original article

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The influence of tumor- and treatment-related factors on the development of local recurrence in osteosarcoma after adequate surgery. An analysis of 1355 patients treated on neoadjuvant Cooperative Osteosarcoma Study Group protocols

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Background: Local recurrence (LR) in osteosarcoma is associated with very poor prognosis. We sought to evaluate which factors correlate with LR in patients who achieved complete surgical remission with adequate margins.

Patients and methods: We analyzed 1355 patients with previously untreated high-grade central osteosarcoma of the extremities, the shoulder and the pelvis registered in neoadjuvant Cooperative Osteosarcoma Study Group trials between 1986 and 2005. Seventy-six patients developed LR.

Results: Median follow-up was 5.56 years. No participation in a study, pelvic tumor site, limb-sparing surgery, soft tissue infiltration beyond the periosteum, poor response to neoadjuvant chemotherapy, failure to complete the planned chemotherapy protocol and biopsy at a center other than the one performing the tumor resection were significantly associated with a higher LR rate. No differences were found for varying surgical margin widths. Surgical treatment at centers with small patient volume and additional surgery in the primary tumor area, other than biopsy and tumor resection, were significantly associated with a higher rate of ablative surgery.

Conclusions: Patient enrollment in clinical trials and performing the biopsy at experienced institutions capable of undertaking the tumor resection without compromising the oncological and functional outcome should be pursued in the future.

Key words: biopsy, limb-sparing surgery, local recurrence, osteosarcoma, surgical margin width

introduction

Complete surgical resection of the primary tumor is one of the prerequisites for long-term survival in osteosarcoma [1, 2], and the development of local recurrence (LR) is associated with very poor prognosis [3, 4]. Several studies have shown that pelvic tumor site [5, 6], response to preoperative chemotherapy [7, 8] and the quality of surgical margins [7, 9] according to Enneking's classification [10] correlate with LR, the latter being to date the only known prognostic factor which can be influenced by the treating physicians.

All available studies have concentrated on the comparison of inadequate (intralesional, marginal or contaminated [11]) and adequate (wide or radical) margins [2, 4–7, 9, 12–14]. However, no study has examined which surgical margin width in bone and soft tissue is necessary to ensure local control in patients with adequate margins, with arbitrary recommendations in well-known textbooks for orthopedic

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surgery varying from 3 to 7 cm [15, 16]. Furthermore, previous studies included patients after intralesional resections [2, 5–7, 9, 12–14], in whom the LR can be viewed as a secondary progression of residual tumor. Multivariate analyses have, expectedly, shown that inadequate margins is the most important factor influencing LR [9, 17], possibly obscuring the importance of other factors in patients undergoing wide or radical resections, as is the case for the vast majority of osteosarcoma patients today [9, 14, 18]. Moreover, several tumor- and treatment-related factors have never been examined.

As a result, we conducted this study of osteosarcoma patients with adequate surgical margins to evaluate which factors correlate with LR and identify potential improvements in the multimodal treatment algorithm.

patients and methods

patients

Between January 1986 and December 2005, 1802 consecutive patients with previously untreated histologically confirmed high-grade central osteosarcoma of the extremities, the shoulder and the pelvic girdle were enrolled in neoadjuvant trials of the Cooperative Osteosarcoma Study Group (COSS) and achieved a complete surgical remission of all detectable tumor foci with adequate margins. Patients with primary metastases were included if they achieved complete surgical remission, as 5-year overall survival (OS) rates of ~50% have been shown for this subgroup [19]. All studies were approved by the appropriate ethics and/or protocol review committees. Informed consent was required from all patients and/or their legal guardians, depending on the patients' age.

Fourteen patients underwent secondary amputations shortly after limb-sparing procedures due to surgical complications and were not included in this analysis. Neither progress letters nor surgery and pathology reports were available for 433 patients, leaving 1355 patients as subjects of this study. A LR developed in 76 of those patients.

