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Original Article

Meta-analysis of the prognosis after surgical treatment of osteosarcoma complicated by pathologic fracture

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Abstract: Aim: To evaluate the prognosis of surgical treatment of osteosarcoma complicated by pathologic fracture. Materials and methods: We searched articles in PubMed, Web of Science, and Embase for studies published up to January 1, 2022, that reported the surgical prognosis of osteosarcoma patients complicated with/without pathologic fracture. The specific outcome indicators used in the meta-analysis included the local recurrence rate (LRR), distant metastasis rate (DMR), overall survival (OS) rate and disease-free survival (DFS) rate after surgical treatment such as amputation or limb salvage in the pathologic fracture group and non-pathologic fracture group. Crude and adjusted Odds Ratio (OR) with 95% confidence intervals were used to compare data between the case group and control group. Fifteen studies and 3839 patients were included in the final meta-analysis. Results: The difference between the pathologic fractures group and the non-pathologic fracture group was not statistically significance in LRR analysis (OR = 1.27, 95% CI: 0.88-1.84, P > 0.05); however, a statistically significant difference was found between two groups in DMR (OR = 1.42, 95% CI: 1.03-1.95, P < 0.05). For survival rates, the following ORs were found: 3-year OS (OR = 1.71, 95% CI: 1.25-2.35, P < 0.05); 5-year OS (OR = 1.41, 95% CI: 1.06-1.87, P < 0.05); 3-year DFS (OR = 1.88, 95% CI: 1.20-2.94, P < 0.05); and 5-year DFS (OR = 1.49, 95% CI: 1.10-2.03, P < 0.05). The pooled estimate of OR is 1.48 (95% CI: 0.72-3.04, P > 0.05) for local recurrence and 1.82 (95% CI: 0.92-3.60, P > 0.05) for distant metastasis in the amputation group and the limb salvage group for osteosarcoma patients with pathologic fractures, respectively. Our analysis indicated that patients with a pathologic fracture have a higher risk of DMR after surgery, but there is no significant difference in LRR between patients with a pathologic fracture and without. Additionally, in osteosarcoma patients with a pathologic fracture, there was no difference in LDR or DMR between limb-salvage surgery and amputation. Conclusion: Complicated with pathologic fracture is a negative prognostic indicator of osteosarcoma, and its poor survival rates (both OS and DFS) may be associated with a higher DMR. For osteosarcoma patients with pathologic fractures treated with standard treatment, LRR and DMR exhibit no significant difference between amputation and limb-salvage surgery.

Keywords: Osteosarcoma, pathologic fracture, limb salvage surgery, oncology prognosis, meta-analysis

Introduction

Osteosarcoma is the most common primary bone malignant tumor in children and adolescents [1]. Its incidence is about 0.3/100000 [2]. The tumor occurs mainly at the ends of the long bones of the limbs, especially the distal femur and proximal tibia [1]. Osteosarcoma is characterized by extreme malignancy, strong local invasiveness, highly active cellular components, marked atypia, and lack of matrix [3, 4], resulting in the susceptibility to pathologic fractures.

5~10% of osteosarcoma patients undergo pathologic fractures during diagnosis or preoperative treatment [5]. Since pathologic fractures can cause local hematomas, tumor cells may spread through adjacent tissues and enter the surrounding joints and blood vessels [6], resulting in difficulty of complete surgical removal and a probability of distant metastasis [7]. Therefore, the prognosis of osteosarcoma patients with pathologic fractures is clinically controversial.

Some studies have found that the limb osteosarcoma patients with pathologic fractures have a high LRR, which significantly shortens the patient's survival time and reduces the patient's quality of life [8]; while other studies believe that pathologic fractures do not change the patients' LRR [9-11]. The lower survival rate is associated with earlier lung metastases. In addition, it is generally believed that as long as the limb local osteosarcoma does not invade the surrounding blood vessels and nerves, limb salvage surgery should be the first choice [12], but the surgical decision-making is difficult when they complicate pathologic fractures. Some surgeons believe that complete removal of the tumor as soon as possible can effectively prevent the progression of the disease caused by the fractures, so early amputation should be listed as an option for osteosarcoma patients with pathologic fractures [13-15]. However, a few surgeons indicate that the limb salvage surgery has begun to be used to treat highly malignant local osteosarcoma, and even in those patients with pathologic fractures, the clinical benefit observed was acceptable [9, 16, 17]. Although limb local osteosarcoma patients with pathologic fractures were not rare clinically, only a few studies have specifically compared the prognosis of limb salvage and amputation. It has not been determined whether limb salvage surgery has a negative effect on survival or tumor recurrence, because of conflicting results in these studies.

