ANTICANCER RESEARCH *40*: 5319-5325 (2020)
doi:10.21873/anticanres.14539

Clinical Outcome of Surgically Treated Leiomyosarcoma of the Extremities: A Retrospective Overview

ANNELIES VAN BEECK[1], MICHIEL VAN DE SANDE[2], VERONIEK VAN PRAAG[2], DIETMAR DAMMERER[3], JOZEF MICHIELSEN[1], THOMAS SCHUBERT[4], BILAL KAPANCI[5], FELIX SHUMELINSKY[5], JOHAN SOMVILLE[1] and SANDER DIJKSTRA[2]

[1]*University Hospital Antwerp, Antwerp, Belgium;*
[2]*LUMC Leiden, Leiden, the Netherlands;*
[3]*Medical University of Innsbruck, Innsbruck, Austria;*
[4]*Cliniques Universitaires Saint-Luc, Service d'Orthopédie et de Traumatologie de l'Appareil Locomoteur, Brussels, Belgium;*
[5]*Chirurgie Orthopédique – Traumatologie, Clinique des Tumeurs Conjonctives et Osseuses, Institut Jules Bordet, Brussels, Belgium*

Abstract. *Aim: This study was interested in extremity leiomyosarcoma with focus on clinical outcome after surgery with or without adjuvant therapy. Patients and Methods: A retrospective case series of all patients with leiomyosarcoma, surgically treated between 2000 and 2015 and a minimum follow-up of 2 years, was drawn from institutional databases in Belgium and the Netherlands. Postoperative complications were reported with the Radiation Therapy Oncology Group (RTOG) and the Henderson classification. Results: Seventy-five patients were operated on, of whom 47 underwent (neo)adjuvant therapy. Infection was observed in 11 patients, seven associated with (neo)adjuvant radiotherapy. Dermatological complaints were observed in 26 patients, 10 associated with (neo)adjuvant radiotherapy. Overall survival was 60%. Local recurrence occurred in 11 (15%) patients. Conclusion: This study describes favourable clinical outcome following (neo)adjuvant radiotherapy. In the future, larger databases on leiomyosarcoma should enhance the power of these findings and define the benefits of adjuvant therapy in leiomyosarcoma.*

Leiomyosarcoma is a rare malignant tumour that can originate in the soft tissue or bones. It most frequently occurs in the middle aged to older population (50-70 years). Leiomyosarcomas of the soft tissue preferentially occur in the retroperitoneum and the great blood vessels (*i.e. vena cava*) and are divided into three groups: Uterine, abdominal (retroperitoneum and gastro-intestinal) and non-visceral (somatic) (1). In the limbs, leiomyosarcoma accounts for 2-10% of all soft-tissue tumours. They can also arise from bone but this is even rarer (1-4).

This study focused on leiomyosarcoma located in the limbs (extremity leiomyosarcoma (eLMS). In such cases, the depth can vary from (sub)cutaneous to intramuscular and the neoplasm can even infiltrate the bone. In general, it presents as a (small) local mass, without initial symptoms. However, the tumour can compromise vital structures when expanding, resulting in pain, neurological deficit and limb oedema (3, 5, 6).

Magnetic resonance imaging (MRI) generally shows an isointense (T1), hypointense (T2) or hyperintense (T2 with fat suppression) lesion with common relation to neurovascular structures. Depending on its aggressivity, it can appear to be inhomogeneous due to necrosis or display central bleeding. Its presence can be well-circumscribed or infiltrative with the surrounding tissue (7).

Histopathology is very characteristic, showing intersecting, dense groups of spindle cells. Most tumours present as highly cellular, although sections with fibrosis and myxoid tissue can occur, especially in large tumours (5).

Immunocytology is positive for desmin, smooth muscle actin and H–cadesmin, however these are not specific for leiomyosarcoma (5). Candidate genes on chromosomes 1, 5, 12, 17, 20 were investigated and found to have with possible correlation with leiomyosarcoma (5).

For treatment of eLMS there are multiple modalities. Surgery is often combined with (neo)adjuvant chemo- and radiotherapy (RT), with the intent to increase local control and overall survival while maintaining limb function (8, 9).

