

Research Article

Treatment-Related Prognostic Factors in Managing Osteosarcoma around the Knee with Limb Salvage Surgery: A Lesson from a Long-Term Follow-Up Study

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Purpose. The aim of this study was to assess the treatment-related factors associated with local recurrence and overall survival of patients with osteosarcoma treated with limb-salvage surgery. **Patients and Methods.** Treatment-related factors were analyzed to evaluate their effects on local recurrence-free survival (LRFS) and overall survival (OS) in 182 patients from 2004 to 2013. **Results.** The mean length of follow-up was 73.4 ± 34.7 months (median, 68 months; range, 12-173 months), and 63 patients died by the end of the follow-up. The 5-year and 10-year overall survival rates were $68.6 \pm 6.6\%$ and $59.4 \pm 10.6\%$, respectively. Univariate analysis showed that treatment-related prognostic factors for overall survival were prolonged symptom intervals ≥ 60 days, biopsy/tumor resection performed by different centers, previous medical history, incomplete preoperative chemotherapy (< 8 weeks), and prolonged postoperative interval > 21 days. In the multivariate analysis, biopsy/tumor resection performed by different centers, incomplete implementation of planned new adjuvant chemotherapy, and delayed resumption of postoperative chemotherapy (> 21 days) were risk factors for poor prognosis; biopsy/tumor resection performed by different centers and tumor necrosis $< 90\%$ were independent predictors of local recurrence. **Conclusion.** For localized osteosarcoma treated with limb-salvage surgery, it is necessary to optimize timely standard chemotherapy and to resume postoperative chemotherapy to improve survival rates. Biopsies should be performed at experienced institutions in cases of developing local recurrence.

1. Introduction

Osteosarcoma is a very rare malignant bone tumor with a high predilection for the area surrounding the knee joint [1]. Since the 1980s, neoadjuvant chemotherapy with limb-salvage surgery (LSS) has become the current standard for the management of high-grade osteosarcomas. Amputation offers better local control, but it confers no clear survival benefit over LSS [2–4], whether in patients with osteosarcoma who respond poorly to chemotherapy or not. The goal of LSS is to preserve a functioning limb without increasing the risk of tumor recurrence. However, there is still concern about the adverse impact of limb-salvage surgery on local recurrence and overall survival due to closer resection margins [5–8].

For those patients with high-grade osteosarcoma around the knee without initial metastases, the surgical margin

and the presence of tumor necrosis are generally accepted prognostic factors for local recurrence and overall survival [1, 9–17]. The prognostic relevance of other factors, such as tumor site and size, histologic subtype, neurovascular infiltration, elevated alkaline phosphatase (ALP), elevated lactate dehydrogenase (LDH), and age, is still controversial [18–22]. Other treatment-related factors, such as symptom intervals (SI) [23, 24], incomplete preoperative chemotherapy [25, 26], and delay of resumption of postoperation chemotherapy [27, 28], are still not clear. Because of these contradictory reports, the relevance of treatment-related prognostic factors in patients with osteosarcoma needs further elucidation, especially for those patients who prefer limb sparing. Indeed, the identification of patients with a favorable prognosis and of those with a poor prognosis may be used to adjust treatment and surveillance schedules [29, 30]. This is particularly

important for patients who are at risk for local recurrence and inferior survival who have been treated with limb sparing. A reasonable accurate estimate of overall survival and development of local recurrence before treatment decision-making would be helpful to avoid upsetting patients and their parents or confusing them with impractical hope. Therefore, we want to assess the influence of several treatment-related prognostic factors in a large series of patients treated with limb-salvage surgery from East China in long-term follow-up, excluding those patients with primary metastases, which may lead to paradoxical conclusions. We wish to pay more attention to the timing of planned new adjuvant chemotherapy and resumption adjuvant chemotherapy and to try and identify the time intervals, including symptom interval, preoperative chemotherapy duration, and preoperative interval and postoperative interval, which can serve as prognostic factors.

2. Patients and Methods

We conducted a retrospective, single-center review of patients with osteosarcoma around the knee after limb-salvage surgery between January 2004 and December 2013. During that time, 254 patients were treated for osteosarcoma around the knee. The study was approved by the Institutional Review Board. The exclusion criteria included metastatic disease at initial presentation (28 patients), limb amputation as the primary procedure (17 patients), initial age ≥ 60 years (14 patients), and incomplete follow-up records (13 patients). 182 patients were included in the final analysis.

2.1. Assessment of Patient, Tumor, and Treatment-Related Variables. Age, sex, tumor site, symptom interval, pathological fracture status, previous biopsy history, previous medical history, serum alkaline phosphatase level, preoperative chemotherapy duration, preoperative interval, bone margin length, histologic response (tumor necrosis), tumor size, neurovascular infiltration, postoperative interval, presence of local recurrence, metastatic disease, and overall survival were recorded for each patient (Table 1). For the 182 patients, the median age at diagnosis was 18 years (mean, 21.2 ± 7.6 years; range, 12 to 59 years). There were 114 male patients (62.6%; median age, 18 years; range, 12 to 59 years) and 68 female patients (37.4%; median age, 19 years; range, 12 to 55 years). 103 osteosarcomas (56.6%) were detected in the second, 50 (27.5%) in the third, and 29 (15.9%) in the fourth decade of life or later. The average symptom interval was 68.2 days (median, 65 days; range, 23 to 750 days), and there were 98 patients with a prolonged SI of more than 60 days. Pathologic fracture occurred in 8 patients (4.4%) before primary surgery, 31 patients (17%) underwent biopsy outside of our hospital, and 17 patients (9.3%) presented with previous medical history. Regarding the histological subtypes, there were 134 (73.6%) osteoblastic osteosarcomas, 24 (13%) chondroblastic osteosarcomas, 10 (5.5%) fibroblastic osteosarcomas, and 14 (7.9%) telangiectatic osteosarcomas.

TABLE 1: Patient characteristics.