In this study, the results of previous studies were systematically and comprehensively analyzed by meta-analysis, in order to provide a reasonable reference for the choice of treatment methods for limb local osteosarcoma patients with pathologic fracture.

Materials and methods

Search strategy and selection criteria

According to the PRISMA 2009 checklist criteria, we conducted a comprehensive search of the published literature via PubMed, Embase, and Web of Science of Controlled Trials database for articles that reported the outcomes of osteosarcoma patients with/without pathologic fractures. We identified studies by using the following search terms in the title and abstract of these articles: ((pathologic fracture) OR (pathological fracture)) AND (osteosarcoma). The search terms were kept broad so as to cover all possibilities for applicable studies, and trace the references that have been included in the literature, to expand the scope of the search. The deadline for the search is January 1, 2022.

After reviewing the titles and excluding the literature that did not meet the requirements, two researchers (Wu and Yuan) independently reviewed all abstracts: full texts of articles that might meet the criteria for consideration were extracted for further analysis. We manually searched the reference lists of these articles to identify articles for further analysis. After that, according to the pre-set inclusion and exclusion criteria, eligible articles were selected for final analysis. Differences between the authors were resolved by consensus.

All comparative articles recording the clinical outcome of osteosarcoma patients with/without pathologic fractures were included. Additionally, we only included studies with clearly defined clinical outcome indicators. If an article included people with a variety of different tumors, it was included only when reporting the outcomes of patients with limb local osteosarcoma. Exclusion criteria include animal studies; osteosarcoma in Enneking stage III; benign and other malignant tumors; no control group; reports of clinical outcome indicators are missing or unclear (eg: unable to extract data from patients with limb local osteosarcoma); individual case reports, and non-English articles or conference abstract. The articles selected for the final analysis were independently graded by using the Newcastle-Ottawa Scale (NOS) to further assess the quality of non-randomized studies in meta-analysis.

Data extraction and study assessment

We evaluated the final included articles, and obtained the following information from each article: year of publication; first author; study design; study population characteristics of the pathologic fracture group and non-fracture group; treatment; outcome measures; study endpoint; follow-up time and conclusion. The specific outcome indicators used in the meta-analysis included the LRR and DMR, OS rate and DFS rate after surgical treatment such as amputation or limb salvage surgery in the pathologic fracture group and non-pathologic fracture group.

Studies used the Kaplan-Meier curves described OS and DFS rates. We used Engauge Digitizer 11.1 professional software to extract the follow-up time and survival rate at corresponding time points from the survival curve.

Although only two of the OS rate, DFS rate, LRR and DMR were given in the study, we can estimate the rest from the above data.

Statistical analysis

Stata 14.0 software was used to analyze the data. The heterogeneity of the included studies is tested, and the I^2 value is used to measure the degree of homogeneity between multiple groups of studies (the smaller the I^2 value, the stronger the homogeneity). If there is statistical homogeneity between the studies ($P > 0.1$, $I^2 < 50\%$), the fixed-effects model is used for analysis; if there is statistical heterogeneity between the studies ($P < 0.1$, $I^2 > 50\%$, we analyze the source of the heterogeneity, and conduct a subgroup analysis of the factors that may cause the heterogeneity; if statistical heterogeneity is present without clinical heterogeneity or the difference was not statistically significant between the two groups, the random-effects model is adopted for analysis; if the two groups show great heterogeneity, a descriptive analysis is used. If necessary, sensitivity analysis is adopted to test the stability of the results. OR and 95% confidence interval (CI) were used to analyze the effect of pathologic fractures on the prognosis of limb local osteosarcoma patients, and a "forest plot" was drawn. The Begg's funnel chart was used to test publication bias, and $P < 0.05$ represented a significant difference.