Correspondence to: Annelies Van Beeck, MD, Consultant Orthopaedic Traumatology and Musculoskeletal Oncology, University Hospital of Antwerp, Wilrijkstraat 10, 2650 Edegem, Belgium. Mob: +32 472596736, e-mail: annelies.vanbeeck@gmail.com

Key Words: Leiomyosarcoma, extremity, soft-tissue sarcoma, oncologic, clinical outcome, sarcoma, surgical.

In this multicentre retrospective, study our aims were to evaluate (i) mid- to long-term event-free survival, (ii) complications related to multimodality treatment, and (iii) functional outcome in relation to the treatment modalities for a population of patients with isolated eLMS.

Patients and Methods

Using institutional databases from four reference centres, we retrospectively studied consecutive patients with primary eLMS who were surgically treated between 2000 and 2015, with a minimum follow-up of 2 years or who experienced an event before 2 years of follow-up.

Patients were recruited from institutional databases from University Hospital Antwerp (n=7), Leiden University Medical Centre (n=39), Institut Jules Bordet (n=25) and Cliniques Universitaires Saint-Luc (n=4). Inclusion criteria were: Surgical resection with curative intent, and histopathological confirmation of eLMS. Exclusion criteria were retroperitoneal and uterine leiomyosarcoma.

The following items were investigated: Tumour location, depth (subcutaneous- subfascial), grade [Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC)] (10), size (cm), surgical margins (R0-2) (11), additional therapy (chemo-/radiotherapy) and complications (*e.g.* postoperative pain, biomechanical complaints, dermatological problems, wound healing and infections).

Clinical outcome was documented at every follow-up visit according to European Society for Medical Oncology guidelines: Local recurrence (yearly MRI) and metastases, especially in the lung, with chest radiographs every 3 months for the first 2 years, every 6 months until 5 years and then annually (12).

With regard to diagnostic work-up, all patients underwent local MRI with gadolinium, biopsy, computed tomography of the chest/positron-emission tomography–computed tomography. Seventy-five patients were eligible for the study; of these, 45 (60%) were alive at final review after a median follow-up of 74 months.

Pleomorphic, myxoid, dedifferentiated, poorly differentiated or no further specification subtypes are described in the literature. In our population a great variety was present. The most common type in our study was pleomorphic (30.2%) (Table I).

Statistical analysis. To avoid any kind of bias and misinterpretation of the data, an independent statistician and Author of this study carried out the statistical analysis. A Mann–Whitney *U*-test was used to compare the quantitative variables. Chi-square test was used for categorical variables. All time-to-event endpoints were calculated using the Kaplan–Meier method. Log-rank test was used to compare the survival distributions. A two-tailed probability value of less than 0.05 was considered statistically significant. Statistical analyses were performed using SPSS, version 24.0 (IBM, Armonk, NY, USA).

Results

At the time of diagnosis, the average age of the included patients was 63 (range=33-94) years. There was equal distribution between male (n=42) and female (n=33) (1.3:1) patients. The mean follow-up duration was 4 (range=0-15) years. Because of postoperative complications (sepsis n=1; perioperative bleeding n=1) follow-up was sometimes only a few days; these two patients were excluded from further analysis. The median tumour size was 9.7 cm (standard deviation=5.0, range=1.0-22.0 cm) (Table I). Sub-fascial location was given in 54 patients; 25 patients had accompanying metastasis, which in 18 patients were located in the lungs. However, invasion of lymph nodes (n=3), bone (n=4), kidney (n=3), liver (n=2), retroperitoneum (n=1) was also reported.

Surgical resection with intended free margins was the most common treatment (n=58; superficial in 14, deep in 44): R0, R1 or R2 were achieved in seven (three superficial, four deep), 27 (five superficial, 22 deep) and 24 (six superficial, 18 deep) patients, respectively. Amputation was performed in 11 patients (Table I). In six (8%) patients, it was not possible to retrieve the type of resection from the medical records. Reconstruction was performed with endoprosthesis in three patients, inlay allograft in one patient and seven patients underwent soft-tissue reconstruction (*i.e.* split skin graft in three, vascular bypass in three and musculocutaneous flap in one).

Table I. *Baseline characteristics and treatment modalities*.