	Number of patients (%)
Gender	
female	68(37.4%)
male	114(62.6%)
Age at diagnosis	21.2 \pm 7.6 years, 12-59
31-59 years old	29(15.9%)
21-30 years old	50(27.5%)
10-20 years old	103(56.6%)
Site	
distal femur	118(64.8%)
proximal tibia	64(35.2%)
Symptom intervals	68.2 \pm 69.7 days, 23-750
<60 days	84(46.2%)
\geq 60 days	98(53.8%)
Pathologic fracture	
not occurred	174(95.6%)
occurred	8(4.4%)
Center performing the biopsy/the tumor resection	
same	151(83%)
different	31(17%)
Previous medical history	
no	165(90.7%)
yes	17(9.3%)
Elevated initial ALP	
no	42(23.1%)
yes	140(76.9%)
Bone margin width	
\geq 3 cm	161(88.5%)
\geq 2 cm	21(11.5%)
Neurovascular infiltration	
no	122(67%)
yes	60 (33%)
Tumor size	
<10 cm	106(58.2%)
\geq 10 cm	76(41.8%)
Histological subtypes	
osteoblastic	134(73.6%)
chondroblastic	24(13%)
fibroblastic	10(5.5%)
telangiectatic and other	14(7.9%)
Tumor necrosis	
\geq 90%	70(38.5%)
<90%	112(61.5%)
Preoperative chemotherapy duration	10.8 \pm 2.1weeks, 4-16
8-12 weeks	110(60.4%)
>12 weeks	38(20.9%)
<8 weeks	34(18.7%)
Preoperative interval	13.1 \pm 4.1days, 7-25
<14 days	104(57.1%)
\geq 14 days	78(42.9%)
Postoperative interval	23 \pm 10.1 days, 7-60
\leq 14 days	30(16.5%)
15-21days	75(41.2%)
>21 days	77(42.3%)

Symptom interval (SI) was defined as the time from the first onset of symptoms or signs to a definitive diagnosis and initiation of treatment [24].

Previous medical history was defined as the patients having accepted inadequate treatment due to an erroneous diagnosis, including erroneous drug and surgical treatment, before they were referred to professional musculoskeletal oncologists. Patients diagnosed with secondary osteosarcoma were also assessed and included in this group.

At diagnosis, the serum ALP levels were measured in international units (IU), and the activity of ALP was estimated by the p-nitrophenyl phosphate method. ALP ranges of 60.0-300.0 IU/L for patients ≤ 14 years and 38.0-115.5 IU/L for patients > 15 years were considered normal.

Responses to neoadjuvant chemotherapy (tumor necrosis) were graded on the basis of the amount of tumor necrosis in the resected specimen. More than 90% tumor necrosis was regarded as a good response; a cut-off of 90% tumor necrosis is usually used to distinguish good and poor responders [31].

Standard chemotherapy followed the protocols of IOR/OS-4 [32]. The standard length of preoperative chemotherapy duration was 10 weeks of 2 cycles of multidrug therapy. The preoperative interval was defined as the time from the end of preoperative chemotherapy to the primary surgery.

Neurovascular infiltration was defined as tumor growth outside of the normal compartment and infiltration of soft tissue, such as the nerve and vasculature, which can be inspected by enhanced MRI preoperatively and confirmed during surgery and by pathological examination. Tumors measuring at least 10 cm in length of the involved bone or more were defined as large and all others as small.

The postoperative interval was defined as the time from primary surgery to the resumption of postoperative chemotherapy.

2.2. Diagnosis, Treatment, and Surveillance. Diagnosis of osteosarcoma, established by clinical and radiological findings, was confirmed on core needle biopsy or open biopsy instead of fine biopsy. Thereafter, 2 cycles of neoadjuvant chemotherapy were given to patients. The chemotherapy protocol was IOR/OS-4 [32]. Histologic response to preoperative chemotherapy was evaluated and graded according to previously reported criteria [31].

Surgical excision of the primary tumor involved en bloc resection of the overlying biopsy tract with the tumor. Resection of the tumor and reconstruction of the bone defect were performed according to the operating instructions provided by Enneking et al. [33]. Proximal and distal bony margins were defined by the respective treatment protocol according to Enneking's classification. Detailed bone and soft tissue margin widths were guided by Kawaguchi et al. [34, 35]. The surgical margin was determined by 3 techniques: macroscopic inspection of the specimen, careful dissection, and histologic examination. Tumor size, neurovascular infiltration, and tumor necrosis were also recorded via pathological examination by macroscopic inspection.

Postoperative chemotherapy was given once the wound healed adequately. The chemotherapy protocol was modified

if the tumor response was poor according to IOR/OS-4. Postoperative follow-up was performed every 2-3 months in the first two years, every 4 months until 5 years, and every 6 months in the following years. Imaging modalities included bone scans, chest computed tomography (CT) scans, abdominal ultrasounds, and positron emission tomography (PET) scans.

Seventy patients showed good response to neoadjuvant chemotherapy with tumor necrosis $\geq 90\%$. The average preoperative chemotherapy duration was 10.8 ± 2.1 weeks, and patients were grouped according to their length of preoperative chemotherapy: 110 patients (60.4%) with a duration of 8-12 weeks, 38 patients (20.9%) with a duration greater than 12 weeks, and 34 patients (18.7%) with a duration less than 8 weeks due to noncompliance or severe drug toxicity. Seventy-eight patients (42.9%) underwent primary surgery after 14 days from the end of preoperative chemotherapy, while 77 patients (42.3%) had a delay of greater than twenty-one days to the resumption of chemotherapy (Table 1).

2.3. Statistics. Kaplan and Meier estimates were used to assess overall survival (OS) and local recurrence-free overall survival (LRFS) [36]. For survival analysis, the primary end points were time to death, so overall survival was measured from the date of diagnosis to death or the endpoint of follow-up. LRFS was defined as the time from the date of primary surgery to the day when local recurrence was confirmed by biopsy or surgery. Univariate and multivariate Cox proportional hazards regression analyses were performed to determine which parameters were significant. A 95% confidence interval level was used; $p < 0.05$ was considered as significant to identify factors predictive of local recurrence and overall survival. The multivariate logistic regression model included all the potential predictors. Predictors were excluded (one by one) if the p value of the log likelihood ratio test was greater than 0.10. Predictor exclusion was continued until all the remaining predictors had p values less than 0.10, which was then defined as the final prediction model. SPSS Version 20.0 (SPSS Inc., Chicago, IL) was used for all statistical analyses.