Results

Study selection and characteristics

A total of 329 studies in the three databases of PubMed, Embase, and Web of Science were searched. After viewing the titles and abstracts, 118 studies were excluded because they did not report an association between pathologic fractures and the prognosis of osteosarcoma patients; another 136 studies were excluded because they were either reviews, case reports, or animal studies; 32 other articles were also excluded because they were non-English literature or conference abstract. After a detailed evaluation of the remaining 43 studies, we excluded 9 studies because they did not arrange a control group or were duplicate studies. Of the remaining 34 papers, 19 were eliminated because there was no data available after the full text review (eg: lack of information on patients with localized osteosarcoma of the extremity; the sample size of the control group or the case group is less than 4). Fifteen studies were finally included (**Figure 1**).

As shown in **Table 1**, all studies were conducted during 1992 to 2016, with sample sizes ranging from 9 to 982 patients. Of these included studies, seven were conducted in Asia [11, 18-23], four in North America [8, 24-26], and four in Europe [9, 10, 13, 27]. According to the NOS standards, all included studies were judged to be of high quality (**Table 2**). All were retrospective cohort studies. Thirteen reports were single-center and two were multi-institutional. In the pathologic and non-pathologic fracture groups, eight studies provided LRR, six provided DMR, five provided 3-year OS rate, five provided 3-year DFS rate, four provided 5-year OS rate, and six provided 5-year DFS rate. Eight studies provided data on local recurrence after amputation or limb salvage surgery in patients with pathologic fractures; another six studies provided data on distant metastasis after surgery.

Difference of the OS and DFS between the pathologic fracture group and the non-fracture group

A meta-analysis of five studies about OS was conducted over a 3-year period, and there is no statistical heterogeneity among these studies ($P = 0.641$, $I^2 = 0.0\%$), so the fixed-effects model was used for analysis. The pooled analysis results of the two groups showed that OR = 1.71 (95% CI: 1.25 to 2.35), $P < 0.05$. The pooled OR is clearly located to the right of the invalid line, which indicates the 3-year OS rate is significantly different between patients with pathologic fractures and without. The osteosarcoma patients with pathologic fractures have a lower 3-year OS rate.

Four studies analyzed the 5-year OS and these studies exhibited no statistical heterogeneity ($P = 0.440$, $I^2 = 0.0\%$), so the fixed effects model was used for analysis. The pooled OR = 1.41 (95% CI: 1.06~1.87), $P < 0.05$, located on the right side of the invalid line, indicating that the risk of death in pathologic fractures group is higher than group without pathologic fractures.

The results of the analysis of DFS are consistent with the above. Four studies reported 3-year DFS, and there was no statistical heterogeneity among studies ($P = 0.986$, $I^2 = 0.0\%$),