Baseline characteristic		Value
Age, years	Median (range)	63 (33-94)
Gender	Male	42 (56)
	Female	33 (44)
Tumour size at diagnosis, cm	Median (range)	9.7 (1-22)
Location, n (%)	Upper limb	14 (19)
	Lower limb	61 (81)
Depth, n (%)	Superficial	21 (28)
	Intramuscular	54 (72)
FNCLCC grade, n (%)	1	4 (5)
	2	22 (29)
	3	48 (64)
	Not specified	1 (1)
Treatment, n (%)		
Surgery	Amputation	11 (15)
	Wide	24 (32)
	Marginal	27 (36)
	Intralesional	7 (9)
	Unknown	6 (8)
Adjuvant therapy	Yes	1 (1)
Neoadjuvant ChT	No	74 (99)
	Missing data	0
	Yes	7 (9)
Neoadjuvant RT	No	68 (91)
	Missing data	0
	Yes	16 (21)
Adjuvant ChT	No	59 (79)
	Missing data	0
	Yes	32 (43)
Adjuvant RT	No	42 (56)
	Missing data	1 (1)

FNLCC: Fédération Nationale des Centres de Lutte Contre le Cancer; ChT: chemotherapy; RT: radiotherapy.

(Neo)adjuvant therapy was administered to 47 (63%) patients. The most common adjuvant therapy was radiotherapy (RT) (n=32; 43%), followed by adjuvant chemotherapy (n=16; 21%), neoadjuvant RT (n=7; 9%) and finally neoadjuvant chemotherapy (n=1; 1%). For neoadjuvant RT, a standard dose of 50 Gy (25×2 Gy) was given. For adjuvant RT, the dose was higher, at an average of 60 Gy, with a different distribution during therapy (higher dosage at the beginning of treatment.)

Multimodality therapy (adjuvant RT and adjuvant chemotherapy) was administered to 11 (15%) patients. Chemotherapy included doxorubicin alone or in combination with ifosfamide, adriamycin or etoposide. In this study, trabectedin was used once as a palliative treatment.

Eleven (15%) patients were diagnosed with local recurrence after a median time of 28 (range=6-96) months. Kaplan–Meier analysis showed a significant influence of adjuvant chemotherapy on local recurrence (Mann-Whitney *U*-test, $p=0.006$).

Metastasis appeared in 30 (40%) patients. Overall, 20 (27%) patients had metastasis at a median of 16 (range=0-93) months.

Multiple metastases at presentation were seen in six (8%) patients. Within short-term follow-up (≤2 years), metastases were diagnosed in 22 (29%) patients in the following locations: Lung in 17, lymph nodes in three, renal vein in one, liver in one, and bone in two. At long-term follow-up (>2 years) other patients presented with metastases in lung in three, lymph nodes in one, bone in two, neck in one, retroperitoneum in one, and liver in one. Multiple metastases were present in eight (17%) patients and led to a significant reduction in overall survival (Figure 1).

There were 30 (40%) mortalities, 21 (21/75; 28%) of which were due to the progression of leiomyosarcoma. One patient had a perioperative complication needing an amputation, which was refused by the patient. The patient consequently died less than 24 h later. Another patient died of postoperative infection. These patients were excluded from further analysis. For the remaining seven patients, the cause of death could not be determined from the medical records.

The literature shows negative predictive factors for survival and recurrence in extremity soft-tissue sarcomas to be tumour size (>5 cm), grade (FNCLCC classification (26) and depth (superficial versus deep). These factors were also analysed in the current study (Figure 2). Patients with primary non-metastatic eLMS were selected for evaluation of these risk factors. No significant difference in overall survival or local recurrence was observed for these risk factors. Margins themselves were negatively associated with local recurrence (Figure 3), however, not with overall survival. In that regard, tumour grade is more important (13).

Complications that were analysed are shown in Table II. Postoperative pain was described in 12 patients. Functional complaints were voiced by one patient with soft-tissue reconstruction after resection. Postoperative infection was observed in 11 (15%) patients. Of these 11 patients seven received (neo)adjuvant, six adjuvant and one neoadjuvant RT. Dermatological symptoms (*i.e.* dermatitis or superficial burns), nearly all temporary, were seen in 26 (35%) out of 75 patients, in 10 of whom this was during and after adjuvant RT in 32 (10/32, 31%) (Table III).

