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Long-term Outcome of 181 Patients With Liposarcomas of the Extremity and Truncal Wall

OLE GOERTZ[1,2], ANDREAS PIEPER[1], HENRIK LAUER[1,2], INGO STRICKER[3], MEHRAN DADRAS[1], BJÖRN BEHR[1], MARCUS LEHNHARDT[1] and KAMRAN HARATI[1]

[1]*Department of Plastic Surgery, BG-University Hospital Bergmannsheil, Bochum, Germany;*
[2]*Department of Plastic Surgery, Martin-Luther Hospital, Berlin, Germany;*
[3]*Institute of Pathology, Ruhr-University Bochum, Bochum, Germany*

Abstract. *Background/Aim: Liposarcomas (LS) are one of the most common entities within the heterogenous group of soft tissue sarcomas. The aim of this study was to identify prognostic indicators in patients with LS of the extremities and truncal wall. Patients and Methods: We analysed the influence of potential prognostic factors on local recurrence-free survival (LRFS) and overall survival (OS) in 181 patients who were suitable for surgical treatment with curative intent. Results: The median follow-up period was 7.1 years. The 5-year LRFS and OS rates were 79.1 and 93.3%. The 5-year OS rate was 94.7% in patients with R0-resected primary tumors and 72.7% in patients with R1/R2-status (p=0.023). In multivariate analysis, only histologic grade was found to be an independent prognostic factor of OS. Conclusion: Negative margins were not an independent prognostic factor in our series. Tumor biology reflected by histologic grade dictated the outcome.*

Soft tissue sarcomas (STS) are a rare and heterogenous group of malignant tumors with an incidence rate of 6 per 100,000 inhabitants per year (1). Here, liposarcomas (LS) are the most common sub-entity comprising about 20% of all STS (2, 3). The peak incidence is at 55 years and men are more frequently affected than women (3). In accordance to other STS, LS can occur throughout the body, but about 60% of all LS are located in the deep soft tissues of the upper legs (3, 4).

Histologically, LS can be divided into well-differentiated, dedifferentiated, myoid/round cell and pleomorphic subsets (5). In all patients with localized LS without simultaneous metastases, the mainstay of therapy is limb-sparing surgical resection with negative margins (6, 7). Due to their rarity, there have been only few studies that have exclusively analysed prognostic factors and the role of surgical margins in patients with LS (3, 8-11). Most of them also included patients with retroperitoneal LS, although this subgroup has a different oncological behavior than somatic LS, occurring in the extremities and the truncal wall (12-15).

Regarding surgical treatment, negative margins have been determined to be an important factor for improving overall survival and local control in STS, in general (7, 16-18). However, the attainment of negative margins in the extremities and the truncal wall is often difficult and can lead to notable functional impairment. The aim of this study was to assess the clinical behavior of extremity and truncal wall LS. In particular, we focused on the prognostic impact of surgical margins and negative surgical margin widths in patients with microscopically clear margins.

Correspondence to: Dr. Kamran Harati, Department of Plastic Surgery, BG-University Hospital Bergmannsheil, Buerkle-de-la-Camp-Platz 1, Bochum, D-44789, Germany. Tel: +49 2343023445, Fax: +49 2346379, e-mail: kamran.harati@t-online.de

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Patients and Methods

Patients. Between 1996 and 2017, 181 patients with primary LS of the extremities and truncal wall were treated surgically with curative intent at the BG-University Hospital Bergmannsheil Bochum. Patients with simultaneous distant metastases or chemotherapy were excluded to maintain a homogenous cohort. The analyses were restricted to patients for whom we had full information on the outcome. Patient follow-up information was obtained from our database, medical records and patient correspondence. The local ethics committee approved the study.

Treatment. All patients were treated surgically with a curative intent. The goal was the achievement of negative margins wherever feasible. A negative margin of one fascial layer was intended in patients with epifascial tumors. The indication for adjuvant radiotherapy was given by our tumor board or the tumor boards of the referring institutes. All patients usually underwent a follow-up management which included chest X-rays and MRIs every three months in the first two years after resection. Afterwards, the follow-up examinations were conducted every six months for three more years.