As all COSS trials mainly targeted patients younger than 40 years of age with primary, localized, high-grade central osteosarcoma of the extremities, 868 patients were actual study participants. The remaining 487 patients were registered in the COSS registry, treated according to the same general guidelines and followed prospectively.

diagnostic staging, primary treatment and follow-up

Conventional radiographs of the affected bone were required in all studies, whereas the use of cross-sectional imaging modalities [computed tomography (CT) and magnetic resonance imaging (MRI) scans] depended on their availability. Chest radiographs and ^{99}Tc-methylene diphosphonate bone scans were used to detect metastases, while chest CT scans became mandatory in 1991. The great majority of the biopsy specimens were reviewed by the protocols' reference pathologists' panels.

The details of primary treatment have been described elsewhere [1, 20, 21]. Briefly, all patients were to receive pre- and postoperative chemotherapy according to the COSS protocol active at the time of enrollment. All protocols included high-dose methotrexate with leucovorin rescue, doxorubicin and cisplatin. Ifosfamide was used in varying combinations, while carboplatin and etoposide were introduced in the COSS-96 trial for high-risk patients with poor response to chemotherapy.

Primary tumor surgery was scheduled between weeks 9 and 11 in all protocols. In the presence of primary metastases, the sequence of surgical procedures varied, but resection of the primary tumor was usually carried out before resection of metastases [19].

Routine follow-up included clinical examinations and conventional radiographs of the primary tumor site and the chest at regular intervals. A full diagnostic work-up was required in all cases of suspected local or systemic relapse. The diagnosis of recurrence was based on the assessment of the treating institutions.

data collection and definition of variables

Data concerning patient demographics, tumor characteristics, first-line therapy and follow-up were collected prospectively, coded and entered into an electronic database as previously described [1]. Further details regarding tumor characteristics at presentation and primary treatment were collected retrospectively from pathology, surgery and radiology reports, progress letters, status reports forms and telephone notes available at the data center. The study charts of all 1802 patients were reviewed and relevant information was coded into following variables: age, with a cut-off at the cohort's median; soft tissue infiltration—histologically documented tumor infiltration of the soft tissue beyond the periosteum; surgical margin width in bone/soft tissue—the distance of the tumor to the surgical margin in bone/soft tissue recorded in the pathology report; pathological fracture—the presence of a pathological fracture at diagnosis or its development during treatment or at an unknown point; treatment of pathological fracture—conservative or operative; treatment modification—whether the planned chemotherapy protocol could be administered to its end or not; additional surgery—surgical procedures in the primary tumor area, other than biopsy and resection; center performing the biopsy; center performing the primary tumor resection; center volume—big/small = centers operating more/less than one patient per year per 5-year period.

statistical analysis

This analysis is based on follow-up data as of May 2008. All parameters were first evaluated with univariate techniques. Fisher's exact test was used to compare unrelated samples. Nonparametric analyses were carried out with the Mann–Whitney *U* test. OS at 5 and 10 years, LR rates and postrelapse survival at 2 and 5 years were calculated with the Kaplan–Meier method [22]. Survival curves were compared with the log-rank test [23]. Multivariate analysis was carried out with the Cox proportional hazards model [24]. Only variables that were significantly associated with the development of LR in univariate analysis were included in the multivariate model. Statistical calculations were carried out with the SPSS software version 16.0 (SPSS, Inc., Chicago, IL). All *P* values are two-sided; a $P < 0.05$ was considered significant.

results

patient and tumor characteristics

There were 805 male (59.4%) and 550 female (40.6%) patients. The median age at diagnosis was 15 years (range, 2–70 years; mean, 16.29 years). Most patients had at diagnosis a primary (97.9%), nonmetastatic (89.0%) osteosarcoma of the lower extremity (85.4%) and were study participants (64.1%; Table 1). The distribution of patients in 5-year period groups is shown in Table 2.