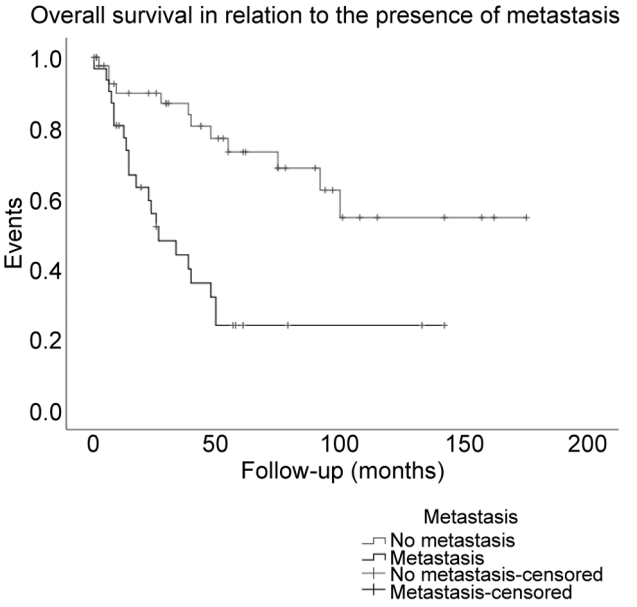

Figure 1. *Overall survival function according to distal metastasis ($p<0.05$).*

Discussion

To the best of our knowledge, to date no study has described the oncological and clinical outcome of eLMS. We thus attempted to answer the question whether they behave differently than other soft-tissue sarcomas and whether treatment or follow-up should be altered.

At the four centres, a resection with wide margins was the first treatment goal. However, this was not always achievable due to tumour size and adjacent neurovascular structures. For the purpose of limb salvage, a marginal to intralesional resection with or without reconstruction of soft tissue, vascular bundle or replacement with artificial joint was considered the best treatment possibility. This depended on the presence of distant metastases at presentation, the patient's age and tumour location. In a small percentage of the cases where the neurovascular bundle was involved by the tumour, amputation was the only surgical solution with intent for cure. During the study period, the incorporation of (neo)adjuvant therapy became more and more the standard