3. Results

3.1. Prognostic Factors for Overall Survival. The 5-year and 10-year overall survival rates were $68.6 \pm 6.6\%$ and $59.4 \pm 10.6\%$, respectively (Figure 1). The mean length of follow-up was 73.4 ± 34.7 months (median, 68 months; range, 12-173 months), and 63 patients had died by the end of follow-up.

Univariate analysis showed that the prognostic factors for overall survival were young age at diagnosis, prolonged symptom intervals ≥ 60 days, biopsy/tumor resection performed by different centers, previous medical history, elevated ALP at diagnosis, neurovascular infiltration, tumor size ≥ 10 cm, tumor necrosis $< 90\%$, incomplete preoperative chemotherapy (< 8 weeks), and prolonged postoperative interval > 21 days. In the multivariate analysis, the risk factors were young age at diagnosis, biopsy/tumor resection performed by different centers, elevated ALP at diagnosis, tumor size ≥ 10 cm, tumor necrosis $< 90\%$, prolonged postoperative interval

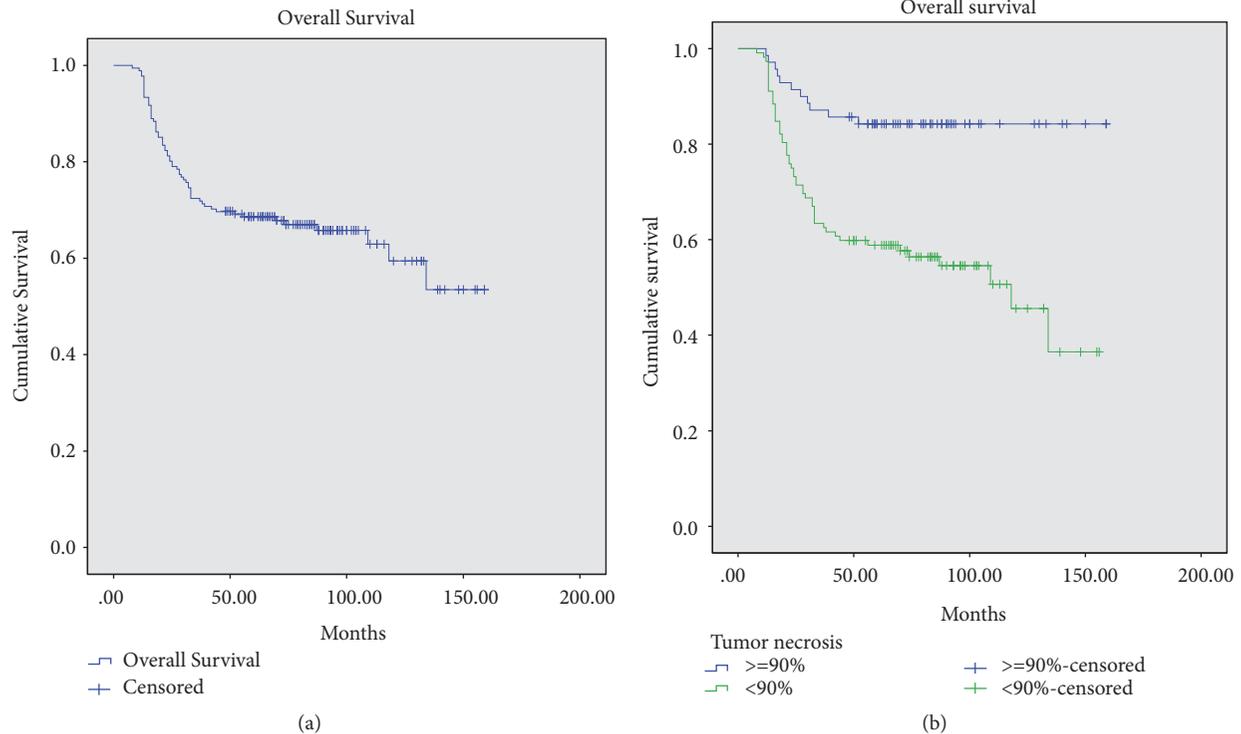


FIGURE 1: Overall survival for 182 patients and overall survival for patients with tumor necrosis $\geq 90\%$ and not ($p < 0.001$).

> 21 days, and shorter preoperative chemotherapy (< 8 weeks) (Table 2).

The 5-year overall survival for patients with tumor necrosis $\geq 90\%$ and patients with tumor necrosis $< 90\%$ was $84.2 \pm 8.6\%$ and $58.9 \pm 9.2\%$ ($p < 0.001$) (Figure 1). The 5-year overall survival for patients with a prolonged symptom interval (SI) ≥ 60 days and patients with a shorter SI was $62.2 \pm 9.6\%$ and $76.1 \pm 8\%$, respectively ($p = 0.062$) (Figure 2). Among the 112 patients with tumor necrosis $< 90\%$, the 5-year overall survival of 59 patients who had a prolonged symptom interval (SI) ≥ 60 days was $47.4 \pm 12.7\%$, much worse than that ($71.7 \pm 12.2\%$) in 53 patients with a shorter SI ($p = 0.014$) (log rank test) (Figure 2).

The 5-year overall survival rates for patients with different postoperative intervals (PSIs) were $83.3 \pm 13.3\%$ (PSI, < 14 days), $69.3 \pm 10.4\%$ (PSI, 14-21 days), and $62.3 \pm 10.8\%$ ($p = 0.041$) (Figure 3). The 5-year overall survival rates for patients with different preoperative chemotherapy durations were $74.5 \pm 8.2\%$ (8-12 weeks), $68.4 \pm 14.7\%$ (> 12 weeks), and $49.6 \pm 16.9\%$ (< 8 weeks) ($p = 0.015$) (Figure 3).