Tumor size ranged from 1.5 to 31 cm (median, 9 cm; mean, 9.56 cm). According to the American Joint Committee on Cancer staging system (6th edition) [25], 731 patients (53.9%) had T2 tumors (Table 1). Tumor infiltration of the soft tissue beyond the periosteum had been documented in 321 patients

Table 1. Univariate analysis of local recurrence and limb-salvage rates

	Patients	%	Local recurrence rate (%)				*P* (log rank)	Limb-sparing surgery (%)		*P* (Fisher's exact)
			2-year	SE	5-year	SE		Yes	No	
Eligible	1355	100	3.8	0.5	5.9	0.7				
Age										
<16	766	56.5	3.3	0.7	4.9	0.8	0.135	59.3	40.7	<0.0001
≥16	589	43.5	4.4	0.9	7.3	1.1		73.2	26.8	
Sex										
Male	805	59.4	3.6	0.7	5.8	0.9	0.807	64.3	35.7	0.597
Female	550	40.6	3.9	0.8	6.1	1.1		66.7	33.3	
Secondary osteosarcoma										
No	1327	97.9	3.7	0.5	5.9	0.7	0.724	65.0	35.0	0.07
Yes	28	2.1	7.3	5.0	7.3	5.0		82.1	17.9	
Primary metastases										
No	1206	89.0	3.5	0.5	5.5	0.7	0.068	66.6	33.4	0.006
Yes	149	11.0	6.3	2.0	9.3	2.6		55.0	45.0	
Study participant										
Yes	868	64.1	1.9	0.5	3.6	0.7	<0.0001	64.0	36.0	0.153
No	487	35.9	7.0	1.2	10.0	1.5		68.0	32.0	
Tumor site										
Pelvis	35	2.6	18.0	6.7	31.7	9.1	<0.0001	77.1	22.9	0.153
Extremity all	1320	97.4	3.4	0.5	5.3	0.7		65.0	35.0	
Lower extremity	1157	87.7	3.2	0.5	5.2	0.7	0.711	62.1	37.9	<0.0001
Upper extremity	163	12.3	4.5	1.6	5.9	1.9		85.9	14.1	
T stage										
T1	575	42.4	3.2	0.7	4.7	0.9	0.227	75.1	24.9	<0.0001
T2	731	53.9	4.1	0.8	6.9	1.0		57.2	42.8	
							0.244			0.846
T3	28	2.1	11.0	6.0	11.0	6.0		60.7	39.3	
Unknown	21	1.6								
T1 versus T3							0.112			0.117
Soft tissue infiltration										
No	531	39.2	3.4	0.7	4.1	0.9	0.002	79.3	20.7	<0.0001
Yes	321	23.7	6.8	1.4	9.4	1.7		53.3	46.7	
Unknown	503	37.1								
Pathological fracture										
No	1176	86.8	3.3	0.5	5.6	0.7	0.208	66.7	33.3	0.017
Yes	175	12.9	7.2	2.0	8.0	2.1		57.1	42.9	
At diagnosis	111	63.4	5.6	2.2	5.6	2.2	0.163	66.7	33.3	0.0004
During treatment	41	23.4	10.3	4.9	13.5	5.7		34.1	65.9	
At unknown point	23	13.2								
Unknown	4	0.3								
No versus during treatment							0.047			<0.0001
Treatment of pathological fracture ($n = 175$)										
Conservative	158	90.3	7.2	2.1	8.1	2.3	0.875	57.6	42.3	0.799
Operative	17	9.7	7.1	6.9	7.1	6.9		52.9	47.1	
Limb-sparing surgery										
Yes	885	65.3	4.7	0.7	7.5	0.9	0.001			
No	470	34.7	2.0	0.7	2.8	0.8				
Type of surgery										
Ablative	230	17.0	2.7	1.1	3.2	1.2	0.048			
Limb sparing	885	65.3	4.7	0.7	7.5	0.9				
							0.003			
Rotationplasty	240	17.7	1.3	0.7	2.4	1.0				
Type of resection[a]										
Wide	1126	83.1	3.6	0.6	6.2	0.8	0.613			
Radical	229	16.9	4.5	1.4	4.5	1.4				