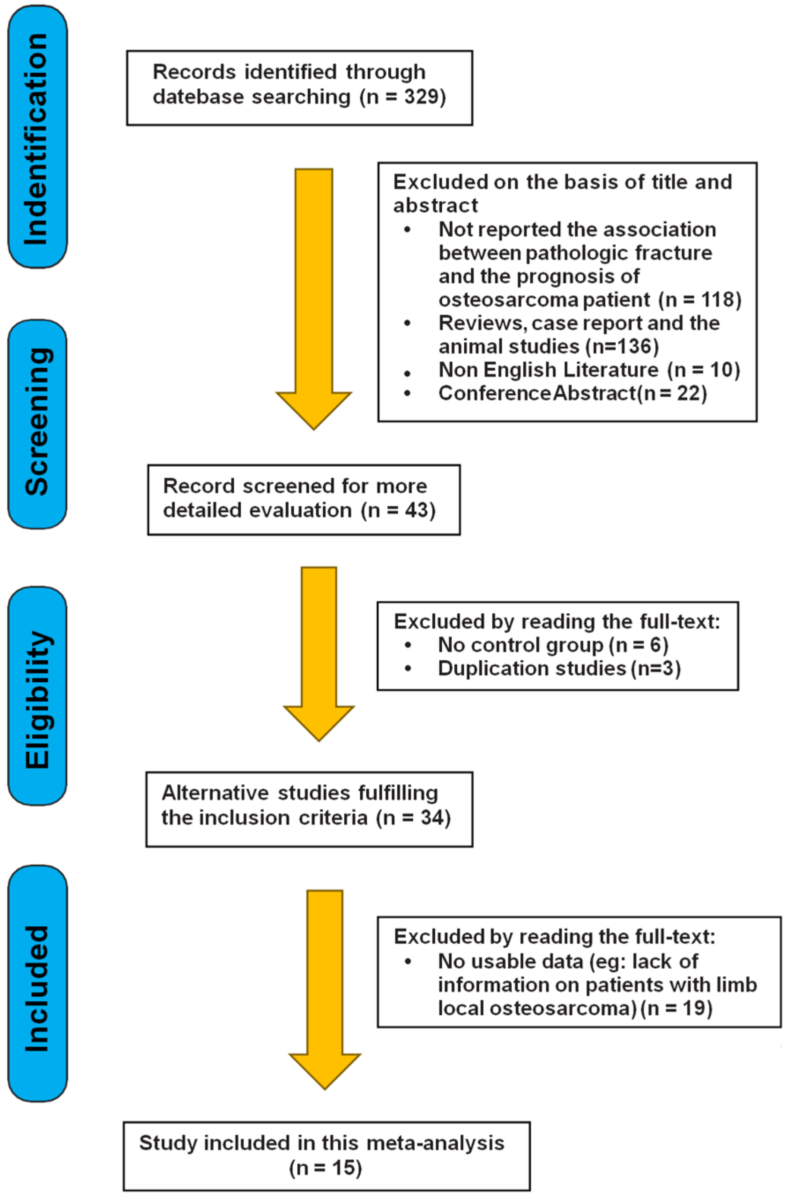

Figure 1. Flow chart showing the selection process for the included studies

so the fixed effects model was used for analysis. The pooled analysis result of pathologic fractures group and non-pathologic fractures group showed that the 3-year DFS difference between the two groups was statistically significant (OR = 1.88, 95% CI: 1.20 to 2.94; P < 0.05).

Six studies reported the 5-year DFS, and there was no statistical heterogeneity among these studies (P = 0.256, I^2 = 23.7%), so the fixed effects model was used for analysis. The pooled analysis results of the pathologic fracture group and the non-pathologic fracture group showed that the difference in 5-year DFS between the two groups was statistically significant (OR = 1.49, 95% CI: 1.10 to 2.03; P < 0.05). The results showed that in comparison to the pathologic fracture group, the non-fracture group not only had a significant increase in the 3-year and 5-year OS rate, but also in the DFS rate in the same period (**Figure 2**).

Comparison of postoperative LRR and DMR between pathologic fracture group and non-pathologic fracture group

The LRR after surgery of eight studies was meta-analyzed. There was no statistical heterogeneity among these studies (P = 0.262, I^2 = 21.1%), so the fixed-effects model was used for analysis. The pooled OR = 1.27 (95% CI: 0.88 to 1.84), P > 0.05, crossing the invalid line. It can be considered that pathologic fractures have no statistically significant effect on the LRR of limb local osteosarcoma after surgery (**Figure 3A**).

At the same time, a meta-analysis of the DMR after surgery in the six studies showed that there was no statistical heterogeneity among these studies (P = 0.765, I^2 = 0.0%), so the fixed-effects model was used for analysis. The pooled OR = 1.42 (95% CI: 1.03 to 1.95), P < 0.05, located on the right side of the invalid line. It can be considered that the pathologic fracture has an effect on the DMR after surgery of limb local osteosarcoma. The risk of metastasis in the group with a pathologic fracture was higher than that in the group without (**Figure 3B**).

