■ ONCOLOGY

Preoperative surgical risk stratification in osteosarcoma based on the proximity to the major vessels

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Aims
The aim of this study was to determine the risk of local recurrence and survival in patients with osteosarcoma based on the proximity of the tumour to the major vessels.

Patients and Methods
A total of 226 patients with high-grade non-metastatic osteosarcoma in the limbs were investigated. Median age at diagnosis was 15 years (4 to 67) with the ratio of male to female patients being 1.5:1. The most common site of the tumour was the femur (n = 103) followed by tibia (n = 66). The vascular proximity was categorized based on the preoperative MRI after neoadjuvant chemotherapy into four types: type 1 > 5 mm; type 2 ≤ 5 mm, > 0 mm; type 3 attached; type 4 surrounded.

Results
Limb salvage rate based on the proximity type was 92%, 88%, 51%, and 0% for types 1 to 4, respectively, and the overall survival at five years was 82%, 77%, 57%, and 67%, respectively (p < 0.001). Local recurrence rate in patients with limb-salvage surgery was 7%, 8%, and 22% for the types 1 to 3, respectively (p = 0.041), and local recurrence at the perivascular area was observed in 1% and 4% for type 2 and 3, respectively. The mean microscopic margin to the major vessels was 6.9 mm, 3.0 mm, and 1.4 mm for types 1 to 3, respectively. In type 3, local recurrence-free survival with limb salvage was significantly poorer compared with amputation (p = 0.025), while the latter offered no overall survival benefit. In this group of patients, factors such as good response to chemotherapy or limited vascular attachment to less than half circumference or longitudinal 10 mm reduced the risk of local recurrence.

Conclusion
The proximity of osteosarcoma to major blood vessels is a poor prognostic factor for local control and survival. Amputation offers better local control for tumours attached to the blood vessels but does not improve survival. Limb salvage surgery offers similar local control if the tumour attachment to blood vessels is limited.

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Osteosarcoma is the most common malignant primary bone tumour, arising predominantly in the femur, tibia, and humerus.[1-3] The current management of high-grade osteosarcoma is limb salvage combined with neoadjuvant and adjuvant chemotherapy.[4,5] This approach has significantly improved the long-term survival and limb salvage rates throughout the last decades,[6-9] and has also contributed to the development of different surgical techniques.[10-12] However, there is still controversy regarding which are the most appropriate surgical strategies after neoadjuvant chemotherapy when the tumour involves the main vasculature of the limb.[13,14]

To date, a variety of clinical studies have attempted to identify prognostic factors for local recurrence (LR) and survival in patients with osteosarcoma following neoadjuvant treatment. The prognostic factors for survival include age,[8] sex,[15] tumour location,[16] tumour size,[8,15] type of surgery,[17,18] presence of LR,[18] surgical margin,[8,16] and tumour response to neoadjuvant chemotherapy,[8,16,17,19,20] the last two factors influencing LR-free survival (LRFS).[21,22] However, the

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correlation between the vascular proximity to the tumour and the surgical outcomes has been unclear.

Recently, the Birmingham Classification was reported.[23] This method introduced a new concept of margins based on the distance in millimetres from the tumour to the resected normal tissue and provided a postoperative stratification of the prognosis based on the response to chemotherapy and margin. One of the advantages of this system is the more reproducible and reliable evaluation of the surgical margins, in contrast with that of Enneking et al.[24] However, the Birmingham Classification does not permit preoperative predictions in order to select the best surgical alternative. Thus, a complementary preoperative assessment tool is still required.

The aim of this study was to analyze the risk of LR and survival depending on the proximity of the tumour to the main vascular structures, in patients presenting with high-grade osteosarcoma in the limbs. The following clinical questions were asked: 1) does the vascular proximity modify the survival or the risk of LR?; 2) how safe is limb salvage when the tumour is close to or attached to the major vessels?; and 3) what is the actual microscopic margin in patients with limb salvage when the tumour is attached to the major vascular bundles on preoperative MRI?