3.2. Prognostic Factors for Local Recurrence. The incidence of local recurrence (LR) in this study was 13.7% (25/182), and the 5-year LR-free survival was $85.3 \pm 5.3\%$ (Figure 4). The 5-year overall survival for patients with local recurrence was $40 \pm 19.2\%$, which was significantly lower than that for patients without local recurrence ($73.2 \pm 6.9\%$) ($p < 0.001$) (Figure 4).

Univariate analysis showed that prognostic factors for LR-free survival were biopsy/tumor resection performed by

different centers, neurovascular infiltration, tumor size ≥ 10 cm, and tumor necrosis $< 90\%$. Patients with a previous medical history or a larger tumor size were inclined to develop local recurrence, although it was not significant. However, in the multivariate analysis, only biopsy/tumor resection performed by different centers and tumor necrosis $< 90\%$ were independent predictors of local recurrence. There was no significant difference in the probability regarding sex, age, bone margin width, elevated ALP level at diagnosis, preoperative chemotherapy duration, preoperative interval, and postoperative interval (Table 3).

For patients who underwent biopsy by different centers, their 5-year LR-free survival was $58.1 \pm 19.6\%$ and was much worse than that of those whose biopsy was performed in the same center ($p < 0.001$) (Figure 5). The 5-year LR-free survival for patients with necrosis $< 90\%$ was $80.2 \pm 7.6\%$, significantly worse than those with necrosis $\geq 90\%$ ($p = 0.008$) (Figure 5).

4. Discussion

In this study, we presented a long-term assessment of overall survival and local recurrence in relation to prognostic factors among patients with nonmetastatic high-grade osteosarcoma around the knee. We found an overall cumulative 5- and 10-year survival rate of $68.6 \pm 6.6\%$ and $59.4 \pm 10.6\%$, respectively, with a mean follow-up of 73.4 months. The overall survival in our study is on par with most data [1, 9, 20, 22]. The incidence of local recurrence (LR) in this study was 13.7% (25/182), and the 5-year LR-free survival was $85.3 \pm 5.3\%$. Our local recurrence rate of 13.7% is slightly higher than

TABLE 2: Summary of univariate and multivariate Cox proportional hazards model for overall survival. HR: hazards ratio; LRT: likelihood rate testing.

	Univariate LRT <i>p</i> values and HR (95%)	Multivariate LRT <i>p</i> values and HR (95%)
Gender	0.771	
female	Ref.	
male	0.927(0.557-1.543)	
Age at diagnosis	0.026	
31-59 years old	Ref.	Ref.
21-30 years old	2.849(0.952-8.530)	0.038 2.268(1.065-10.029)
10-20 years old	3.686(1.322-10.283)	0.026 3.304(1.156-9.447)
Site	0.533	
distal femur	Ref.	
proximal tibia	0.845(0.497-1.437)	
Symptom intervals	0.066	0.193
<60 days	Ref.	Ref.
≥60 days	1.622(0.969-2.715)	1.443(0.830-2.509)
Pathologic fracture	0.248	
not occurred	Ref.	
occurred	0.313(0.043-2.260)	
Center performing the biopsy/the tumor resection	0.044	0.001
same	Ref.	Ref.
different	1.817(1.017-3.247)	2.797(1.503-5.207)
Previous medical history	0.045	0.108
no	Ref.	Ref.
yes	1.997(1.016-3.927)	1.928(0.865-4.294)
Elevated ALP at diagnosis	0.041	0.013
no	Ref.	Ref.
yes	1.678(1.022-2.756)	2.001(1.156-3.463)
Bone margin width	0.701	
≥3 cm	Ref.	
≥2 cm	1.157(0.549-2.436)	
Neurovascular infiltration	0.049	0.182
no	Ref.	Ref.
yes	1.654(1.003-2.727)	1.479(0.832-2.628)
Tumor size	0.034	0.003
<10 cm	Ref.	Ref.
≥10 cm	1.708(1.041-2.802)	2.199 (1.311-3.690)
Histological subtypes	0.654	
osteoblastic	Ref.	
chondroblastic	0.765(0.347-1.688)	
fibroblastic	0.458(0.111-1.884)	
telangiectatic and other	0.800(0.289-2.216)	
Tumor necrosis	<0.001	0.001
≥90%	Ref.	Ref.
<90%	3.504(1.827-6.720)	3.287(1.665-6.491)
Preoperative chemotherapy duration	0.019	
8-12 weeks	Ref.	Ref.
>12 weeks	1.081(0.556-2.099)	0.434 0.745(0.357-1.556)
<8 weeks	2.210(1.251-3.903)	0.008 2.249(1.232-4.105)

TABLE 2: Continued.

	Univariate LRT <i>p</i> values and HR (95%)		Multivariate LRT <i>p</i> values and HR (95%)	
Preoperative interval	0.701			
<14 days	Ref.			
>=14 days	0.906(0.547-1.501)			
Postoperative interval	0.051			
<=14 days	Ref.		Ref.	
15-21days	1.965(0.749-5.153)		0.051	2.687(0.998-7.236)
>21 days	2.913(1.139-7.451)		0.036	2.844(1.068-7.572)