Table 1. Characteristics and summary of outcome data of included studies

Study/year	Region	Study type	Case/n (PF/non-PF)	LR/n (PF/non-PF)	DM/n (PF/non-PF)	OS/% (PF/non-PF)		DFS/% (PF/non-PF)		LSS/AMP (in PF)		
						3-year	5-year	3-year	5-year	Case/n	LR/n	DM/n
Glasser et al./1992 [24]	USA	Retrospective cohort; single center	48/231	/	/	/	/	/	81.0/77.0	/	/	/
Scully et al./1996 [25]	USA	Retrospective cohort; single center	/	/	/	/	/	/	/	10/6	3/0	6/2
Abudu et al./1996 [13]	UK	Retrospective cohort; single center	/	/	/	/	/	/	/	27/13	5/0	12/4
Scully et al./2002 [8]	USA	Retrospective cohort; multi center	52/55	11/2	12/11	/	/	66.1/77.0	55.0/77.0	30/22	7/4	5/7
Bacci et al./2003 [9]	Italy	Retrospective cohort; single center	46/689	2/33	17/236	/	65.0/67.0	/	59.0/61.0	35/11	1/1	13/4
Bramer et al./2007 [10]	Netherlands	Retrospective cohort; single center	56/428	8/60	/	/	/	/	/	44/12	7/2	/
Kim et al./2009 [18]	Korea	Retrospective cohort and case control; single center	37/74	4/4	19/28	/	/	/	37.8/56.8	33/4	4/0	/
Ferguson et al./2010 [26]	Canada	Retrospective cohort and case control; single center	24/168	/	/	52.0/78.0	52.0/68.0	44.0/63.4	44.0/60.0	/	/	/
Cho et al./2010 [19]	Korea	Retrospective cohort; single center	38/339	/	19/118	/	/	/	/	/	/	/
Xie et al./2012 [20]	China	Retrospective cohort; single center	28/171	4/15	14/64	50.5/71.0	45.4/61.9	45.1/62.4	40.0/54.9	/	/	/
Zuo et al./2013 [21]	China	Retrospective cohort; single center	15/50	4/7	4/16	66.7/75.3	/	53.3/66.5	/	10/5	3/1	2/2
Malagelada et al./2014 [27]	Spain	Retrospective cohort; single center	/	/	/	/	/	/	/	5/4	/	2/2
Liu et al./2015 [22]	China	Retrospective cohort; single center	30/118	/	/	66.7/83.0	66.7/82.3	/	/	/	/	/
Deng et al./2015 [11]	China	Retrospective cohort; multi center	95/887	10/107	/	61.5/68.3	59.4/63.1	/	/	59/36	5/1	/
Poudel et al./2017 [23]	India	Retrospective cohort; single center	8/87	0/15	/	/	/	/	/	/	/	/

(All studies were conducted during 1992 to 2016, with sample sizes ranging from 9 to 982 patients. Of these included studies, seven were conducted in Asia, four were conducted in North America, and four were conducted in Europe. PF, pathological fractures group; non-PF, non-pathological fracture group; OS, overall survival; DFS, disease-free Survival; AMP, amputation; LSS, limb salvage surgery; LR, local recurrence, DM, distant metastasis)

Table 2. Newcastle-Ottawa scale for the assessment of the quality of included studies

Study/year	Selection				Outcome				Totol score
	Case definition adequacy	Representativeness of case	Selection of controls	Definition of controls	Comparability of cases and controls	Ascertainment of exposure	Same method of ascertain-ment for cases and controls	Non-response rate	
Glasser et al./1992 [24]	★	★	★	★		★	★	★	7
Scully et al./1996 [25]	★	★	★	★	★	★	★	★	9
Abudu et al./1996 [13]	★	★	★	★	★	★	★	★	8
Scully et al./2002 [8]	★	★	★	★	★★	★	★	★	9
Bacci et al./2003 [9]	★	★	★	★	★	★	★	★	8
Bramer et al./2007 [10]	★	★	★	★	★	★	★	★	8
Kim et al./2009 [18]	★	★	★	★	★	★	★	★	8
Ferguson et al./2010 [26]	★	★	★	★	★	★	★	★	8
Cho et al./2010 [19]	★	★	★	★	★	★	★	★	8
Xie et al./2012 [20]	★	★	★	★	★	★	★	★	8
Zuo et al./2013 [21]	★	★	★	★	★★	★	★	★	9
Malagelada et al./2014 [27]	★	★	★	★	★	★	★	★	8
Liu et al./2015 [22]	★	★	★	★		★	★	★	7
Deng et al./2015 [11]	★	★	★	★	★	★	★	★	8
Poudel et al./2017 [23]	★	★	★	★		★	★	★	7

According to the Newcastle-Ottawa Scale (NOS) standards, the quality evaluation results show that 3 studies scored 7 points, 10 scored 8 points, and 2 scored 9 points, indicating that the quality of these literature is high and the credibility of this study is good.