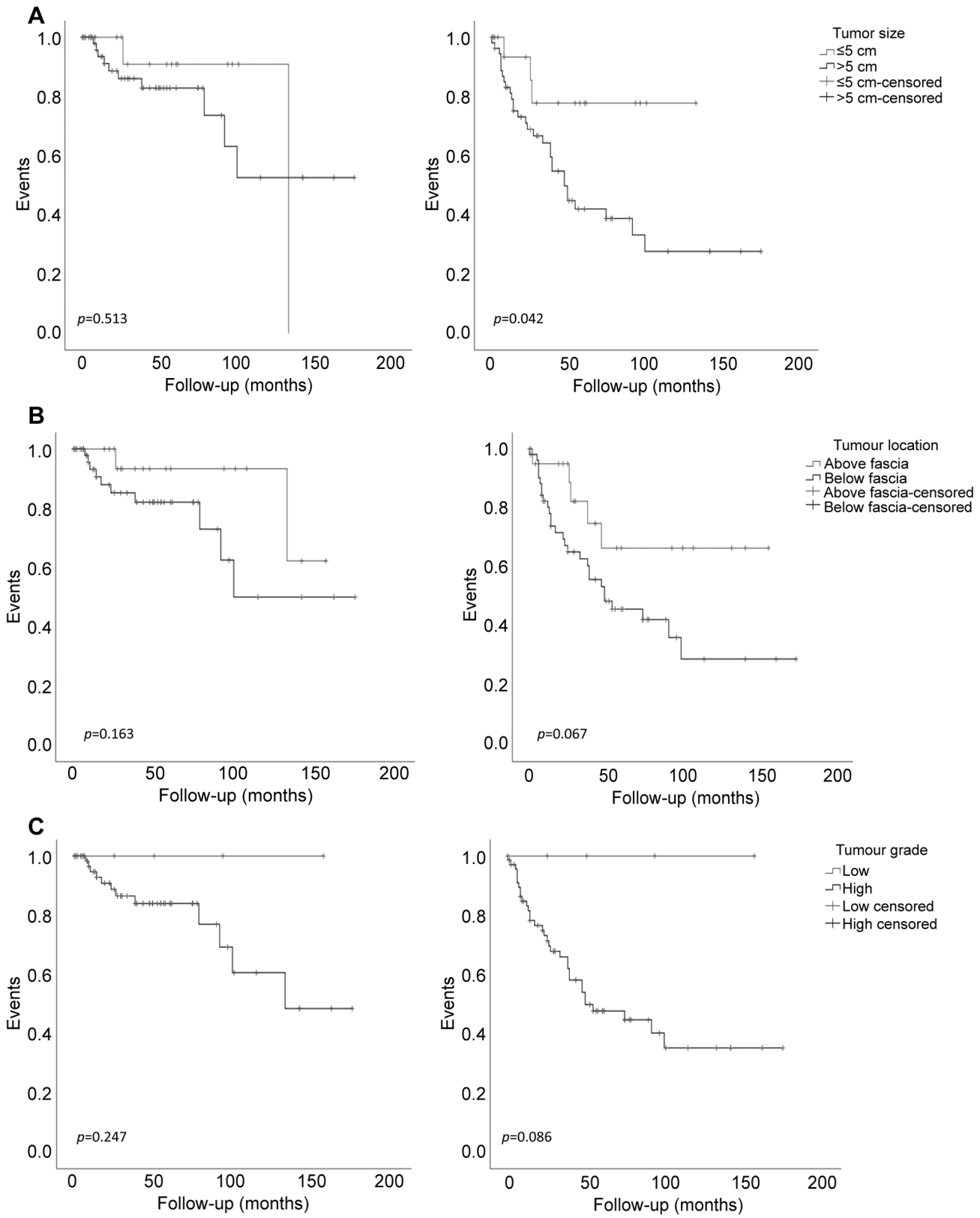

Figure 2. *Local recurrence (left) and survival (right) according to tumour size (cut-off 5 cm) (A), location in regard to fascia (above versus below) (B), and according to Fédération Nationale des Centres de Lutte Contre le Cancer tumour grade (Grade: Low: 1; high: 2-3) (C).*

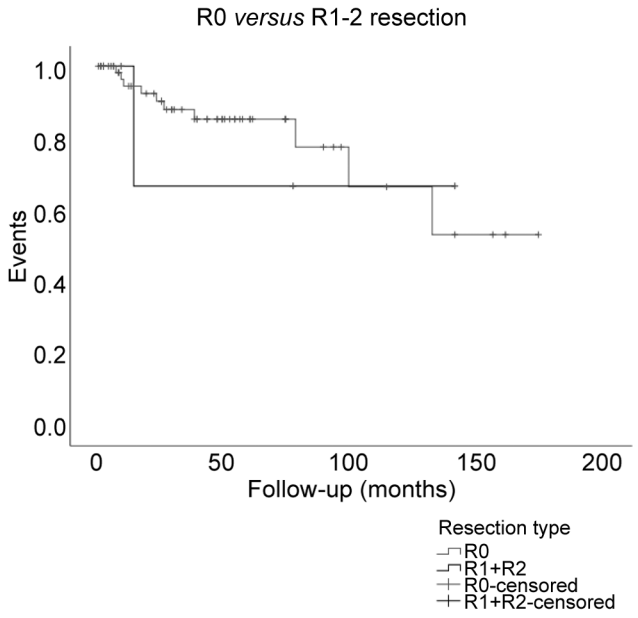

Figure 3. *Influence of resection type on local recurrence/local control (R0 versus R1-2 resection). No significant difference was found.*

Table II. *Multiple and variable location of metastasis.*

Median follow-up time to metastasis (range), months	16 (0-92)
Number of patients	30
Location, n (%)	
Multiple	8 (27%)
Lung	20 (67%)
Bone	6 (20%)
Lymph nodes	4 (13%)
Liver	3 (10%)
Kidney	2 (7%)
Adrenal gland	1 (3%)
Retroperitoneum	1 (3%)
Brain	1 (3%)
Neck	1 (3%)
Unknown	7 (23%)

of therapy. (Neo)adjuvant RT particularly gained popularity in the multimodality treatment of eLMS in our study population. A review of the literature showed that the initial idea, namely creating a proper wide resection with free tumour margins, is mandatory for the best chance for survival (8); this has been discussed anew and over-ruled (1, 14). Positive surgical margins give less local control but were described by Harati *et al*. as being of no significant influence in overall survival and dissemination (1). Regarding these findings, other factors for overall survival must be of more importance than local control. Harati *et al*. stated for eLMS, head, neck and the trunk wall that histological grade was a significant prognostic factor for local recurrence and disease-free survival and was associated with tumour size and depth (1). Our study agrees with these results, however, only the size of the tumour led to a significant difference in survival.