Table 1. (*Continued*)

	Patients	%	Local recurrence rate (%)				*P* (log rank)	Limb-sparing surgery (%)		*P* (Fisher's exact)
			2-year	SE	5-year	SE		Yes	No	
Surgical margin width bone (≤2 cm only, *n* = 123), mm										
1–10	47	38.2	4.5	3.1	9.9	4.7	0.776			
11–20	76	61.8	6.9	3.0	11.5	3.8				
Response										
Good	826	61.0	1.8	0.5	3.1	0.6	<0.0001	67.4	32.6	0.045
Poor	515	38.0	6.7	1.1	10.2	1.5		61.9	38.1	
Unknown	14	1.0								
Additional surgical procedures										
No	1095	80.2	4.3	0.6	6.6	0.8	0.402	66.7	33.4	0.006
Yes	70	5.2	4.5	2.5	11.0	4.4		50.0	50.0	
Unknown	190	14.0								
Modification of treatment plan										
No	1044	77.0	2.7	0.5	4.4	0.7	0.0001	64.1	35.9	0.343
Yes	211	15.6	7.9	1.9	11.2	2.3		67.8	32.2	
Unknown	100	7.4								
Center performing the biopsy/the tumor resection										
Same	882	65.1	2.6	0.5	4.2	0.7	0.0001	65.6	34.4	0.572
Different	406	30.0	6.4	1.2	10.1	1.6		64.0	36.0	
Unknown	67	3.9								
Center volume										
Big	1034	76.3	3.8	0.6	6.1	0.8	0.761	69.9	30.1	<0.0001
Small	321	23.7	3.6	1.1	5.4	1.3		50.5	49.5	

[a]According to the Enneking classification [10].
SE, standard error.

Table 2. Patient distribution per 5-year periods

	N	%
1986–1990	233	17.2
1991–1995	324	23.9
1996–2000	445	32.8
2001–2005	353	26.1

(23.7%), 531 patients had no infiltration (39.2%), while no adequate data were available for 503 patients (37.1%).

Among 175 patients (12.9%) with a pathological fracture, 158 patients (90.3%) underwent conservative and 17 (9.7%) operative treatment. Seventy patients (5.2%) had additional surgery in the primary tumor area (Table 1).

primary treatment

All eligible patients underwent pre- and postoperative chemotherapy. A good histological response (<10% of the tumor viable in histology) was found in 826 patients (61.0%; Table 1). Treatment modifications were recorded in 211 patients (15.6%).

Limb-sparing procedures were carried out in 885 patients (65.3%), rotationplasty in 240 (17.7%) and amputations in 230 patients (17.0%). The surgical margin width in bone was only considered in the 1126 patients (83.1%) who underwent a wide and not a radical surgical resection [10]. Available for 909 patients (80.7%), it ranged from 1 to 350 mm (median, 50.0 mm; mean, 62.3 mm). For limb-sparing procedures, the median and mean amounted to 45.0 and 48.1 mm, respectively. Forty-seven patients had a margin width in bone of up to 10 mm and 76 patients between 11 and 20 mm.

The surgical margin width in soft tissue was considered only in the 224 patients with a wide surgical resection and a documented infiltration of the soft tissue beyond the periosteum. Available for 115 patients (51.3%), it had a median value of 5 mm (range, 1–120 mm; mean, 12.9 mm). Due to the high amount of missing data, this factor was not evaluated further.