Patients and Methods

Eligibility. This study included all patients with a diagnosis of a primary osteosarcoma treated between January 2007 and December 2015 at our institution. The inclusion criteria were a diagnosis of high-grade osteosarcoma located in the limbs, and a minimum of two years' follow-up for survivors. A total of 343 eligible cases were identified. Patients were excluded if they presented with metastasis at diagnosis (n = 79 (23%)), they were managed without neoadjuvant chemotherapy (n = 7 (2%)), they had final surgery in another institution (n = 4 (1%)), they did not undergo surgical treatment (n = 9 (3%)), the follow-up was performed elsewhere (n = 13 (4%)), they were treated with rotationplasty (n = 4 (1%)), or they died from complications from chemotherapy (n = 1 (0.3%)).

Prognostic variables. The following data were extracted from the database: sex, age at diagnosis, primary tumour location, tumour size, histological subtype according to Fletcher's classification,[25] tumour stage (UICC, eighth edition),[26] presence of pathological fractures, vascular proximity on the preoperative MRI after neoadjuvant chemotherapy, type of surgery (limb salvage or amputation), surgical margin based on the Enneking system (radical, wide, marginal, or intralesional),[24] closest margin to the tumour, histological response to neoadjuvant chemotherapy, presence or absence of vascular invasion, and oncological outcome including LRFS and overall survival (OS). The protocol of neoadjuvant chemotherapy was based on the European Osteosarcoma Intergroup (EOI) or European and American Osteosarcoma Studies (EURAMOS) trials.[27,28] The vascular proximity was defined as the minimum distance between the tumour and the main vascular bundle. This distance was measured on the axial slices of preoperative T1-weighted MRI obtained during the periods between the last course of neoadjuvant chemotherapy and surgical resection in order to eliminate possible oedema.[29] Histological examination was performed by pathologists experienced in evaluating bone sarcomas. Microscopic margins on the histological slides were measured in millimetres from the resection surface to the tumour. The histological response was assessed in the resected specimen after surgery and chemotherapy-induced necrosis was reported as a percentage of the total tumour area. Patients were classified according to the necrosis rate as good responders (≥ 90% necrosis) and poor responders (< 90% necrosis). The necrosis was also subcategorized into four groups: grade 1 (< 50%), grade 2 (50% to 89%), grade 3 (90% to 99%), and grade 4 (100%).[30]

Statistical analysis. All statistical analyses were performed using the SPSS statistical software (version 23; IBM Corp., Armonk, New York). OS was defined as the period from the date of diagnosis to the censored date of tumour-related death or last follow-up for survivors. LRFS was defined as the period from the date of diagnosis to the censored date of LR. OS and LRFS were estimated with the Kaplan–Meier method, and comparisons were assessed with the log-rank test. Multivariate analysis was conducted with the Cox proportional hazards model. p-values < 0.05 were considered to be statistically significant.

Results

Patient characteristics. A total of 226 participants matched the inclusion criteria. The clinicopathological characteristics of patients set are supplied in Supplementary Table i. The mean follow-up period was 61 months (6 to 120). Median age at diagnosis was 15 years (4 to 67) with the ratio of male to female patients being 1.5:1. The most common site of the tumour was the femur (n = 103 (46%)) followed by tibia (n = 66 (29%)). The median size of the tumour was 10.0 cm (2.3 to 28.8) and osteoblastic subtype was the most prevalent (58%). Pathological fractures were identified in 28 patients (12%) who required cast immobilization or traction while undergoing preoperative chemotherapy. A total of 173 patients (77%) had limb-salvage surgery; 148 (65%) had endoprosthetic replacements; ten patients (4%) had simple excision of expendable bones without reconstruction for example of the fibula or scapula. There were 53 amputations (23%). In terms of histological response to chemotherapy, 109 patients (48%) were good responders and 117 patients (52%) were poor responders. Vascular invasion was present in 14 patients (6%).

