneous spindle cell proliferations.[3, 4]

The clinical behavior of cutaneous LMS has been difficult to establish because these tumors have not been separately distinguished from soft tissue LMS in most retrospective series. Cutaneous LMS, for instance, is thought to have a rather indolent course and better prognosis than those of subcutaneous and deeper origins.[5] Cutaneous LMS does have a risk of local recurrence, as high as 40% in some earlier series.[6] Massi and colleagues reported a 6% recurrence for cutaneous LMS confined to the dermis but an 18.1% incidence of recurrence for those cutaneous LMS with subcutaneous extension.[7] Distant metastases are more commonly associated with subcutaneous LMS, whereas those with cutaneous LMS do not appear to have the same risk of metastasis. Subcutaneous LMS, thought to arise from smooth muscle of small vessels, and have been reported to have a tendency to metastasize earlier with a worse prognosis.[5, 8] In contrast, findings from a review of 225 patients with nonvisceral soft tissue LMS form the Scandinavian Sarcoma group, revealed no patients with strictly cutaneous LMS whom metastasized or died of tumor-related causes.[9]

Some treatment-related issues remain unresolved for cutaneous LMS. For instance, while many published series recommend wide excision, few specify the actual surgical margin used. A variety of margins have been described as being appropriate for resection in the literature including narrow excision, wide excision or even Mohs micrographic surgery. [10-14] However, no consensus as to the most appropriate margin of resection currently exists. We have found that standardization of the surgical margin of resection to be useful at our own institution when treating other rare soft tissue tumors, such as dermatofibrosarcoma protuberans.[15, 16] We therefore set out to review our own single institution experience for the diagnosis and management of cutaneous LMS using a median of 1 centimeter (cm) for margin of resection

Methods

An IRB-approved, single institution, retrospective review was performed for patients treated at Moffitt Cancer Center (Tampa, FL, USA) from 2005-2010 who underwent resection for cutaneous LMS. Patients with insufficient data for analysis, visceral-origin LMS (gastrointestinal, gynecologic, or retroperitoneal), atypical fibroxanthoma, dermatofibrosarcoma protuberans or other non-cutaneous LMS were excluded. Patients with cutaneous LMS arising from the dermis were further analyzed. Cutaneous or dermal LMS with subcutaneous extension was included while those LMS originating in the subcutaneous tissues or LMS originating from a blood vessel were excluded.

Pre-operative staging evaluation, method of biopsy and treatment were determined from the electronic medical record or outside documents when patients were referred to Moffitt Cancer Center for consultation or further treatment. The margin of resection was recorded in centimeters (cm) as less than 1.0 cm, 1.0 cm, 1.1-1.5 cm, 1.6-2.0 cm, or other as determined from the dictated operative note when available.

Tumor size was recorded in cm with mitotic figures noted when present. The diagnosis of cutaneous LMS was verified by a sarcoma pathologist (MMB) or dermatopathologist (JLM) and immunohistochemistry was performed when necessary to support or confirm the diagnosis of cutaneous LMS or exclude other entities. Smooth muscle tumors with evidence of nuclear pleomorphism and > 1 mitosis/10 high-power field (HPF) were diagnosed as leiomyosarcoma. The tumors were evaluated for nuclear atypia (mild, moderate, and severe), grade (1, 2, and 3 FNCLCC), mitotic activity (count of the most mitotically active area in 10 consecutive HPF, i.e. x400) and presence (and/or percentage) of tumor necrosis. Immunohistochemical results, in addition to morphology, were recorded with immunoreactivity to smooth muscle actin and/or desmin as confirmative of smooth muscle origin.

Adjuvant treatment, when administered, was noted. Recurrence and length of follow up were recorded in months from the date of original diagnosis. Follow up status was defined as no evidence of disease (NED), alive with disease (AWD) or dead of disease/other causes. Descriptive statistics were measured using SPSS 19.0 software (Cary, NC).