As mentioned, (neo)adjuvant therapy is more often combined with surgery to obtain better local control. Given the current literature, data on (neo)adjuvant therapy, especially RT, in eLMS are limited and therefore clinical outcome post-radiation was documented in this study using the Radiation Therapy Oncology Group classification (1, 9, 14, 15). Although acute postoperative complications due to neoadjuvant RT often lead to second operations such as wound debridement and flap reconstruction, in the long-term, fewer surgical complications but more RT-associated disabilities occur. In the case of neoadjuvant RT, less fibrosis and subcutaneous necrosis is seen since better planning is possible and the tumour is easier to delineate (9). This was confirmed in our study, where wound infection and dermatitis were the most common complications, both non-significant, following surgery combined with neoadjuvant RT. These symptoms mostly presented in the acute setting and did not cause significant discomfort in the long term.

(Neo)adjuvant chemotherapy is less often combined with RT in the treatment of leiomyosarcoma. Our study had only one patient who received neoadjuvant chemotherapy without RT. Therefore, the possible effects of neoadjuvant chemotherapy remain under discussion for both eLMS and other soft-tissue sarcomas of the extremities. High-grade, deep and large (>5 cm) soft-tissue sarcomas are regarded as possible candidates for chemotherapy, although benefits and toxicity are not yet in perfect equilibrium (16, 17). A recent meta-analysis confirmed that conventional chemotherapy does not contribute to better overall survival and therefore chemotherapy is generally not used for such tumours (18). The best-known chemotherapy is the combination of the anthracyclines doxorubicin and ifosfamide (16, 17). Gronchi *et al*. compared the use of histiotype-tailored chemotherapy (gemcitabine and carbazapine for leiomyosarcoma) with standard chemotherapy. No significant difference in overall survival was seen, with doses in both groups needing to be reduced due to toxicity (16).

A new adjuvant treatment is trabectedin, a novel agent that prolongs survival, especially in patients with uterine leiomyosarcoma. This angiogenesis inhibitor has been reported to induce more response in tumours with loss of expression of breast cancer 1 (BRCA1), *e.g*. breast cancer. Uterine leiomyosarcoma also shows a loss of expression of BRCA1 and therefore good results (19). This association has not yet been described for non-visceral tumours. However, Galizia *et al*. published a case report on a leiomyosarcoma

Table III. *Postoperative complications of (neo)adjuvant radiotherapy.*

	General			Adjuvant radiotherapy			Neoadjuvant radiotherapy		
Postoperative complication	n (%)	Total, n	Missing data, n	n (%)	Total, n	Missing data, n	n (%)	Total, n	Missing data, n
Infection	11 (15%)	73	2	6 (19%)	31	3	1 (17%)	6	2
Skin (dermatitis)	29 (39%)	75	0	12 (39%)	31	2	4 (57%)	7	1
Biomechanical limits	2 (3%)	73	2	0 (0%)	11	0	0 (0%)	7	2
Pain	13 (18%)	73	2	5 (17%)	30	4	1 (17%)	6	3

of the thigh with lung metastasis, where stable disease was achieved for 17 months (20). Further investigation is needed to determine systemic possibilities for the treatment of (metastatic) leiomyosarcoma not originating from the uterus. This remains a challenge for future investigations of leiomyosarcoma and soft-tissue sarcomas in general. If proper treatment can be administered, this might contribute to a reduction in distal metastasis and therefore improve overall survival.

When reviewing the literature, other studies were seen to have obtained significant results concerning tumour behaviour and association with histological grade of leiomyosarcoma (1, 21). Harati *et al*. confirmed that the resection margin is not significant as compared to the tumour grade, location and size (1). A deeper and larger tumour confers a poorer outcome, certainly when its histological grade is higher (1, 21).

For the time being, patient-specific treatment of eLMS is the priority because patients often present at higher age and with associated comorbidities. These patient characteristics are of major importance in custom tailoring the best treatment, for example, avoiding the risk of RT in a patient with diabetes and venous deficiency.