Histopathological classification. The tumors were diagnosed and classified using the guidelines of the French Federation of Cancer Centres and the World Health Organisation (5, 19). An experienced soft tissue pathologist analysed all specimens. To assess the surgical margins, all resected tumors were fixated with formalin and the tumor surface was dyed with ink.

Statistical analysis. In this retrospective analysis, we determined the prognostic influence of several patient-, tumor- and treatment-related factors. The overall survival (OS) was the time between resection of the primary tumor to the date of death from any cause or the end of follow-up. The local recurrence-free survival (LRFS) was defined as the time period between resection of the primary tumor to the date of local recurrence or end of follow-up in recurrence-free patients. The Kaplan-Meier method was used to estimate all survival rates including 95% confidence intervals (CIs). The survival rates were compared via univariate log-rank test. Variables that reached $p<0.1$ in the univariate analysis were included in the multivariate analysis to assess potential independent prognostic factors. Multivariate analyses were conducted using the Cox hazards model. The data analysis was performed using the statistical program Stata (Version 11.2, StataCorp, College Station, TX, USA).

Results

Follow-up and patient characteristics. The median follow-up time was 7.1 years after resection of the primary tumor. The median age was 57.0 years (range=17.8-86.3 years). There were 83 female (45.9%) and 98 male (54.1%) individuals. The histologic grading of the tumors was G1 in 92 cases (50.8%), G2 in 58 (32.0%) and G3 in 31 (17.1%). In total, 42 patients (23.2%) had one or more local recurrences, whereas 25 patients (13.8%) developed distant metastases.

Treatment characteristics. A total of 170 patients (93.9%) were resected with microscopically negative margins (R0) in one or more surgical steps. 6 patients (3.3%) were left with microscopically positive margins (R1) and 5 (2.8%) with macroscopically positive margins (R2). In patients with positive margins, the tumors were locally too advanced for complete re-resection or further surgical treatment would have led to major functional impairment which was not accepted by the patients.

Adjuvant radiotherapy was performed in 52 patients (28.7%) after surgical removal of their primary tumor. The median overall dose was 60.0 Gray (range=32.0–74.0 Gray).

Univariate analysis of LRFS. The 5-year rate of LRFS was 79.1% (95%CI=71.3-84.9) for the entire cohort (Table I). Patients treated with adjuvant radiotherapy tended to have a more favorable LRFS than patients whose primary tumors were not treated with radiotherapy [5-year LRFS: 86.8 (70.9-94.3) *vs*. 76.2 (66.7-83.4]), although the difference was not statistically significant in the univariate analysis ($p=0.157$). The surgical margin status did not have a statistically significant influence on LRFS (Figure 1). Moreover, the impact of the closest negative margin width was determined within the R0 cohort. It was available for 148 of the 170 R0-resected patients (87%). Here, univariate analysis of the categorized negative margin widths revealed that close and wide clear margins led to similar LRFS.

Univariate analysis of OS. The 5-years OS rate was 93.3% (95%CI=87.8-96.3) for the entire series. Histologic grade, tumor site and margin status were the factors that had a prognostic significance on OS in univariate analysis (Table II). Patients with high-grade G3 lesions had a significantly worse OS than patients with intermediate G2 or low-grade G3 tumors [5-year OS: G1 98.9% (92.2-99.8) *vs*. G2 93.5% (80.6-97.9) *vs*. G3 73.9% (50.4-87.5); $p<0.001$]. Truncal localization was associated with a significantly diminished OS compared with extremity lesions [5-year OS: Trunk 81.3% (52.5-93.5) *vs*. upper extremity 92.6% (73.5-98.1) *vs*. lower extremity 94.3% (86.9-97.6); $p=0.0381$]. Notably, tumor size and depth did not alter OS in univariate analysis. Patients with negative margins had a significantly more favorable OS than patients with positive margins [5-year OS: R0 95.1% (87.4-98.1) *vs*. R1/R2 89.9% (78.8-95.3); $p=0.023$] (Figure 2). Within the R0 subgroup, the clear margin width did not influence OS significantly. In contrast to our findings for LRFS, adjuvant radiotherapy of the primary tumor did not alter OS.