Results

Patient Demographics

A total of 33 patients underwent evaluation and treatment for cutaneous LMS from 2005-2010. Ninety-seven % of patients were Caucasian, 25 patients (76%) were male with a median age of 63.5 years (range, 20-91 years). Primary tumor location involved the lower extremity in 15 (46%), head and neck in 9 (27%), upper extremity in 7 (21%) or trunk in 2 (6%). Shave biopsy was the most frequent method of diagnosis, followed by excision and punch biopsy.

Pre-operative staging studies, performed at the discretion of the treating physician, included chest CT in 14 (42%), diagnostic chest radiograph in 13 (39%), and whole body PET imaging in 4 (12%), all of which were negative for metastatic disease. No patient received radiation to the primary tumor site prior to surgical resection. (Table 1)

Primary Tumor Characteristics

All tumors were cutaneous or dermal LMS in origin. The median tumor size was 1.3 cm (range, 0.4-3.5 cm) with a majority of tumors having low-grade histology (88%). (Figure 1 and 2) The remaining was higher grade. Mitoses were recorded in 76% of patients ranging from 1-58/10HPF. (Table 2) Immunohistochemistry was performed in 27 patients (82%). Smooth muscle actin was positive in all tumors tested. Desmin was tested in 20 patients (61%) with expression present in 14 (42%). S100 was tested in 24 (73%) and was negative in 23 (96%). (Figure 3)

Primary Tumor Resection

The definitive margin of resection used after referral to Moffitt Cancer Center was 1.0 cm in the majority of patients (22/33, 67%). One patient (3%) had a 1.2 cm margin used, four patients (12%) underwent resection with a 1.5 cm margin and 4 (12%) had a 2.0 cm surgical margin. Two patients (6%) underwent resection with a margin less than 1.0 cm. (Figure 4) One of the patients who underwent resection with an initial 1.0 cm margin required temporary AlloDerm coverage of the scalp defect. Once negative margins were confirmed, planned extirpation of the temporary biologic dressing with definitive skin graft coverage was performed. We have used this technique for other pathologies prior to definitive coverage while awaiting permanent pathologic margin assessment in situations where further resection may be required. [17]

In total, two patients (6%) had a positive margin after initial resection using at least a 1.0 cm margin (both underwent initial resection with a 1 cm margin). The first patient was able to be re-excised to negative margins using an additional 1 cm margin. The remaining patient had a 1.0 cm tumor located at the nasolabial fold. A 1.0 cm margin was used and the area was covered with a rotational cheek flap. On final pathologic analysis, the nasal mucosal margin was microscopically positive. This patient did not undergo further resection, rather was treated with adjuvant radiation. Therefore, the final margin of resection was negative in 97% (32/33 patients). (Table 3)

Adjuvant Therapy

Adjuvant radiation was administered to 5 patients (15%) after resection. All of the patients received radiation therapy based on multidisciplinary tumor board recommendation. One patient received adjuvant radiation for the presence of subcutaneous extension of cutaneous LMS on final pathology. While two patients who had positive margins after tumor resection (one of which underwent re-excision), both received adjuvant radiation therapy. The other two patients received XRT due to multidisciplinary tumor board recommendations, neither had high-grade tumors nor positive margins. These two patients were treated earlier in the current series. No patient received adjuvant chemotherapy.

Complications and Outcomes

Complications were observed in 3 patients (9%). The patient with the nasolabial fold tumor whom underwent rotational flap advancement with the positive mucosal margin developed facial asymmetry after resection. This was ultimately self-limiting and resolved after 3 months. Cellulitis developed in one patient that responded to oral antibiotics. The remaining patient developed a non-healing scalp wound that required serial office debridement and ultimately healed by secondary intention.