Local control. The overall rate of LR was 8% (n = 19). The five-year and ten-year LRFS was 91% and 89%, respectively (Supplementary Fig. aa). Median LR-specific survival was 14 months (6 to 83). Univariate log-rank analysis showed that surgical margin, chemotherapy response, and presence of vascular invasion were factors significantly associated with an increased risk of LR (Supplementary Table i, Supplementary Fig. b). Multivariate analysis demonstrated significant associations between LR and response to neoadjuvant chemotherapy (chemotherapy necrosis < 90%, hazard ratio (HR) 5.52, 95% confidence interval (CI) 1.58 to 19.25 *vs* chemotherapy necrosis ≥ 90%, HR 1; p = 0.007) and vascular invasion (present HR, 3.77; 95% CI, 1.12 to 12.70 *vs* absent HR 1; p = 0.033) (Supplementary Table ii). Surgical margins stratified by the Enneking system did not reach statistical significance at multivariate analysis. Poor response to neoadjuvant chemotherapy was the most significant factor associated with LR.

Table I. Clinical outcome based on the proximity between the tumours and the major vessels

Outcome	Type 1 (> 5 mm)	Type 2 (≤ 5 mm)	Type 3 (attached)	Type 4 (surrounded)
Patients, n (%)	65 (*29*)	86 (*38*)	72 (*32*)	3 (*1*)
Type of surgery, n (%)				
Limb-salvage surgery	60 (*92*)	76 (*88*)	37 (*51*)	0 (*0*)
Amputation	5 (*8*)	10 (*12*)	35 (*49*)	3 (*100*)
Surgical margin, n (%)				
Radical	1 (*2*)	2 (*2*)	15 (*21*)	2 (*67*)
Wide	57 (*88*)	59 (*69*)	34 (*47*)	1 (*33*)
Marginal	3 (*5*)	22 (*26*)	21 (*29*)	0 (*0*)
Intralesional	0 (*0*)	1 (*1*)	2 (*3*)	0 (*0*)
Mean microscopic distance (in patients with limb-salvage surgery), mm				
Distance to the direction of the vessel	6.9	3.0	1.4	N/A
Closest margin to any directions	5.4	2.3	1.3	N/A
Local recurrence, n (%)				
Total	4 (6)	6 (*7*)	9 (*13*)	0 (*0*)
Perivascular area per total of local recurrence	0 (*0*)	1 (*1*)	3 (*4*)	N/A
Five-year survival (%)				
Local recurrence-free survival	*94*	*94*	*86*	*100*
Overall survival	*82*	*77*	*57*	*67*