Limitations of this study are its retrospective nature and the small study population. The retrospective nature contributed to the difficulty experienced in obtaining all necessary information since medical files were not digitised before 2007. This can be avoided in future studies.

In conclusion, soft-tissue sarcomas and eLMS remain a challenge to treat. As for many pathologies, the treatment has undergone considerable evolution over the years and more possible treatment modalities are yet to come. Whether eLMS behave much differently than other soft-tissue sarcomas of the extremities with regard to known risk factors, treatment outcome, and survival is not clearly known. Retrospective studies analysed soft-tissue sarcomas of the extremities in general, with eLMS as a possible diagnosis. In that respect, some risk factors are of importance in predicting local recurrence or overall survival (13). New treatment options are continuously being investigated to improve overall survival and local control. Systemic, immuno-, and targeted therapy have to prove their efficacy in addition to generally used (neo)adjuvant radiotherapy.

Conflicts of Interest

There were no conflicts of interest to declare.

Authors' Contributions

Annelies Van Beeck: Principal investigator, study design, study protocol, data collecting, writing, and editing. Michiel Van de Sande: Study design, study protocol, writing, proof reading and editing. Veroniek Van Praag: Data collecting, proofreading. Jozef Michielsen: Data collecting, proof reading. Dietmar Dammerer: Interpreting data, statistics, revising and proofreading. Thomas Schubert: Data collecting. Bilal Kapanci: Data collecting. Felix Shumelinsky: Data collecting. Johan Somville: Data collecting. Sander Dijkstra: Critical revising, supervision, proofreading.

References

1 Harati K, Daigeler A, Lange K, Niggemann H, Stricker I, Steinau HU, Lehnhardt M and Goertz O: Somatic leiomyosarcoma of the soft tissues: A single-institutional analysis of factors predictive of survival in 164 patients. World J Surg *41(6)*: 1534-1541, 2017. PMID: 28116485. DOI: 10.1007/s00268-017-3899-5

2 Landry MM, Sarma DP and Boucree JB, Jr.: Leiomyosarcoma of the buttock. J Am Acad Dermatol *24(4)*: 618-620, 1991. PMID: 2033140.

3 Bibbo C and Schroeder M: Review of vascular leiomyosarcoma and report of a case localized to the greater saphenous vein of the ankle. J Foot Ankle Surg *50(3)*: 329-335, 2011. PMID: 21435912. DOI: 10.1053/j.jfas.2011.01.002

4 Sasaki T, Kawashima H, Ariizumi T, Yamagishi T, Oike N, Umezu H, Inagawa S, Hotta T, Endo N and Ogose A: Denosumab as a potential therapeutic option for leiomyosarcoma with osteoclast-like giant cells: A case report. Mol Clin Oncol *8(1)*: 30-33, 2018. PMID: 29387393. DOI: 10.3892/mco.2017.1489

5 Fletcher CD, Unni KK and Mertens F: Pathology and genetics of soft tissue and bone. WHO Classification of Tumours, 3rd Edition, Volume 5, 2002.

6 Reix T, Sevestre H, Sevestri-Pietri MA, Szychta P and Pietri J: Primary malignant tumors of the venous system in the lower extremities. Ann Vasc Surg *12(6)*: 589-596, 1998. PMID: 9841691.

7 O'Sullivan PJ, Harris AC and Munk PL: Radiological imaging features of non-uterine leiomyosarcoma. Br J Radiol *81(961)*: 73-81, 2008. PMID: 17681989.

8 Erinanc H, Ozulku M and Terzi A: Recurrence of primary vascular leiomyosarcoma five years after initial diagnosis in the lower extremity. Case Rep Oncol Med *2018*: 3094616, 2018. PMID: 29971175. DOI: 10.1155/2018/3094616

9 Levy A, Bonvalot S, Bellefqih S, Vilcot L, Rimareix F, Terrier P, Belemsagha D, Cascales A, Domont J, Mir O, Honore C, Le Cesne A and Le Pechoux C: Is preoperative radiotherapy suitable for all patients with primary soft tissue sarcoma of the limbs? Eur J Surg Oncol *40(12)*: 1648-1654, 2014. PMID: 25130960. DOI: 10.1016/j.ejso.2014.06.014

10 Coindre JM: Histologic grading of adult soft tissue sarcomas. Verh Dtsch Ges Pathol *82*: 59-63, 1998. PMID: 10095417.