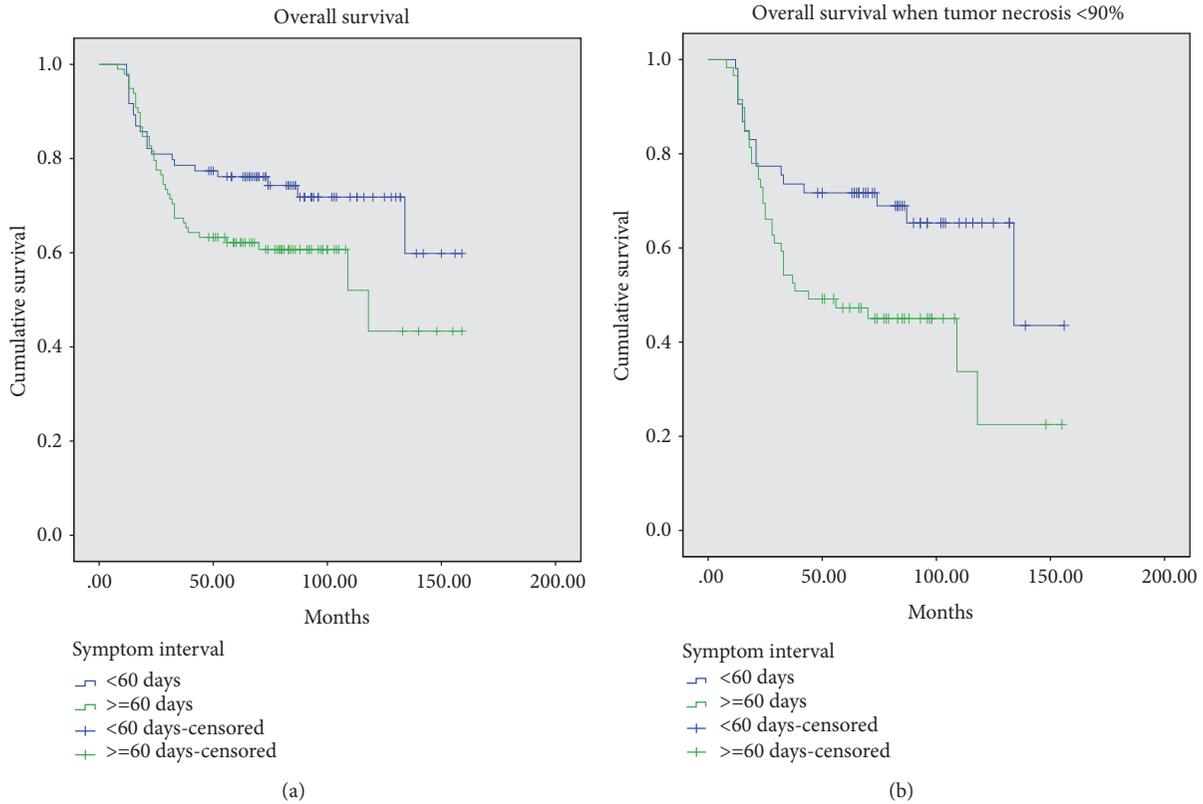


FIGURE 2: Overall survival for 182 patients with different symptom interval ($p=0.062$) and for 112 patients with tumor necrosis <90% classified with different symptom interval ($p=0.014$).

that presented in some reported data [6, 12, 37, 38], but these data are equal to data from a larger series report [2, 8, 39–41].

In this study, we found that several factors are significant for an unfavorable prognosis after rigorous statistical analysis. These independent factors are listed as follows and coincide with reports from previous literature: young age [9], elevated ALP at diagnosis [9, 42], large tumor size [1, 9, 20, 43], tumor necrosis <90% [1, 8, 12, 18, 43], prolonged postoperative interval >21 days [27], and nonstandard chemotherapy [44, 45]. Sex [8, 22], pathologic fracture [8, 46], and histological subtypes [8, 20, 22] are not prognostic factors, findings which are identical to our outcomes.

Although there is a tendency towards worse overall survival for patients with symptom delays of longer than 60 days, we are unable to find a positive correlation ($p=0.193$,

HR=1.443 (0.830-2.509)) in the multivariate analysis between a prolonged SI and overall survival; that is, latency of diagnosis and new adjuvant chemotherapy is not associated with poor prognosis. However, when adjusted for lower tumor necrosis (<90%), patients with an SI longer than 60 days had adverse 5-year overall survival of $47.4\pm 12.7\%$, which was much worse than that ($71.7\pm 12.2\%$) in patients with a shorter SI ($p=0.014$). This indicates that we should adjust adjuvant therapy and intense surveillance for those patients with a longer SI and a poor chemotherapy response. Similar results that no positive correlation exists between the SI and the outcome of osteosarcoma patients have been shown in other reports [1, 23, 24]. Some studies even show that the SI is shorter in patients with metastatic disease than in patients with localized disease, and patients with a longer duration