N/A, not applicable

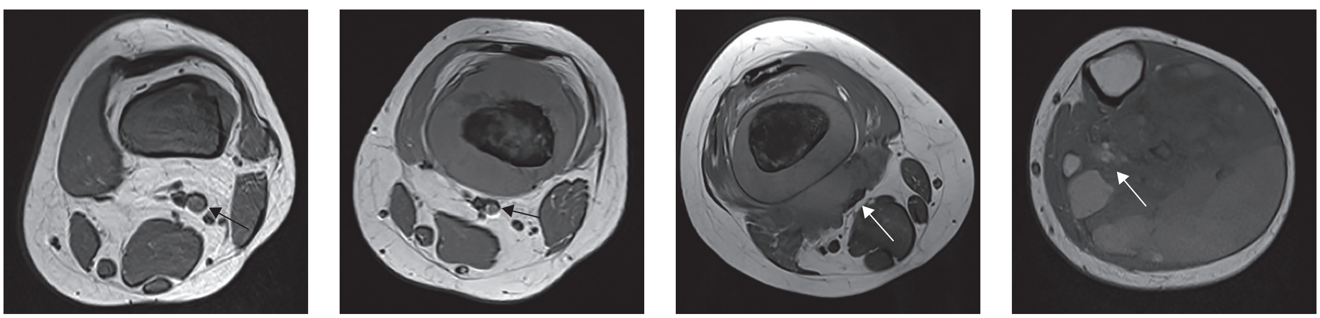


Fig. 1a Fig. 1b Fig. 1c Fig. 1d

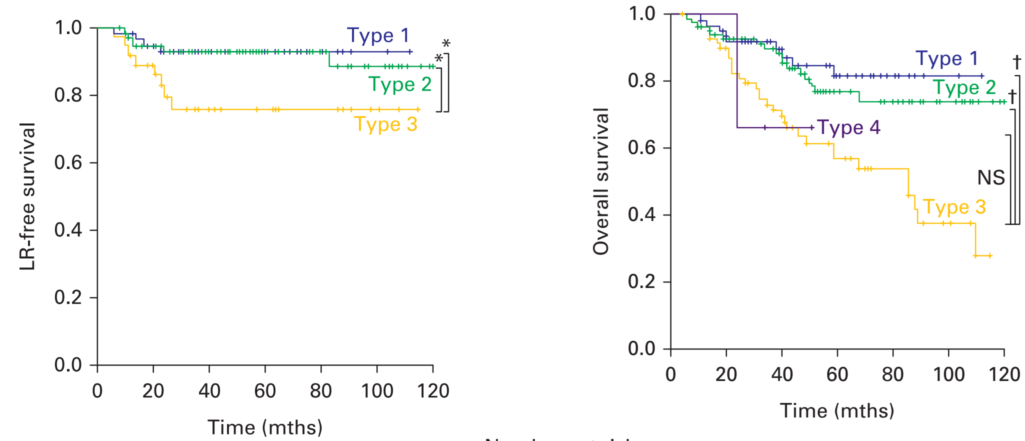
Patterns of the proximity to the major vessels. Distance of the major vascular bundle (arrows) from the tumour was classified into four types: a) type 1, > 5 mm; b) type 2, ≤ 5 mm and > 0 mm; c) type 3, attached to the tumour; and d) type 4, surrounded by the tumour.

Overall survival. The five-year and ten-year OS for the patient cohort was 71% and 60%, respectively (Supplementary Fig. ab). Univariate analysis showed that sex, tumour stage, type of surgery (limb salvage or amputation), surgical margin, response to neoadjuvant chemotherapy, presence of vascular invasion, and local recurrence were the significant prognostic factors that indicated a poor survival (Supplementary Table i, Supplementary Fig. c). Multivariate analyses using the Cox proportional hazard model demonstrated significant associations between tumour-related death and tumour stage IIB (HR 2.58; 95% CI, 1.18 to 5.63 *vs* stage IIA HR 1; p = 0.017), < 90% chemotherapy necrosis (HR 2.44; 95% CI, 1.28 to 4.63 *vs* > 90% chemotherapy necrosis HR 1; p = 0.006), and presence of LR (HR 4.43; 95% CI, 2.21 to 8.89 *vs* absence of LR HR 1; p< 0.001) (Supplementary Table ii). The other factors identified at univariate analysis did not reach statistical significance in the multivariate analysis.

Outcomes according to the vascular proximity. Based on the proximity of the tumour to the major vessels, 65 patients (29%) were type 1 (> 5 mm from the tumour), 86 patients (38%) type 2 (≤ 5 mm from the tumour), 72 patients (32%) type 3 (attached to the tumour), and three patients (1%) type 4 (surrounded by the tumour) (Table I, Fig. 1).

In type 1, five-year LRFS was 94% and five- and ten-year OS was 82% (Table I, Fig. 2). Limb salvage was performed in 60 patients (92%) and amputation was performed in five (8%). The reasons for amputation included radical local control for a pathological fracture, patient's decision for better postoperative function, or hemiplegia because of a central nervous system disorder. Surgical margin was radical in one patient (2%), wide in 57 patients (88%), and marginal in three patients (5%). In patients treated with limb salvage, the mean microscopic surgical margin to the major vascular bundle was 6.9 mm (1 to 20), and the mean closest margin in all directions was 5.4 mm (0.5 to 34). LR was identified in four patients (6%); surgical margins were wide in three and marginal in one. No patient presented with LR from the perivascular area.