11 Gundle KR, Kafchinski L, Gupta S, Griffin AM, Dickson BC, Chung PW, Catton CN, O'Sullivan B, Wunder JS and Ferguson PC: Analysis of margin classification systems for assessing the risk of local recurrence after soft tissue sarcoma resection. J Clin Oncol *36(7)*: 704-709, 2018. PMID: 29346043. DOI: 10.1200/JCO.2017.74.6941

12 Henderson ER, O'Connor MI, Ruggieri P, Windhager R, Funovics PT, Gibbons CL, Guo W, Hornicek FJ, Temple HT and Letson GD: Classification of failure of limb salvage after reconstructive surgery for bone tumours: A modified system including biological and expandable reconstructions. Bone Joint J *96-B(11)*: 1436-1440, 2014. PMID: 25371453. DOI: 10.1302/0301-620X.96B11.34747

13 van Praag VM, Rueten-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 *83:* 313-323, 2017. PMID: 28797949. DOI: 10.1016/j.ejca.2017.06.032

14 Gladdy RA, Qin LX, Moraco N, Agaram NP, Brennan MF and Singer S: Predictors of survival and recurrence in primary leiomyosarcoma. Ann Surg Oncol *20(6)*: 1851-1857, 2013. PMID: 23354568. DOI: 10.1245/s10434-013-2876-y

15 Svarvar C, Bohling T, Berlin O, Gustafson P, Folleras G, Bjerkehagen B, Domanski HA, Sundby Hall K, Tukiainen E, Blomqvist C and Scandinavian Sarcoma Group Leiomyosarcoma Working Group: Clinical course of nonvisceral soft tissue leiomyosarcoma in 225 patients from the Scandinavian Sarcoma Group. Cancer *109(2)*: 282-291, 2007. PMID: 17154171.

16 Gronchi A, Ferrari S, Quagliuolo V, Broto JM, Pousa AL, Grignani G, Basso U, Blay JY, Tendero O, Beveridge RD, Ferraresi V, Lugowska I, Merlo DF, Fontana V, Marchesi E, Donati DM, Palassini E, Palmerini E, De Sanctis R, Morosi C, Stacchiotti S, Bague 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

17 Pasquali S, Palassini E, Stacchiotti S, Casali PG and Gronchi A: Neoadjuvant treatment: A novel standard? Curr Opin Oncol *29(4)*: 253-259, 2017. PMID: 28607580. DOI: 10.1177/1758834017705588

18 Istl AC, Ruck JM, Morris CD, Levin AS, Meyer CF and Johnston FM: Call for improved design and reporting in soft tissue sarcoma studies: A systematic review and meta-analysis of chemotherapy and survival outcomes in resectable STS. J Surg Oncol *119(7)*: 824-835, 2019. PMID: 30737793. DOI: 10.1002/jso.25401

19 Xing D, Scangas G, Nitta M, He L, Xu X, Ioffe YJ, Aspuria PJ, Hedvat CY, Anderson ML, Oliva E, Karlan BY, Mohapatra G and Orsulic S: A role for BRCA1 in uterine leiomyosarcoma. Cancer Res *69(21)*: 8231-8235, 2009. PMID: 19843854. DOI: 10.1158/0008-5472.CAN-09-2543

20 Galizia D, Palesandro E, Nuzzo AM, Pignochino Y, Aliberti S, Aglietta M and Grignani G: Prolonged disease stability with trabectedin in a heavily pretreated elderly patient with metastatic leiomyosarcoma of the thigh and renal failure: A case report and review of the literature. Oncol Res *20(10)*: 483-490, 2013. PMID: 24308159.

21 Abraham JA, Weaver MJ, Hornick JL, Zurakowski D and Ready JE: Outcomes and prognostic factors for a consecutive case series of 115 patients with somatic leiomyosarcoma. J Bone Joint Surg Am *94(8)*: 736-744, 2012. PMID: 22517390. DOI: 10.2106/JBJS.K.00460

Received July 23, 2020
Revised August 24, 2020
Accepted August 25, 2020