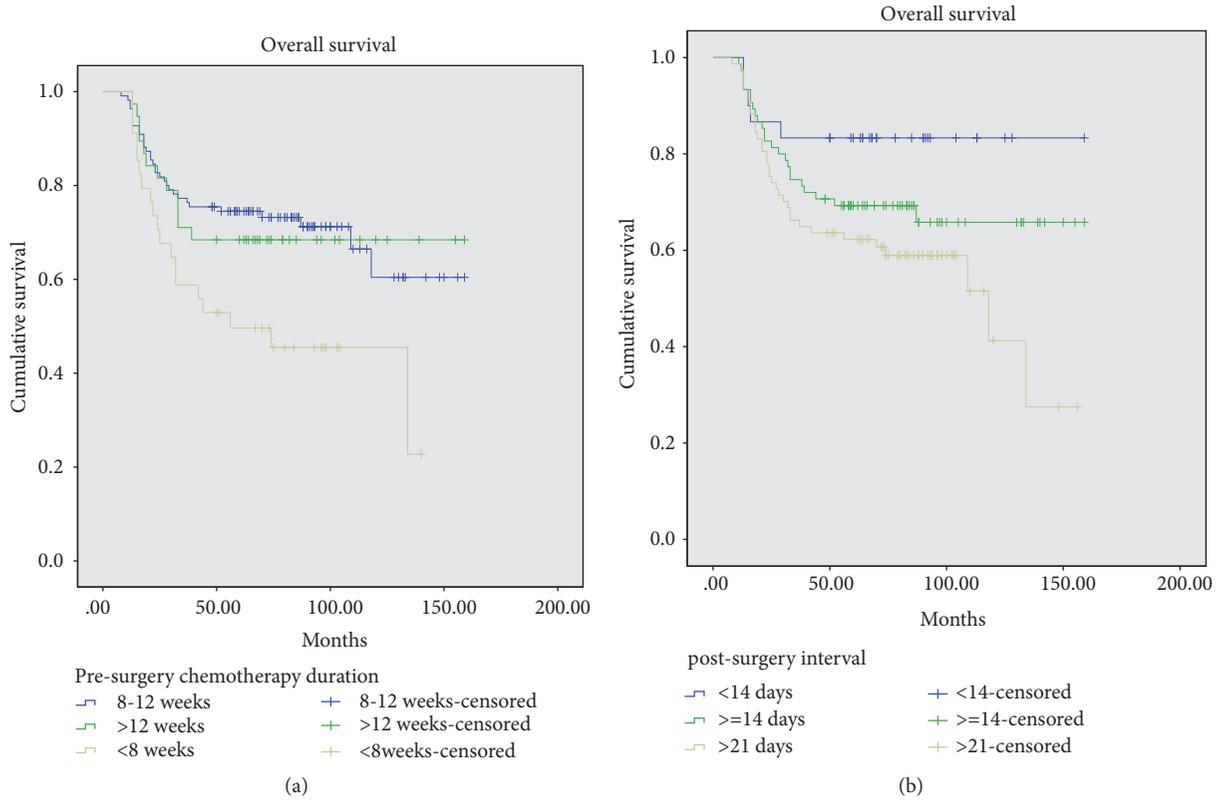


FIGURE 3: Overall survival for patients with different duration of preoperative chemotherapy (74.5±8.2% (8-12 weeks), 68.4±14.7% (>12 weeks), and 49.6±16.9% (<8 weeks), $p=0.015$) and for patients with different postoperative interval (83.3±13.3% (<14 days), 69.3±10.4% (14-21 days), and 62.3±10.8% (>21 days), $p=0.041$).

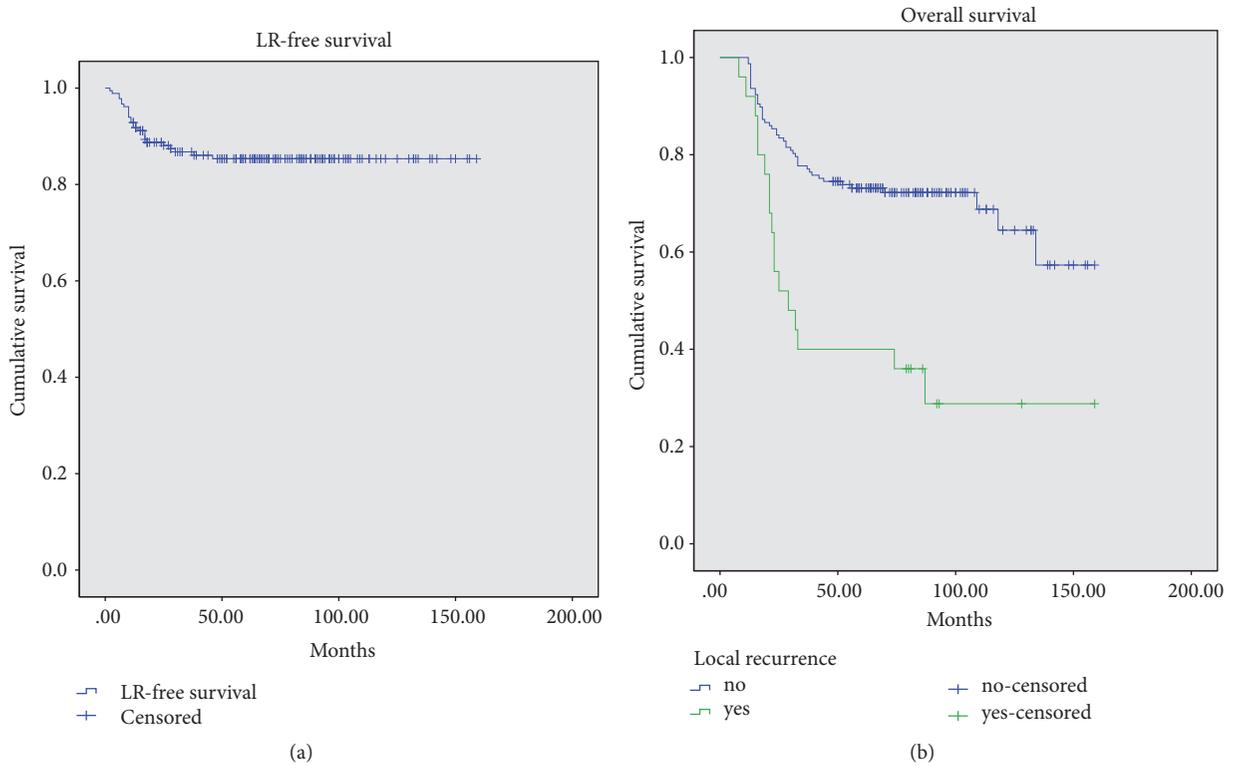


FIGURE 4: Local recurrence-free survival for 182 patients and overall survival for patients with and without local recurrence ($p<0.001$).

TABLE 3: Summary of univariate and multivariate Cox proportional hazards models for LR. HR: hazards ratio; LRT: likelihood rate testing.