In type 2, LRFS at five-years was 94%, and then decreased slightly to 90% at ten years. The five- and ten-year OS was 77% and 74%, respectively (Table I, Fig. 2). Limb salvage was



Numbers at risk

Type 1	59	51	34	21	8	2	0
Type 2	77	64	49	28	22	10	0
Type 3	37	29	15	12	7	3	0

Fig. 2a

Numbers at risk

Type 1	65	57	38	22	8	2	0
Type 2	86	74	58	32	24	11	0
Type 3	72	61	38	25	14	6	0
Type 4	3	3	1	0	0	0	0

Fig. 2b

Kaplan–Meier curves for: a) local recurrence (LR)-free survival in patients with limb-salvage surgery; and b) overall survival based on the vascular proximity. *$p < 0.05$; †$p < 0.01$. NS, not significant.

performed in 76 patients (88%) and amputation in ten (12%). The reasons for amputation were concurrent fracture in the affected limb, unrelated to the oncological condition, the patient's decision, pathological fracture, or progressive disease during neoadjuvant chemotherapy. Surgical margins were radical in two patients (2%), wide in 59 patients (69%), marginal in 22 patients (26%), and intralesional in one patient (1%). Patients treated with limb salvage had a mean microscopic surgical margin to the major vascular bundle of 3.0 mm (0 to 6), while the mean closest margin in all directions was 2.3 mm (0 to 10). LR was identified in six patients (7%), of which surgical margins were wide in three and marginal in three. One patient who had a marginal surgical excision presented with LR within the perivascular area.

In type 3, five-year LRFS was 86% and five- and ten-year OS was 57% and 30%, respectively. These survival rates were the lowest ones observed in all types (Table I, Fig. 2). A total of 37 patients (51%) underwent limb-sparing surgery and 25 (49%) underwent amputation. The surgical margins were radical in 15 patients (21%), wide in 34 (47%), marginal in 21 (29%), and intralesional in two (3%). Despite the observation of the tumours being attached to the major vascular bundles in preoperative MRIs, the actual mean microscopic surgical margin to the major vascular bundles in patients treated with limb salvage was 1.4 mm (0 to 3) (Table I, Supplementary Fig. d), while the mean closest margin in all directions was 1.3 mm (0 to 2). LR was identified in nine patients (13%); the surgical margins were wide in two, marginal in six, and intralesional in one. Three patients with a marginal margin developed LR within the perivascular area.

In type 4, all patients underwent amputation. No patients experienced LR, while five-year OS was 67% (Table I, Fig. 2). Surgical margin was radical in two patients (67%) and wide in one patient (33%).

Comparing the LRFS in all groups, patients treated with limb-salvage surgery and classified as type 3 had a significantly lower survival than patients categorized as type 1 or type 2 (Fig. 2a; log-rank test, $p = 0.030$). No statistical differences were observed in patients treated with amputation (Supplementary Fig. e; $p = 0.433$). The Kaplan–Meier analysis for OS illustrated the significant spread between the categories (Fig. 2b; $p < 0.001$). Type 3 patients had a significantly poorer survival compared with the other types (type 3 HR, 3.22; 95% CI 1.53 to 6.75 *versus* type 1 HR, 1; $p = 0.002$) (Supplementary Table ii), although no significance was reached in the multivariate analysis.

In a subgroup analysis based on the tumour sites, the poorest LRFS was also seen in type 3 patients who had tibial and humeral tumours (Supplementary Fig. f). Patients with femoral tumours had similar recurrence rates regardless of the type of vascular proximity. In patients with tumours of the distal femur and proximal tibia, the lowest LRFS was recorded in type 3, followed by type 2 and 1 (Supplementary Fig. f). The Kaplan–Meier curves for OS showed the poorest prognosis in type 3 in all tumour sites, with statistical significance in patients with tumours in the distal femur ($p = 0.013$) and the proximal tibia ($p = 0.043$) (Supplementary Fig. f).