Multivariate analysis of LRFS and OS. Univariate analysis indicated that only the distribution of the histologic grade was significantly associated with LRFS ($p<0.1$) and, therefore, a multivariate analysis was not conducted for LRFS.In the univariate analysis for OS was significantly ($p<0.1$) associated with age, histologic grade, tumor site and margin status and included in the Cox model to assess independent prognostic factors for OS (Table III). Notably, only the histologic grade emerged as an independent prognostic factor for OS (Table III). This is because tumor site and margin status were dependent on the histologic grade. Tumors that could only be resected with positive margins were usually high-grade tumors and localized at the truncal wall.

Discussion

In the current study, we assessed the long-term outcome of 181 patients with primary LS of the extremities and the truncal wall. The estimated 5-year LRFS and OS rates were 79.1% and 93.3%, respectively. Most of the patients were

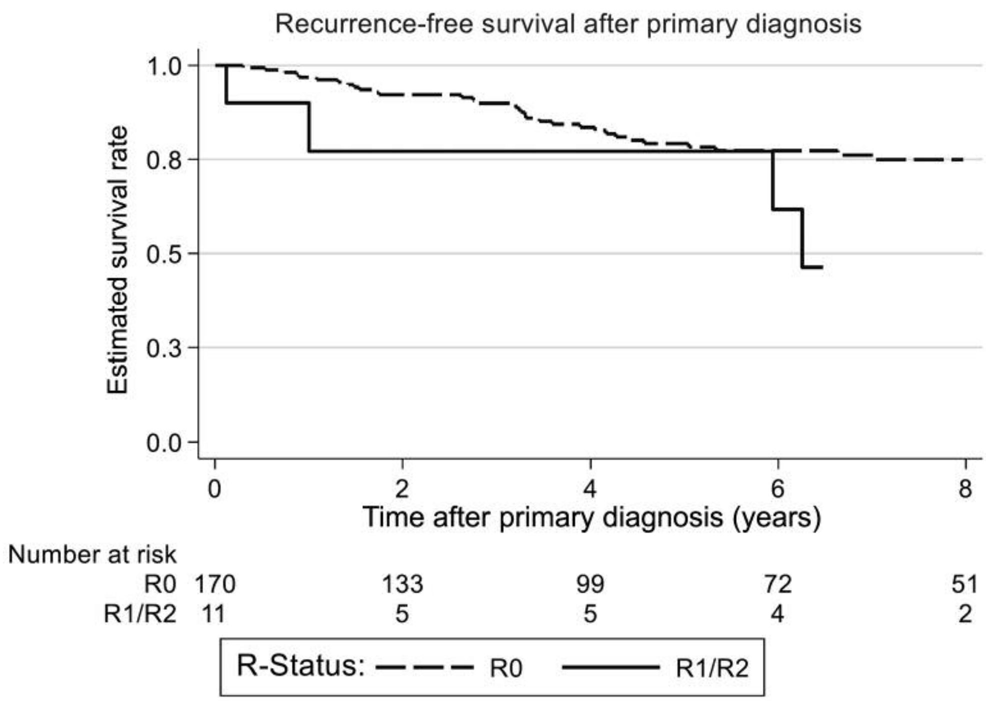

Figure 1. *Estimated Kaplan-Meier curves after primary diagnosis according to LRFS and surgical margin status.*

resected with microscopically negative margins (R0; 93.9%) and only 13.8% developed distant metastases during the median follow-up period of 7.1 years. In univariate analysis, we could only identify the histological grade as a significant predictor of LRFS whereas tumor site, histologic grade and surgical margin status emerged as statistically significant predictors of OS. However, in multivariate analysis only the histologic grade was found to be an independent prognostic factor of OS. This finding is in line with the results of almost all large retrospective studies on LS where the histologic grade dictated the disease outcome (3, 8, 11, 13, 20).