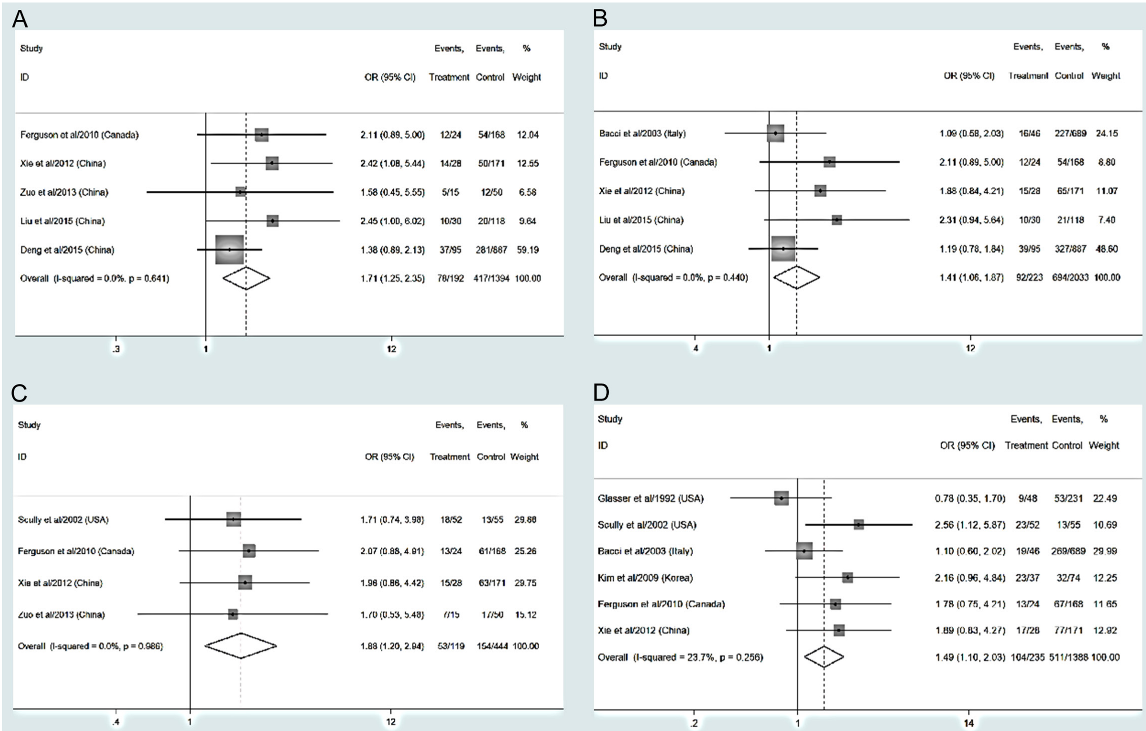

Figure 2. A. Forest plot of the OR for 3-year OS analysis, showed that the 3-year OS rate is significantly different between patients with pathologic fractures and without, and 3-year OS of patients with pathologic fractures were lower (OR = 1.71 (95% CI: 1.25 to 2.35), $P < 0.05$); B. Forest plot of the OR for 5-year OS analysis, indicated that the 5-year OS rate is significantly different between patients with pathologic fractures and without, and 5-year OS of patients with pathologic fractures were lower (OR = 1.41 (95% CI: 1.06 to 1.87), $P < 0.05$); C. Forest plot of the OR for 3-year DFS analysis, showed that the 3-year DFS rate is significantly different between patients with pathologic fractures and without, and 3-year DFS of patients with pathologic fractures were lower (OR = 1.88 (95% CI: 1.20 to 2.94), $P < 0.05$); D. Forest plot of the OR for 5-year DFS analysis, showed that the 5-year DFS rate is significantly different between patients with pathologic fractures and without, and 5-year DFS of patients with pathologic fractures were lower (OR = 1.49 (95% CI: 1.10 to 2.03), $P < 0.05$).

Prognostic differences of different surgical options

A meta-analysis of the amputation rate of the six studies showed that there was no statistical heterogeneity among these studies ($P = 0.401$, $I^2 = 2.3\%$), so the fixed effects model was used for analysis. The pooled OR = 1.825 (95% CI: 1.363 to 2.444), $P < 0.05$, so the result was statistically significant. The amputation rate of limb local osteosarcoma patients with a pathologic fracture was higher than that of those without.

Meta-analysis of the five studies about chemotherapy response showed no statistical heterogeneity among these studies ($P = 0.936$, $I^2 = 0.0\%$). Therefore, the fixed effects model was used for analysis, and the pooled OR = 0.74 (95% CI: 0.53 to 1.02), $P < 0.05$. The result was not statistically significant. Therefore, although the amputation rate of the pathologic fracture group was higher than that of the non-pathologic fracture group, there was no significant difference in the neoadjuvant chemotherapy response between the two groups (**Figure 4**).