Analyzing the outcome in type 3 patients according to the surgical treatment, the Kaplan–Meier curve analysis for LRFS illustrated a significant spread according to the surgical management performed. The five-year LRFS were 96% in patients treated with amputations and 76% in those with limb-sparing surgery (Fig. 3a; log-rank test, $p = 0.025$). Patients with limb salvage were eight times more likely to develop LR than those treated with amputation (HR 8.05; 95% CI 1.01 to 64.39 *vs* HR, 1; $p = 0.049$). No statistical difference in OS were identified in type 3 patients between amputation and limb-sparing surgery (Fig. 3b; log-rank test, $p = 0.842$).

Among type 3 patients with limb-salvage surgery, a clear difference in LRFS was observed between good and poor responders to neoadjuvant chemotherapy with no LR in those who had a 100% necrosis rate (Supplementary Fig. g). No

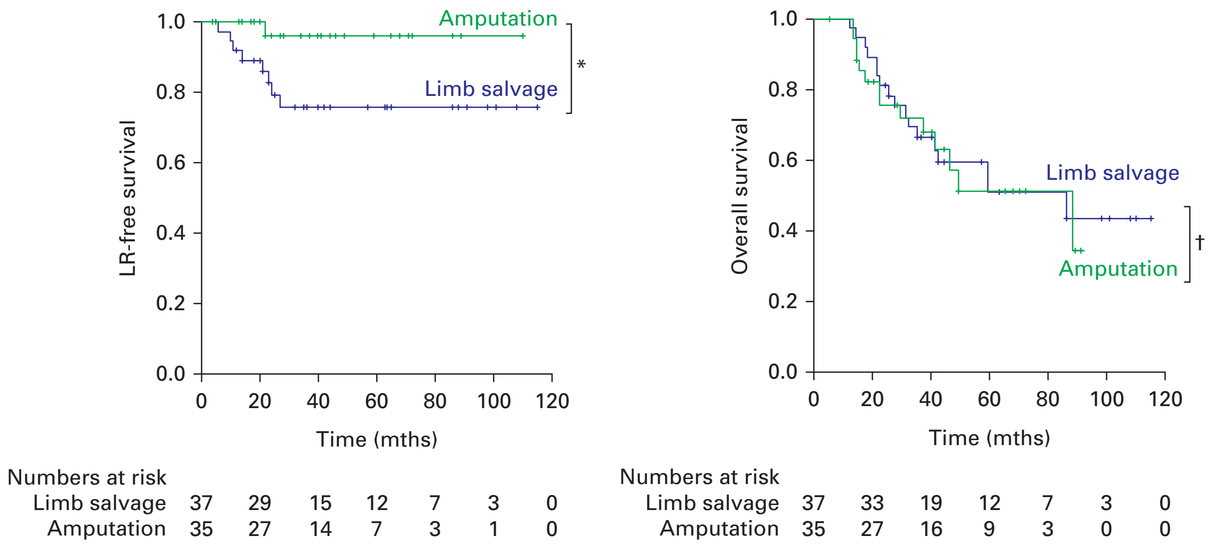


Fig. 3a Fig. 3b

Kaplan–Meier curves for: a) local recurrence (LR)-free survival; and b) overall survival in type 3 patients stratified by the nature of surgery. *p = 0.025; †p = 0.842.