Following gastro-intestinal stroma tumors (GIST), LS are one of the most common subtypes within the heterogenous group of STS. Most of them occur within the extremities and have a relatively favorable disease outcome whereas about one third arise as retroperitoneal LS which exhibit a more aggressive behavior (3, 8). To date, there have been several retrospective studies on LS patients. The reported 5-year survival rates ranged from 75% to 92% (3, 10, 11, 20). However, the study cohorts are not comparable because of the different proportions of patients with low-grade lesions as well as patients with retroperitoneal LS. In the current study, patients with retroperitoneal LS were not included and many patients had with low-grade tumors (51%) which may be the reason why our series had a relatively high 5-year OS rate of 93.3%. The cohort of Dalal *et al*. also contained a high proportion of low-grade lesions (46%), but, in addition, included 33% retroperitoneal LS showed a 5-year survival rate of 83% for their whole series. Hence, a mere comparison of the retrospective analyses is not possible without considering the specific differences of patient cohorts.

One of the main purposes of the current study was to assess the prognostic impact of surgical margins. In univariate analysis, patients with negative margins had a significantly better 5-year OS rate than patients with positive margins (R0 95.1% *vs*. R1/R2 89.9%; p=0.023). However, in multivariate analysis surgical margin status failed to reach statistical significance as an independent prognostic factor of OS. Furthermore, no association between the quality of surgical margins and LRFS was found. Interestingly, the majority of the retrospective analyses on LS reported inconsistent results regarding the prognostic significance of surgical margins. In 2006, Dalal *et al*., from the Memorial Sloan-Kettering Cancer Center (MSKCC) in New York, assessed the outcome of 801 patients with LS arising in the whole body and could not determine any prognostic significance of microscopic surgical margins regarding survival (3). Only patients with macroscopic positive margins (R2) displayed a diminished survival, whereas patients with negative margins (R0) and microscopic positive margins (R1) had a similar outcome. This association has also been reported by two smaller studies involving 94 and 133 patients, respectively (8, 20). However,

Table I. *Results of the univariate analyses regarding LRFS.*

	N	No. of local recurrence	1-year LRFS (95%CI)	2-year LRFS (95%CI)	5-year LRFS (95%CI)	*p* (log-rank)
All patients	181	42	96.4 (92.2-98.4)	91.4 (85.9-94.8)	79.1 (71.3-84.9)	
Age (years)						
≤60	107	24	98.0 (92.3-99.5)	93.8 (86.7-97.2)	81.0 (70.7-87.9)	
>60	74	18	94.1 (84.9-97.7)	87.8 (77.1-93.7)	76.3 (63.0-85.3)	0.446
Gender						
Female	83	22	96.1 (88.5-98.7)	89.3 (79.8-94.5)	76.6 (64.5-85.0)	
Male	98	20	96.6 (89.9-98.9)	93.1 (85.3-96.8)	81.2 (70.1-88.5)	0.651
Tumor size						
≤5 cm	33	11	97.0 (80.4-99.6)	86.3 (67.4-94.7)	75.1 (54.5-87.3)	
>5 cm	148	31	96.3 (91.4-98.5)	92.5 (86.5-95.9)	80.0 (71.2-86.3)	0.242
Tumor depth						
Epifascial	64	16	96.7 (87.5-99.2)	89.7 (78.6-95.3)	80.0 (66.7-88.4)	
Subfascial	117	26	96.2 (90.3-98.6)	92.3 (85.2-96.1)	78.5 (68.1-85.8)	0.994
Tumor site						
Upper extremity	33	11	90.7 (73.9-96.9)	81.2 (62.8-91.1)	74.4 (55.3-86.3)	
Truncal wall	18	4	100 (-)	86.7 (56.4-96.5)	86.7 (56.4-96.5)	
Lower extremity	130	27	97.4 (92.3-99.2)	94.7 (88.6-97.6)	78.7 (68.8-85.8)	0.930*
Grading						
G1	92	18	96.6 (89.9-98.9)	92.0 (84.0-96.1)	83.5 (73.0-90.1)	
G2	58	19	96.0 (84.8-99.0)	91.5 (78.9-96.7)	69.2 (52.7-80.9)	
G3	31	5	96.6 (77.9-99.5)	88.8 (69.2-96.3)	83.6 (61.4-93.6)	0.092*
Margin status (Primary tumor)						
R0	170	37	96.8 (92.5-98.7)	92.2 (86.6-95.5)	79.2 (71.2-85.2)	
R1/R2	11	5	90.0 (47.3-98.5)	77.1 (34.5-93.9)	77.1 (34.5-93.9)	0.301
Negative margin width						
≤1 mm	111	18	98.1 (92.5-99.5)	96.0 (89.8-98.5)	80.8 (70.5-87.8)	
>1 mm and ≤5 mm	21	4	100 (-)	94.7 (68.1-99.2)	82.9 (55.7-94.2)	
>5 mm	16	1	100 (-)	91.7 (53.9-98.8)	91.7 (53.9-98.8)	0.581*
Adjuvant radiotherapy (Primary tumor)						
No	129	35	95.9 (90.5-98.3)	89.9 (83.0-94.2)	76.2 (66.7-83.4)	
Yes	52	7	97.7 (84.9-99.7)	95.3 (82.6-98.8)	86.8 (70.9-94.3)	0.157