	Univariate LRT <i>p</i> values and HR (95%)	Multivariate LRT <i>p</i> values and HR (95%)
Gender	0.241	
female	Ref.	
male	0.625(0.285-1.370)	
Age at diagnosis	0.544	
31-59 years old	Ref.	
21-30 years old	1.947(0.527-7.194)	
10-20 years old	1.366(0.389-4.794)	
Site	0.678	
distal femur	Ref.	
proximal tibia	0.837(0.361-1.940)	
Symptom intervals	0.480	
<60 days	Ref.	
≥60 days	1.334(0.599-2.971)	
Pathologic fracture	0.464	
not occurred	Ref.	
occurred	0.046(0-171.359)	
Center performing the biopsy/the tumor resection	<0.001	0.002
same	Ref.	Ref.
different	4.601(2.082-10.169)	4.099(1.649-10.192)
Previous medical history	0.060	0.931
no	Ref.	Ref.
yes	2.561(0.960-6.835)	0.951(0.308-2.942)
Initial raised ALP	0.301	
no	Ref.	
yes	1.517(0.688-3.344)	
Bone margin width	0.895	
≥3 cm	Ref.	
≥2 cm	1.084(0.325-3.624)	
Neurovascular infiltration	0.007	0.163
no	Ref.	Ref.
yes	4.140(1.826-9.388)	1.838(0.782-4.320)
Tumor size	0.070	0.152
<10 cm	Ref.	Ref.
≥10 cm	2.080(0.043-4.589)	1.871(0.795-4.405)
Histological subtypes	0.340	
osteoblastic	Ref.	
chondroblastic	0.261(0.035-1.944)	
fibroblastic	1.922(0.571-6.470)	
telangiectatic and other	0.477(0.064-3.555)	
Tumor necrosis	0.014	0.022
≥90%	Ref.	Ref.
<90%	3.802(1.304-11.087)	3.536(1.198-10.438)
Preoperative chemotherapy duration	0.783	
8-12 weeks	Ref.	
>12 weeks	0.694(0.234-2.063)	
<8 weeks	0.818(0.275-2.432)	

TABLE 3: Continued.

	Univariate LRT <i>p</i> values and HR (95%)	Multivariate LRT <i>p</i> values and HR (95%)
Preoperative interval	0.336	
<14 days	Ref.	
>=14 days	1.469(0.670-3.220)	
Postoperative interval	0.761	
<=14 days	Ref.	
15-21days	0.934(0.288-3.034)	
>21 days	1.278(0.412-3.964)	

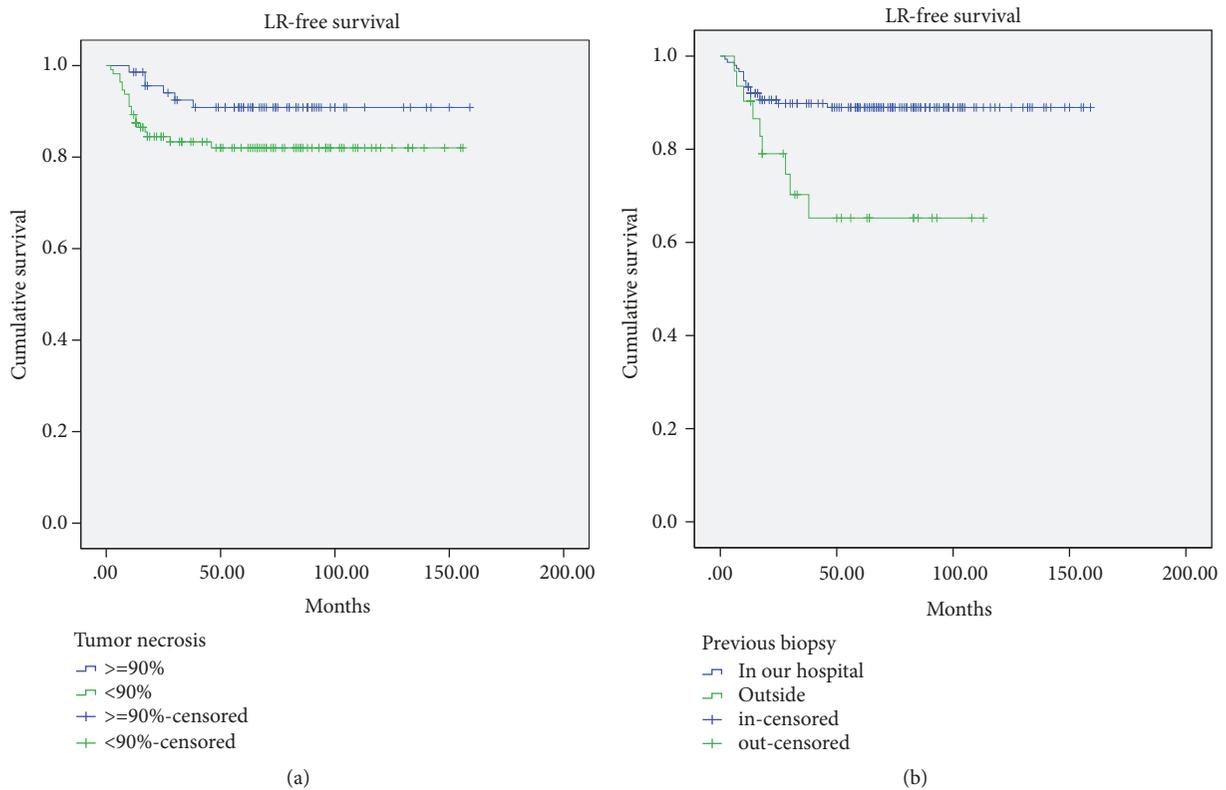


FIGURE 5: Local recurrence-free survival for patients classified with tumor necrosis ($p=0.008$) and biopsy in same center or not ($p<0.001$).

of symptoms appear to have a better prognosis [47, 48]. Interestingly, Bielack et al. [1] found that longer symptom history and treatment delay do significantly correlate with poor chemotherapy response. Jin et al. [49] concluded that adolescents with longer patient delays may incur inferior prognoses. In this cohort, patients with primary metastases that showed aggressive tumor biology were excluded, but we still found a slight tendency towards a poor prognosis for patients with symptom delays ($p=0.066$, 1.622 (0.969-2.715)) in the univariate analysis. We recommend that we should pay more attention to patients with long symptom intervals. We recommend early diagnosis and treatment to shorten the SI in cases of poor survival because prolonged SI leads to poor chemotherapy response. For patients with prolonged SI at diagnosis, standard chemotherapy should be vigorously

executed to obtain good tumor necrosis, avoiding decreasing chemotherapy intensity.