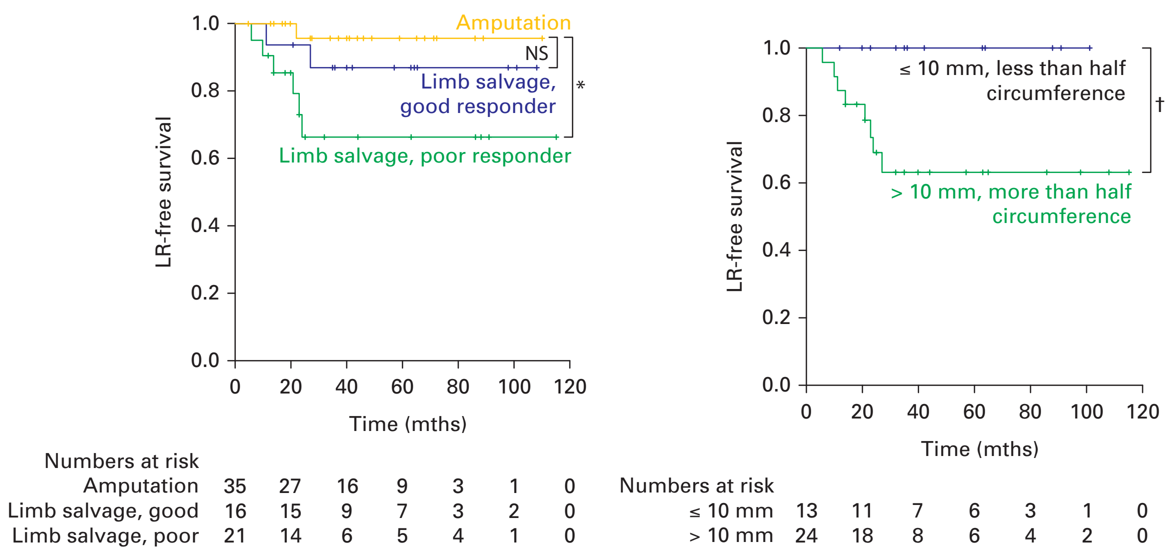


Fig. 4a Fig. 4b

Kaplan–Meier curves for local recurrence-free survival in type 3 patients stratified by: a) the nature of surgery and response to neoadjuvant chemotherapy; and b) the patterns of attachment between the tumour and the major vessels in patients with limb salvage. *p = 0.009; †p = 0.025.

statistical difference in LRFS was observed when comparing patients treated with limb salvage who responded to chemotherapy and patients managed with amputation (Fig. 4a; log-rank test, $p = 0.290$). With regard to the patterns of vascular attachment, LRFS was poorer in patients with the vascular attachment over half of the circumference of the major vascular bundle on the axial MRI (Supplementary Fig. ha; log-rank test, $p < 0.001$). Furthermore, patients who had vascular attachment less than 10 mm longitudinally had no LR (Supplementary Fig. hb; log-rank test, $p = 0.025$). The Kaplan–Meier analysis for LRFS showed a significant difference between patients with limited vascular attachment (< 50% of the circumference or < 10 mm longitudinally) to those with wider attachment (Fig. 4b; log-rank test, $p = 0.025$). These data demonstrated that, while amputation offered better local control with no survival benefit in type 3, the risk of LR by limb salvage was lower if the tumour responded to neoadjuvant chemotherapy or the vascular attachment was limited.

Discussion

The distance between the tumours and the major vessels is one of the most important factors for surgeons to consider when treating patients with osteosarcoma. Although many authors have studied the prognostic factors for LRFS or OS in osteosarcoma,[1,8,9,15-22,24,31-37] there has been no study focusing specifically on the prognostic significance of the vascular proximity of the tumour. Previous studies have demonstrated that the most important predictive factors regarding LR were poor response to neoadjuvant chemotherapy and inadequate surgical margins,[21,22] and those regarding OS were age, tumour size, tumour location, response to neoadjuvant chemotherapy, and pathological fracture.[8,15-20,35] However, several discrepancies have been observed between the various cohorts studied[21,22,31,32,37] and Bramer et al[35] concluded that this might be explained by methodological issues. In our study, the most important prognostic factors for LRFS were the tumour's response to neoadjuvant chemotherapy and also the presence of vascular invasion. Tumour stage, response to neoadjuvant chemotherapy, presence of local recurrence, and development of metastasis were all prognostic factors for OS, and were consistent with the previous reports.[24,35] The proportion of patients presenting with LR (8%) and five- and ten-year OS (71% and 60%) in our cohort was comparable to that of previous studies.[8,21,28,32] In terms of vascular proximity of the tumour, LRFS and OS decreased as the distance between the tumour and the major vasculature reduced, although the difference was not statistically significant in LRFS because of a relatively small number of LR in our cohort. This result confirms that an adequate margin of resection is required in all directions in order to obtain local control. However, it should be noted that LR incidence from the perivascular area increased as the tumours approached the major vessels.