*Global log-rank test for trend of survivor functions. LRFS: Local recurrence-free survival; CI: confidence interval.

a recently published update of the MSKCC cohort by Bartlett *et al*. has found a correlation between microscopic margins and LRFS, but still not survival (13). Another large retrospective study was presented by Oh *et al*. in 2016 including 231 patients with LS in various locations throughout the body (40% extremity, 34% retroperitoneum, 21% trunk, 5% head/neck) (11). They also analysed the influence of surgical margins on disease outcome but could not detect any prognostic significance of surgical margins for LRFS or OS. Finally, Vos *et al*. have published a multi-center analysis including 456 patients with LS of the extremities (10). To date, it is the largest specific analysis of extremity LS patients. Unfortunately, the two involved centers reported quite different rates of R0-resection: One center had an R0-rate of 41% while the other center reported a rate of 84%. Therefore, the impact of surgical margins could not be assessed due to the incongruency of the datasets. Taken together, none of the large studies that assessed the prognostic influence of surgical margins on LS could establish a noticeable association between surgical margins and survival.

Although the quality of surgical margins was not found to be an independent prognostic factor in our series, we attempted to assess whether wide or close negative margins lead to different outcomes within the R0-subgroup. In other words, we attempted to determine the optimal clear margin width. The closest negative margin width was available for 87% of all R0-resected patients. In univariate analysis not significant correlation between the negative margin width and disease outcome was established. However, patients that were resected with a safety margin larger than 5 mm had a slightly better LRFS than patients with closer margin widths, but this distribution failed to reach statistical significance (p=0.581). To date, there have been a few studies that have analyzed the influence of negative surgical margin widths in