Data from eight and six papers were extracted for meta-analysis to compare the LRR and DMR after amputation and limb salvage, respectively

The eight studies used to analyze the LRR were not statistically heterogeneous ($P = 0.690$, $I^2 = 0.0\%$), so the fixed-effects model was used for analysis. The pooled OR = 1.48 (95% CI: 0.72 to 3.04), $P > 0.05$, crossing the invalid line. There was no statistical difference in the LRR between amputation and limb salvage.

The six studies analyzing the rate of distant metastasis also showed no statistical hetero-

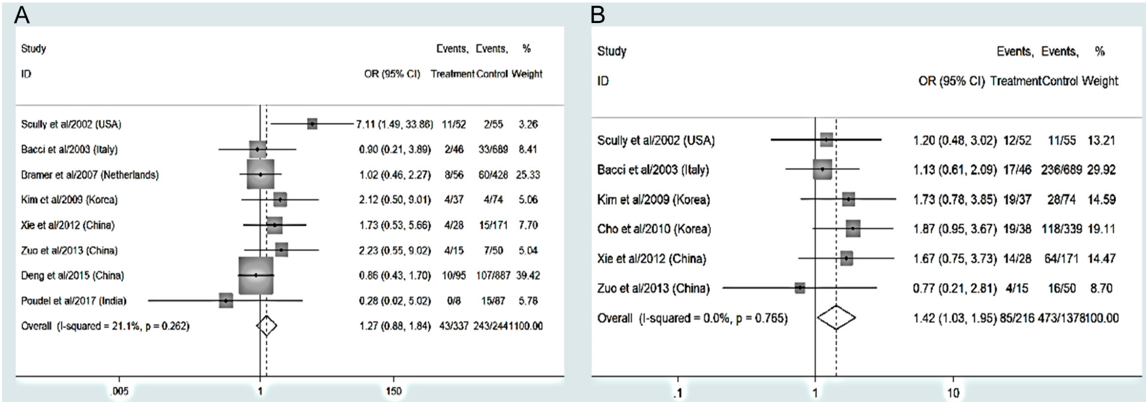

Figure 3. A. Forest plot of the OR for local recurrence analysis, showed the LRR is not significantly difference between patients with pathologic fractures and without, and pathologic fractures have no effect on postoperative local recurrence in patients with osteosarcoma (OR = 1.27 (95% CI: 0.88 to 1.84), P > 0.05); B. Forest plot of the OR for distant metastasis analysis, indicated that the DMR is significantly different between patients with pathologic fractures and without, and the DMR of patients with pathologic fractures were higher (OR = 1.42 (95% CI: 1.03 to 1.95), P < 0.05).

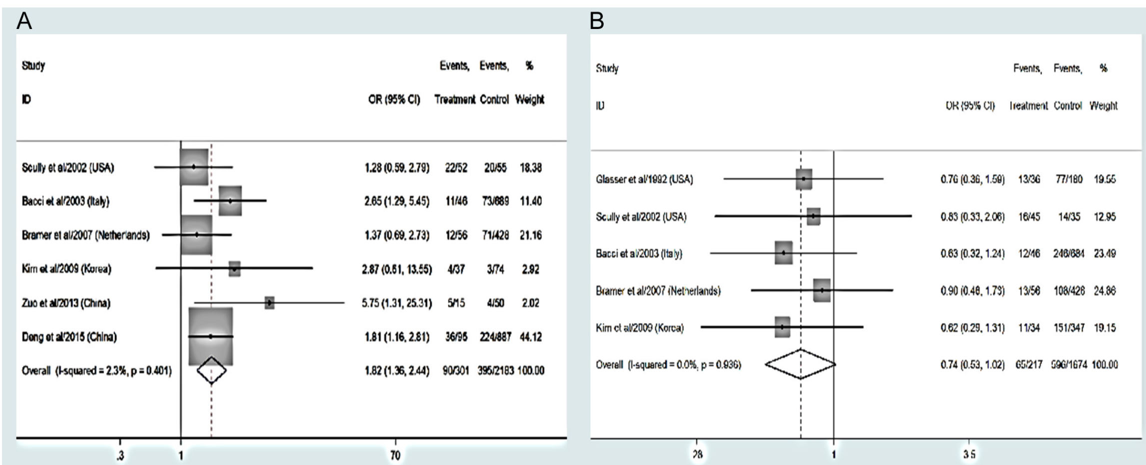

Figure 4. A. Forest plot of the OR for amputation rate analysis, indicated that the amputation rate is significantly different between patients with pathologic fractures and without, and the amputation rate of patients with pathologic fractures were higher (OR = 1.82 (95% CI: 1.36 to 2.44), P < 0.05); B. Forest plot of the OR for chemotherapy response analysis, showed that the chemotherapy response rate is not significantly different between patients with pathologic fractures and without, and pathologic fractures have no effect on chemotherapy response rate in patients with osteosarcoma (OR = 0.74 (95% CI: 0.53 to 1.02), P > 0.05).