We have evaluated the correlation between the vascular proximity on preoperative MRI and the microscopic surgical margin to the major vessels. The mean microscopic margin in type 3 was 1.4 mm in patients with limb salvage, which suggests that normal soft tissues were present between the tumour and the major vessels, even if they appeared to be attached on MRI. van Trommel et al[29] compared the vascular involvement on preoperative MRI and the postoperative pathological findings. They found that among 13 patients whose MRI showed equivocal findings for major vascular involvement of the tumour, none was found to have histopathological involvement. Although no further pathological details were reported in their paper, a vascular sheath or adipose tissue between the tumour and the major vessels might well be present, which Kawaguchi et al[38] argued was a thin barrier comprising of a 2 cm thickness of normal tissue.

Based on the Birmingham Classification,[24] the strongest predictor of LR was a combination of margins $\leq$ 2 mm and a necrosis rate of less than 90%, with the risk of LR as 24% at five years. While this classification can provide a confident prediction of the prognosis based upon the postoperative histopathology, our study provides a prognostic prediction based on preoperative MRI data. Since the microscopic margin of all patients with limb salvage in type 3 were less than 2 mm, they can be classified as type 1b or 2b using the Birmingham Classification, which means that the risk of LR is at least 8% or 24% in five years, respectively.[24] In our study, the risk of LR in type 3 patients with limb salvage surgery was 13% in good responders and 33% in poor responders, which confirms our previous finding that chemotherapy response was a very strong predictor for LR. The problem arises, however, regarding how possible it is to predict tumour response to neoadjuvant chemotherapy preoperatively. Recent reports that may help in this prediction and in surgical planning have reported the efficacy of functional imaging, such as phase contrast-enhancement MRI[39], or 2-(fluorine-18)-fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET)-CT scan,[40].

There are several limitations to our study. First, the quality of the MRI was not always consistent between patients. Our institute is a major referral centre and MRI were sometimes obtained at different local hospitals, which may induce error in assessment of the parameters. Second, there is no formal correlation available to verify preoperative MRI measurements with measured surgical margins, which could lead to a discrepancy in the results. Third, the interpretation of the surgical margin, as defined by Enneking et al,[24] was subjective and might vary depending on who undertook the assessment. For that reason, we applied a clearly defined microscopic margin measured in millimetres, which was objective and reproducible. Fourth, our study did not describe the functional outcomes based on the type of surgery performed. Finally, this was a single-institution retrospective study and future multicentre studies could offer useful prognostic information.

In summary, on the basis of a relatively large series of 226 patients with osteosarcoma of the limbs, we have demonstrated the clinicopathological significance of the proximity to the major vessels and clarified the outcome based on the type of surgery and the proximity of the tumour to these vessels. We found that there was an increased risk of LR and decreased OS as the tumour became close to the major vessels. When the tumour was observed to be attached to a major vascular bundle on preoperative MRI, amputation offered better local control, despite no survival benefit. However, the risks of LR by limb salvage was lower if patients are good responders to neoadjuvant treatment, or the vascular attachment is limited to 10 mm longitudinally or half the circumference of the vascular bundle. We believe that these findings could offer useful prognostic information for treating oncologists and be helpful in advising patients on the management of their osteosarcoma.

Take home message

- The proximity of osteosarcoma to major blood vessels is a poor prognostic factor for local control and survival.
- Amputation offers better local control for tumours attached to the blood vessels but does not improve survival.
- Limb salvage surgery offers similar local control if the radiological attachment of the tumour to major blood vessels is limited.

Supplementary material

Further Kaplan–Meier curves, as well as a table showing patient characteristics and univariate analysis for local recurrence-free survival (LRFS) and overall survival (OS).

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