The tumor resection was carried out at 107 different centers, with 1034 patients (76.3%) operated in big and 321 patients (23.7%) in small centers. Tumor resections per center ranged from 1 to 346 (median, 3; mean, 12.7). The biopsy was carried out at a different center than the resection in 406 patients (30.0%; Table 1).

outcome

After a median follow-up of 5.56 years (range, 0.64–20.8 years) for all patients and 6.67 years (same range) for survivors, the rate of LR for this selected group of patients at 2 and 5 years was 3.8 and 5.9% respectively. OS at 5 and 10 years was 34.9

and 21.2% in the LR group, compared with 80.1 and 74.4% in the nonlocal recurrence (NLR) group ($P < 0.0001$; Figure 1). Survival after local relapse at 5 and 10 years amounted to 21.7 and 19.0%, respectively.

The median time to LR was 1.57 years (range, 0.54–8.56 years; mean, 1.99 years). Patients who developed a LR within the first 12 months had a significantly lower OS than those relapsing between 13 and 24 months ($P < 0.0001$), who in turn faired worse than those with a local relapse developing after 24 months ($P < 0.0001$; Figure 2).

Sixty-three patients in the LR group (82.9%) and 393 patients in the NLR group (30.8%) developed secondary metastases ($P < 0.0001$). Twenty-one patients in the LR group (27.6%) developed metastases after LR, 32 (42.1%) synchronously and 10 (13.2%) before LR. OS was significantly better in patients with secondary metastasis following LR compared with patients developing metastases simultaneously ($P = 0.002$) or before LR ($P = 0.021$). Long-term disease-free survival was not observed in patients in whom secondary metastasis preceded LR.

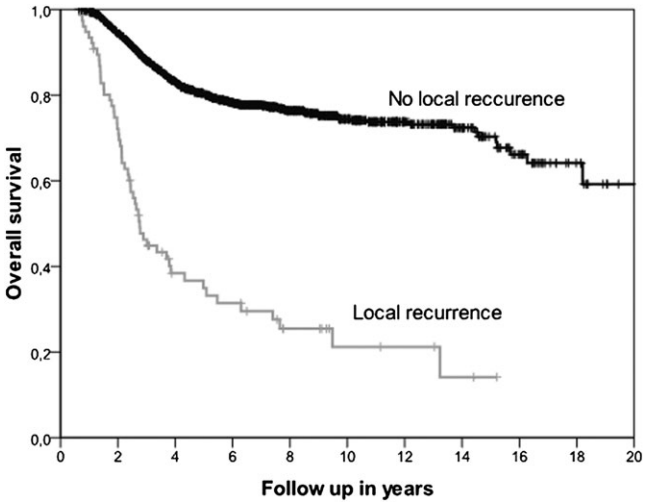

Figure 1. Overall survival according to the presence of local recurrence.

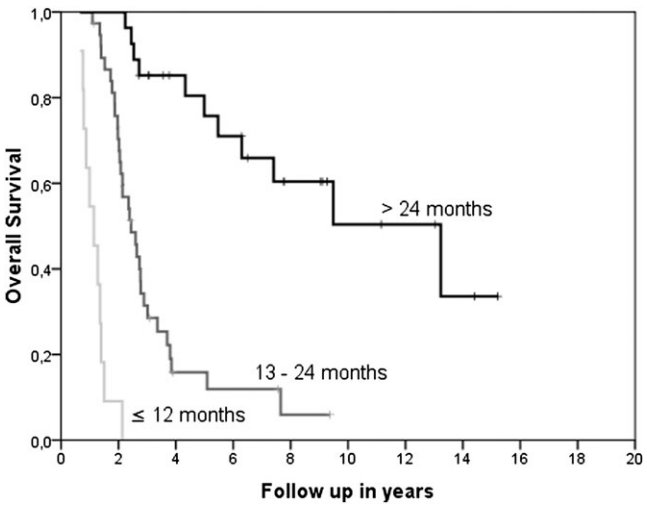

Figure 2. Overall survival according to time to local recurrence.

univariate analysis

There was no significant correlation between patient age (with a cutoff at 16 years), sex, secondary osteosarcoma or primary metastasis and LR rate (Table 1). On the other hand, patients participating in a study faired significantly better than those who were only registered and followed prospectively ($P < 0.0001$; Table 1).