There were no loco-regional recurrences, distant metastases or deaths observed during in the treatment period with a median follow up of 15.5 months (range, 2-49 months). All patients remain without evidence of disease at last follow up. (Table 3)

Discussion

Cutaneous soft tissue sarcomas are rare tumors and account for less than 1% of all soft tissue malignancies.[2, 9, 18] They most commonly affect Caucasian males with a peak incidence in the 5th to 6th decade.[7, 19] These tumors present as solitary, erythematous or brownish well-circumscribed dermal nodules ranging in size from 0.5-3 cm. Because they are dermal-based tumors, they may appear fixed to the epidermis and ulceration may be present.[20] The lower extremities and head and neck locations are the most common sites of involvement as identified in our series and in the literature.[3, 14, 21] Pre-operative staging with cross-sectional imaging (CT thorax and/or PET imaging) appeared to add minimal clinical impact in our experience as more than half of the patients in this series underwent imaging, all of which were negative. The utility of pre-operative staging for cutaneous LMS has not been previously described in the literature.

Multiple institutions have helped describe the behavioral and outcome differences between cutaneous and subcutaneous LMS.[5, 6, 22] Pijpe and colleagues, as well as several others, identified that more superficial tumors appeared to have a better prognosis than those of deeper origin.[22-24] In their series, deeper LMS had a significantly larger tumor size, which could be a possible explanation for the worse outcome observed with the deeper tumors. Massi and others noted the impact of tumor grade on outcome, as the cutaneous LMSs that recurred or metastasized in their series were all high grade.[7] Other prognostic variables such as DNA ploidy[25], Ki 67 proliferative index[26, 27] and mitotic figures[1, 4] have also been identified as markers of worse outcome. The optimal width and impact of margin of resection on outcome, however, has remained less well defined. In fact, the majority of publications concerning cutaneous LMS have made little or no comment regarding the margin of resection performed at the time of excision.

All would agree that negative margins are optimal management for these tumors, but no specific consensus statement exists regarding the preferred or most appropriate margin. Retrospective single-center series and collective reviews have provided some insight into this matter. Bernstein and colleagues from Mayo Clinic recommended a wide margin excision when reporting their experience treating 34 patients over 30 years.[14] Others have suggested using a 3-5 cm margin of excision because of the potential risk of local recurrence and distant metastasis.[20] Narrow margin excision[13] and even Mohs micrographic surgery have also been used.[10, 11, 28] While several small case series using Mohs resection have been described, recurrences have been reported with long-term follow up. Heuther and colleagues reported a 14% incidence of recurrence when treating a spindle cell neoplasms of the skin such as cutaneous LMS with Mohs micrographic technique.[12]

Standardizing an appropriate margin of resection for cutaneous LMS should be a priority. For instance, in an analysis of 84 cases of atypical intradermal smooth muscle neoplasms, Kraft et al. identified that margin status was the most important predictor of recurrence.[19] In that series, 18 (21%) local recurrences were observed after initial excision (12 had positive margins, 1 had a close (< 0.2 cm) margin, 5 had unknown margins). Interestingly, no recurrences were observed when initial excisions were performed with negative margins. At our institution, we have attempted to standardize the surgical margin by taking at least a 1

cm margin at the time of resection. Early in the study period (2006-2009), resection margins were more variable ranging from 0.4-2.0 cm. Since 2010, we have more consistently utilized a resection margin of 1.0 cm for cutaneous LMS. This includes patients who undergo their initial excision at an outside facility with unknown margins and subsequent re-excision with a 1.0 cm margin after referral to our institution. More importantly, only 2 of the 33 patients in this series had microscopic positive margins after 1.0 cm resection. One was able to undergo further re-excision with an additional 1 cm margin to obtain negative margins and the other received adjuvant radiation. Although our follow up is short, thus far we have experienced no local recurrences.