Incomplete preoperative chemotherapy and prolonged preoperative chemotherapy may incur poorer prognosis compared to standard preoperative chemotherapy in our study. Shorter or incomplete preoperative chemotherapy correlates with poor chemotherapy response [50, 51] due to the heterogeneity of patient compliance with chemotherapy or inferior socioeconomic status [44, 45, 52]. Patients with shorter or incomplete preoperative chemotherapy were 2.809 (95% CI, 1.169-6.750) times at risk for poor prognosis in our study. Toxicity, patient choice, and financial inadequacy also resulted in prolonged preoperative chemotherapy duration in our study. Both incomplete preoperative chemotherapy and prolonged preoperative chemotherapy would reduce

the overall dose intensity according to recent investigators [53, 54]. The results of dose-intensity analyses performed by other investigators [25, 26, 55, 56] support the hypothesis that the actual dose intensity delivered determines the outcome of treatment of osteosarcoma. On the other hand, some researchers [57, 58] suggest that as preoperative therapy becomes more prolonged, the correlation of tumor necrosis with DFS (disease-free survival) decreases. Standard chemotherapy, if possible, should be rigorous to achieve a superior prognosis.

Similar to the results of Imran et al. [27], the mean surgery to postoperative chemotherapy interval was 23 ± 10.1 days (7-60 days) in our study, and the median length was 21 days. In the study by Imran et al. [27], overall survival was poorer for patients who had a delay of greater than 21 days before the resumption of chemotherapy compared with that of patients who had a shorter delay. Patients with a good response to the preoperative chemotherapy fared worse when the postoperative chemotherapy was delayed for more than sixteen days after the definitive surgery, whereas the impact of delayed resumption of chemotherapy on the patients with a poor response was not significant. The reason may be that a lengthy delay before the resumption of chemotherapy after definitive surgery could compromise the overall dose intensity. Patients with a poor histological response to preoperative chemotherapy have worse survival when they have a delay in resumption of chemotherapy of more than twenty-four days [57]. Our study confirmed these findings in that patients with a postoperative interval >21 days are inclined to incur poor outcomes (HR=2.844 (1.068-7.572), $p=0.036$). In this study, it seems that patients with a postoperative interval longer than 14 days face a negative ending, and the later they resume chemotherapy, the poorer their outcomes are. Whether intensive chemotherapy would impact the chemotherapy response and the survival thereafter is still controversial [53–56]; thus further study on delayed resumption of postoperative chemotherapy and its impact is still needed.

The local recurrence rate in this study is 13.7%, which is slightly higher than the current international standard (4–10%). Neurovascular infiltration [6, 8], large tumor size, and inferior tumor necrosis [38, 59, 60] are commonly regarded as risk factors for local recurrence. Under the promotion of limb-salvage surgery, these factors have been widely and intensely debated [2, 12, 15, 19, 61, 62]. However, in our study, we attribute the higher incidence of local recurrence to inadequate/close margins and poor tumor necrosis. Reasons for inadequate/close margins include unprofessional biopsy and erroneous/unplanned surgery due to an erroneous diagnosis. In this study, 31 patients (17%) received a biopsy in other medical centers and then asked for limb-salvage surgery in our hospital; 17 patients (9%) received prior surgery, such as intralesional/marginal curettage. These unplanned surgeries may lead to problems in managing wide soft tissue margins due to unplanned approaches. That is why all of these recurrent tumors were located in the soft tissue around the wound or near the neurovascular bundle, although frozen-section histology examination by intraoperative biopsies certified that there were no residual tumor cells. A previous

medical history due to malignant transformation or erroneous diagnosis and treatment has recently been accepted by some researchers as a risk factor [6, 63–65]. Biopsy/tumor resection performed by different centers in this study is a significant predictor of the development of local recurrence and poorer overall survival. This is similar to the reports by Picci et al. [66], Andreou et al. [6], and Poudel et al. [39]. The biopsy approach must be planned so that it can be completely and widely excised at the moment of the resection. The procedure should be performed by an experienced surgical team who will also be handling the definitive surgery. Poor necrosis due to nonstandard chemotherapy (incomplete chemotherapy) is widely accepted as a risk factor for local recurrence. In this study, 72 patients (39.6%) did not achieve complete or standard chemotherapy due to noncompliance with chemotherapy and low socioeconomic status. Thus, only 70 patients (38.5%) had good tumor necrosis ($\geq 90\%$). This is one of the reasons for the high incidence of local recurrence in this study.

Due to the lack of uniformity in patient analyses and methods and statistics that were calculated on study populations whose minimum follow-up was often less than 3 years, a number of clinical and pathologic features show bias in different studies and present with contradictory prognostic significance. However, our present analysis evaluated a large number of patients according to the previously mentioned prognostic variables, followed up for at least 5 years. In our study, data about the variables evaluated were available for almost all patients. The main shortcoming is that data were not derived from a randomized study, but we collected information from each patient prospectively. The tumors of the patients included in this study were somehow heterogeneous in terms of biological behavior and stage, but we rigorously set and executed inclusion and exclusion criteria. We believe that our data provide a meaningful contribution to the previous literature.

5. Conclusion

For localized osteosarcoma treated with limb-salvage surgery, it is necessary to optimize timely standard chemotherapy and to resume postoperative chemotherapy to improve survival rates. Biopsies should be performed at experienced institutions in cases of developing local recurrence.

Data Availability

The data used to support the findings of this study and the datasets used and/or analyzed during the current study are available from the corresponding author upon request (Chunlin Zhang, shzhangchunlin123@163.com).

Ethical Approval

The study received ethical approval from the Institutional Review Board of Shanghai Tenth People's Hospital affiliated to Tongji University.

Consent

Written informed consent was obtained from all patients before surgical treatment including the fact that the data may be included in future publications.

Disclosure

Jianping Hu, Chunlin Zhang, and Kunpeng Zhu are co-first authors. The IRB and ethical committee of the Shanghai Tenth Peoples' Hospital would review the requests because of the patients' information. After the approval of the committee with confirmation of the reasonable requests, the dataset would be freely available.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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