Regarding the primary tumor characteristics, pelvic localization was associated with a significantly higher LR rate, as was soft tissue infiltration (Table 1). OS was significantly higher in patients without soft tissue infiltration (85.1 and 79.7% versus 62.7 and 55.9% at 5 and 10 years, $P < 0.0001$). No significant difference was found between tumors of the lower and upper extremities ($P = 0.711$). Neither tumor size ($P = 0.234$) nor T stage (Table 1) correlated with LR. Patients with pathological fractures developing during treatment had a higher LR rate compared with patients with no pathological fractures (Table 1).

Limb-sparing procedures were associated with a higher LR rate (Table 1), with no differences in disease-specific survival ($P = 0.118$). Surgical margin width in bone did not correlate with the LR rate, neither in the whole group ($P = 0.126$) nor in subgroup analyses of limb-sparing procedures only ($P = 0.692$), margin width of ≤10 mm only ($P = 0.223$), ≤ 20 mm only ($P = 0.379$), or when comparing a width of ≤10 mm with a width of 11 to 20 mm (Table 1).

Patients with a good histological response as well as those who were able to complete the planned chemotherapy protocol had fewer LRs (Table 1). Additional surgical procedures and surgical treatment in a small center did not lead to a higher LR rate, but both factors were significantly associated with a higher rate of ablative surgery (Table 1). Finally, a biopsy at a center other than the one performing the tumor resection was also associated with a significantly higher LR rate ($P = 0.0001$).

multivariate analysis

Soft tissue infiltration was not included in multivariate analysis due to the high amount of missing data. All other factors with a significant correlation to LR in univariate analysis retained their significance in the multivariate model (Table 3).

Table 3. Multivariate analysis of local recurrence-free survival with the Cox proportional hazards model

	Local recurrence-free survival		
	RR	95% CI	*P*
Not a study participant	1.86	1.07–3.21	0.027
Pelvic site	3.18	1.51–6.73	0.002
Limb-sparing surgery	2.99	1.52–5.92	0.002
Poor response	3.76	2.91–6.44	<0.0001
Modification of treatment plan	2.03	1.18–3.49	0.011
Tumor resection carried out at a different center than the biopsy	2.23	1.35–3.68	0.002

RR, relative risk; CI, confidence intervals.

discussion

Our analysis included a selected group of 1355 osteosarcoma patients who achieved a first complete surgical remission with adequate margins, treated over a period of 20 years at 107 different surgical institutions. Inevitably, differences in the surgical philosophy over the years and between the centers caused for some inhomogeneity in our patient cohort, which is one of the limitations of this study, while another is its retrospective nature. However, we believe that the strict inclusion criterion of a histologically documented wide or radical surgical margin and the high number of patients analyzed compensate for any such inconsistencies.

Another limitation lies in the fact that approximately a quarter of the patients were surgically treated at institutions with limited experience, operating less than one patient per year. On the other hand, we included this factor in our analysis to evaluate the hypothesis that experienced centers offer better treatment to patients with a rare tumor such as osteosarcoma. While no differences in LR rates were found, small centers carried out amputations with a significantly higher frequency than big ones. Limb-sparing surgery has been shown to correlate with an improved functional outcome [26, 27], which is why it is the treatment of choice in most cases, provided that the oncological outcome is not put at risk. Therefore, our results support the need to concentrate osteosarcoma care in fewer centers with more experience.

Whether limb-sparing surgery correlates to LR remains controversial, with some studies finding no influence [28, 29] and others reporting a higher LR rate for limb-sparing procedures [14, 18], as was the case in our analysis. It should be noted that the former studies were monoinstitutional and the latter multicentric, which implies a correlation between surgeon volume and local control after limb-sparing procedures. Our data could not confirm this hypothesis, but the calculations were also not adjusted for case-mix.