The role of adjuvant therapy for cutaneous LMS has similarly remained unstandardized and largely anecdotal. Most institutions have reserved the use of adjuvant radiation and/or chemotherapy for the development of recurrence or distant metastasis.[6, 7] As previously mentioned, local recurrence reports after excision of cutaneous LMS range from 6-40%.[6, 7, 12, 19] Confounding this issue further, many series have included both cutaneous LMS and subcutaneous LMS in their series description making the interpretation of these recurrence rate results less clear. Jensen and colleagues, for instance, reported no incidences of recurrence after 5 years of follow up for purely intradermal LMS but 41% of those with subcutaneous origin metastasized and ultimately died of pulmonary metastases.[5] Fields et al similarly reported no distant metastases for those with cutaneous LMS whereas 4 of 12 patients with subcutaneous LMS eventually developed metastases and progressed to tumor-related death.[6] We have not observed distant metastases in any patient and no patient has received adjuvant chemotherapy. We administered adjuvant radiation on an individualized basis, in situations such as positive margins on final pathology with limited options for further resection or those larger cutaneous LMS with extensive subcutaneous extension. In situations of local recurrence development, some have suggested simple re-excision to be sufficient therapy. Kraft et al. noted that 10 of their 18 tumors with local recurrence were able to be re-excised to negative margins without further *additional* recurrence or metastasis. [19] They further surmised that because many of the patients treated in that series underwent initial excision at outside institutions and were referred to their center after the development of recurrence, that appropriate local therapy is most likely sufficient therapy to prevent recurrence.

Conclusions

In conclusion, cutaneous LMS is a low-grade malignancy that affects predominantly elderly male Caucasians in the lower extremities and head and neck. Immunohistochemistry may be utilized to confirm cutaneous LMS or rule out other spindle cell proliferations. Very good oncologic local control and favorable overall outcome are possible with a standardized 1 cm surgical margin of resection. The benefit of preoperative chest imaging and/or adjuvant radiation to the primary tumor site remains unknown in the setting of negative margins. The choice for adjuvant radiation should be individualized and we would recommend a multidisciplinary discussion of the need for adjuvant radiation in patients with larger tumors, persistently positive margins after multiple resections or those cutaneous LMS tumors with extensive subcutaneous extension.

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Figure 1.
Dermal leiomyosarcoma, showing fascicular growth of ovoid spindle cells with mild nuclear pleomorphism and mitotic activity (H&E, 200x)

Figure 2.
Dermal leiomyosarcoma demonstrating diffuse positivity for desmin (200x)

Figure 3.
Immunohistochemical Profile of the Tumor

Figure 4.
Surgical Margin of Resection for Cutaneous Leiomyosarcoma

Table 1

Clinical Characteristics of the Patients

Variable	N (%)
Age	63.5 (20-91)
Caucasian	32 (97)
Gender	
Female	8 (24)
Male	25 (76)
Location	
Cervical	9 (27)
Trunk	2 (6)
UE	7 (21)
LE	15 (46)
Biopsy Method	
Shave	16 (49)
Excision	11 (33)
Punch	6 (18)
Pre-operative Staging	
CXR	13 (39)
CT	14 (42)
PET	4 (12)
MRI Brain	3 (9)
MRI Extremity	5 (15)

Table 2

Histological Characteristics of the Tumors

Variable	N (%)
Median Tumor Size (range in cm)	1.30 (0.4-3.5)
Tumor Grade	
Low	29 (88)
High	4 (12)
Recorded Mitotic Activity	25 (76)
Number of Mitoses (range)	10 (1-58)
Atypical Mitotic Figures	8 (24)
Residual tumor after biopsy	20 (61)
Re-excision	3 (9)
Planned re-excision with AlloDerm	1
Positive margin after initial excision	1
Unknown resection margin at outside	1
Final Margin	
Negative	32 (97)
Positive	1 (3)

Table 3

Treatment and Outcome

Variable	N (%)
Surgical Margin	
1.0 cm	22 (67)
1.5 cm	4 (12)
2.0 cm	4 (12)
<1.0 cm (0.6 & 0.4 cm)	2 (6)
Unknown	1 (3)
Autologous Skin Graft	10 (30)
Full Thickness	5 (15)
Split Thickness	3 (9)
AlloDerm	2 (6)
Adjuvant Radiation	5 (15)
Positive margin (initial/final)	2
Multidisciplinary Recommendation	2
Cutaneous LMS with subcutaneous extension	1
Adjuvant Chemotherapy	0
Recurrence	0
Complication	3 (9)
Non-healing wound	1
Cellulitis	1
Self-limiting facial asymmetry after resection	1
Length of Follow Up in months (median, range)	15.5 (2-49)
Follow Up Status	
NED	33 (100)