Table II. *Results of the univariate analyses regarding OS.*

	N	No. of deaths	1-year OS (95%CI)	2-year OS (95%CI)	5-year OS (95%CI)	*p* (log-rank)
All patients	181	18	98.3 (94.7-99.4)	97.0 (92.9-98.7)	93.3 (87.8-96.3)	
Age (years)						
≤60	107	7	99.1 (93.6-99.9)	99.1 (93.6-99.9)	97.8 (91.3-99.5)	
>60	74	11	97.1 (88.7-99.3)	94.0 (84.7-97.7)	86.7 (75.0-93.2)	0.051
Gender						
Female	83	7	97.5 (90.3-99.4)	97.5 (90.3-99.4)	97.5 (90.3-99.4)	
Male	98	11	99.0 (93.0-99.9)	96.6 (89.8-98.9)	89.3 (79.6-94.6)	0.244
Tumor size						
≤5 cm	33	8	96.7 (78.6-99.5)	93.3 (75.9-98.3)	93.3 (75.9-98.3)	
>5 cm	148	10	98.6 (94.6-99.7)	97.8 (93.3-99.3)	93.1 (86.5-96.5)	0.160
Tumor depth						
Epifascial	64	7	98.4 (89.4-99.8)	96.8 (87.7-99.2)	91.0 (79.6-96.2)	
Subfascial	117	11	98.2 (92.8-99.5)	97.1 (91.3-99.1)	94.7 (87.7-97.8)	0.815
Tumor site						
Upper extremity	33	6	100 (-)	92.6 (73.5-98.1)	92.6 (73.5-98.1)	
Truncal wall	18	5	81.3 (52.5-93.5)	81.3 (52.5-93.5)	81.3 (52.5-93.5)	
Lower extremity	130	7	100 (-)	100 (-)	94.3 (86.9-97.6)	0.038*
Grading						
G1	92	4	100 (-)	98.9 (92.2-99.8)	98.9 (92.2-99.8)	
G2	58	6	96.2 (85.6-99.0)	96.2 (85.6-99.0)	93.5 (80.6-97.9)	
G3	31	8	96.6 (77.9-99.5)	92.5 (73.2-98.1)	73.9 (50.4-87.5)	>0.001*
Margin status (Primary tumor)						
R0	170	15	100 (-)	98.6 (94.7-99.7)	94.7 (89.1-97.4)	
R1/R2	11	3	72.7 (37.1-90.3)	72.7 (37.1-90.3)	72.7 (37.1-90.3)	0.023
Negative margin width						
≤1 mm	111	8	100 (-)	98.0 (92.1-99.5)	93.0 (85.0-96.8)	
>1 mm and ≤5 mm	21	4	100 (-)	100 (-)	100 (-)	
>5 mm	16	1	100 (-)	100 (-)	90.9 (50.8-98.7)	0.190*
Adjuvant radiotherapy (Primary tumor)						
No	129	12	99.2 (94.6-99.9)	97.5 (92.4-99.2)	94.6 (88.2-97.5)	
Yes	52	6	95.6 (83.5-98.9)	95.6 (83.5-98.9)	89.6 (74.3-96.0)	0.344

*Global log-rank test for trend of survivor functions. OS: Overall survival; CI: confidence interval.

soft tissue sarcomas (18, 21, 22). In accordance to our findings, most of them could not detect any beneficial influence of wide negative margins.

Regarding adjuvant treatment modalities, we assessed the impact of adjuvant radiotherapy but not of chemotherapy. To maintain a homogenous cohort, we excluded patients that were treated with adjuvant chemotherapy because only a few patients received chemotherapy after resection of their primary tumor with curative intent. In our institution, most of the patients that had to undergo chemotherapy had locally advanced inoperable tumors or disseminated disease. Regarding adjuvant radiotherapy, treated patients seemed to have a tendency for better LRFS than untreated patients which could be in line with the findings of a randomized, prospective study where adjuvant radiotherapy improved local control in STS patients after limb-sparing surgery (23). Notably, OS was not improved in the radiation treatment group. However, in our series the effect of radiotherapy did not reach statistical significance, but it seems reasonable to include adjuvant radiotherapy in cases of intermediate and high-grade STS (13, 24-26). A recently published analysis

Table III. *Results of multivariate analysis on OS according to Cox proportional hazard model.*

Category (reference)	HR (95%CI)	*p*-Value
Age: >50 years (*vs*. ≤50 years)	3.69 (0.78-17.40)	0.099
Grade: G3 (*vs*. G2)	2.47 (0.12-1.39)	0.151
Grade: G3 (*vs*. G1)	7.61 (0.03-0.50)	0.003
Site: Truncal wall (*vs*. extremity)	2.47 (0.63-9.70)	0.194
Margin status: R1/R2 (*vs*. R0)	2.84 (0.66-12.13)	0.160

OS: Overall survival; CI: confidence interval.