The width of surgical margins in bone did not influence the LR rate in patients undergoing wide resections, even in patients with a comparatively narrow margin. To our knowledge, this is the first time this factor has been evaluated in detail. Our results contradict the need to resect a minimum of 3 cm of healthy bone to ensure local control [15, 16], especially considering that the intraosseous tumor extent in MRI scans has been shown to correlate excellently with the actual tumor extent in pathology [30, 31].

Provided that an adequate surgical margin is ensured, the preservation of a greater amount of healthy bone in more conservative approaches increases the amount of patients who qualify for joint-preservation procedures with an improved functional outcome [32, 33]. Furthermore, it improves the biomechanical result in patients undergoing endoprosthetic replacement by improving the length ratio of the remaining bone to the prosthesis [34]. Aseptic loosening, the most common complication following endoprosthetic replacement [35, 36], has been found to correlate to the amount of bone resected [35]. Moreover, its surgical treatment almost always requires a further resection of the remaining bone [36], a factor that also underlines the need to avoid the unnecessary sacrifice of healthy bone during the initial tumor resection procedures.

Participation in a study protocol was associated with a lower LR rate. Picci et al. [37] recently reported a higher LR rate for patients who were not candidates for study protocols, possibly due to the more unfavorable characteristics of these patients. However, many of the patients in the COSS register were not enrolled in study protocols despite being eligible because systemic treatment did not commence within 3 weeks of diagnostic biopsy, an exclusion criterion in previous COSS studies. Moreover, lack of participation in a study remained an independent prognostic factor for LR in multivariate analysis. While reasons for this remain unclear, recruitment in clinical trials has been shown to lead to improved OS as well [38, 39], possibly due to a better adherence to treatment guidelines.

The influence of systemic treatment on LR has been well documented, with poor responders being at higher risk [7, 8]. Another aspect of this influence appears to be the failure to complete the planned adjuvant chemotherapy that was associated with a higher LR rate in this study. Given the retrospective nature of this analysis and that the reasons for treatment modifications were not always retraceable, the clinical significance of this finding will probably be limited, although it could serve as an additional argument to patients unwilling to subject themselves to several months of systemic treatment.

A poorly performed biopsy has been related to an increased complication rate, delays in treatment and may compromise limb salvage [40–42]. However this is, to our knowledge, the first time it has been shown that patients are at an increased risk of LR if their biopsy is carried out at a center other than the one doing the definitive tumor resection, regardless of the quality of the biopsy. The importance of this finding lies in the fact that this factor can be eliminated by a different surgical approach from the treating physicians, leading to a significantly lower LR rate.

The presence of soft tissue infiltration beyond the periosteum should not be confused with cortex breach and extraosseous tumor spread as the periosteum poses an important barrier to the tumor and is elevated from the cortex but not breached even in cases with a large extraosseous tumor extent [43]. Spanier et al. [44] have shown that the breach of the periosteum correlates with a decreased OS and LR-free survival, both of which findings we were able to confirm in our analysis. However, many studies have ignored the significance of this factor and more than a third of the pathology reports in our analysis made no mention to it. We therefore believe that this aspect of tumor extent should be included in prospective evaluations in future studies as it has the potential to contribute significantly to an accurate tumor staging and the development of risk-adapted treatment plans.

In conclusion, our analysis of a large series of osteosarcoma patients who achieved a first complete surgical remission with adequate margins identified several independent prognostic factors for local control and underscored the significance of others. Some of these factors cannot be influenced as they are tumor related, but may improve patient stratification in future trials. Others, such as patient enrollment in clinical trials and performing the biopsy at experienced institutions capable of undertaking tumor resection without compromising the oncological and functional outcome, should be pursued in the future.

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disclosure

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