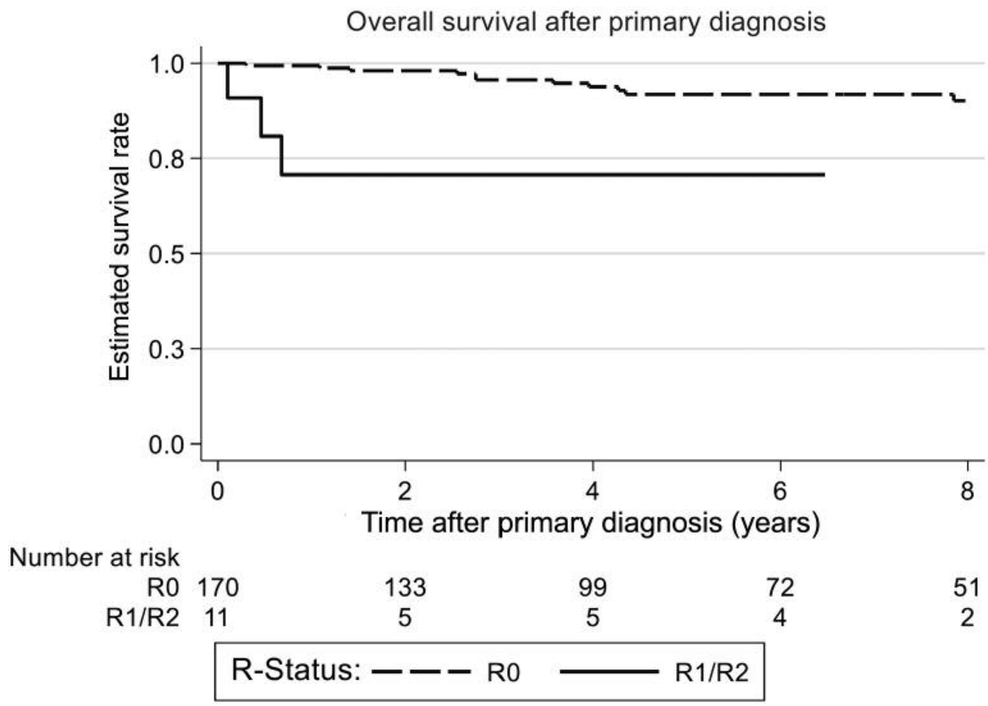

Figure 2. *Estimated Kaplan–Meier curves after primary diagnosis according to OS and surgical margin status.*

by Fonseca *et al*. has assessed the impact of radiotherapy in low-grade LS but could only detect a beneficial influence in patients with recurrent disease (27).

Finally, the current study has several limitations that must be stated. Although being a large analysis on extremity and truncal wall LS, the case numbers of some subgroups are relatively small. The present study revealed that the histologic grade had a stronger impact on OS than surgery or radiotherapy. However, the potential influence of surgery or radiotherapy might have been clearer when more patients had been analysed. Finally, there is a study selection bias which must be acknowledged. The study only included patients that underwent surgical treatment with a curative intent and excluded patients treated with a palliative intent.

In conclusion, data from this study demonstrated that tumor biology ultimately dictates the outcome in patients with extremity and truncal wall LS. The histologic grade was found to be the only independent prognostic factor of OS. In contrast, we could not find an independent prognostic influence of treatment-related factors such as surgical margins or adjuvant radiotherapy. Nonetheless, with regard to the current and previous studies on LS, surgical efforts should aim at negative margins whenever possible. The resections should be function-sparing and combined with adjuvant radiotherapy in intermediate and high-grade lesions. However, radical surgery with the goal of wide negative margins cannot be supported by the presented data.

Conflicts of Interest

All Authors declare that they have no conflict of interest regarding this study.

Authors' Contributions

KH and OG designed the study, drafted the manuscript and performed the statistical analysis. AP and HL collected the data and performed patient follow-up. MD and BB helped to draft the manuscript and participated in the design of the study. IS revised the pathologic slides and helped to draft the manuscript. ML conceived the study and participated in its design and coordination. All Authors read and approved the final manuscript.

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