geneity (P = 0.955, I^2 = 0.0%), so the fixed-effects model was used for analysis. The pooled OR = 1.82 (95% CI: 0.92 to 3.60), P > 0.05, crossing the invalid line. That there was no significant difference in the DMR after amputation and limb salvage (**Figure 5**).

Publication bias

Begg's funnel plots were made by using OS and DFS at 3 and 5 years after the studies included in the meta-analysis were pooled, as well as local recurrence and distant metastasis in the study group and control group. The result confirmed no statistically significant publication bias among these studies (**Figure 6**).

Discussion

Although diagnostic and treatment technology has made progress, mortality of patients with osteosarcoma remains very high [28, 29]. Generally speaking, patients with limb localized osteosarcoma have a better prognosis than

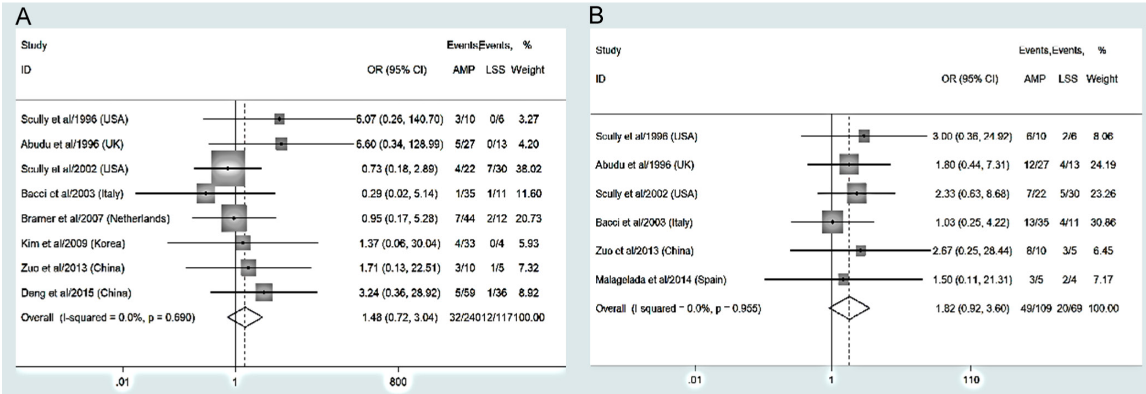

Figure 5. A. Forest plot of the OR for local recurrences analysis after amputation and limb salvage surgery, showed that the LRR was not significantly different between patients after amputation and limb salvage surgery, and limb salvage surgery did not increase LRR (OR = 1.48 (95% CI: 0.72 to 3.04), P > 0.05); B. Forest plot of the OR for distant metastasis analysis after amputation and limb salvage surgery, also showed that the DMR is not significantly different between patients after amputation and limb salvage surgery, and limb salvage surgery did not did not increase DMR (OR = 1.82 (95% CI: 0.92 to 3.60), P > 0.05).

those with secondary metastases [30-32]. However, once tumor pathologic fracture occurs, the treatment becomes more auxiliary and the prognosis is more uncertain. Spontaneous or trauma-inducing pathologic fractures of primary osteosarcomas are common due to changes in bone stress or mechanical damage caused by tumor necrosis after bone biopsy or chemotherapy. The complications of pathologic fracture not only reduce the patients' quality of life, but also affect the treatment decision-making for patients [33]. At present, there remain some disputes concerning the treatment and prognosis of patients with pathologic fracture of limb local osteosarcoma. Bacci et al. performed a retrospective study of 735 patients with local osteosarcoma of extremity and found that although the 5-year OS and DFS rates of osteosarcoma patients with pathologic fractures were inferior to those without, no statistically significant differences were found [9]. The results of Kim et al. also showed that the 5-year DFS rate is not significantly different between osteosarcoma patients with pathologic fractures and those without [18]. But Liu et al. compared 30 osteosarcoma patients with pathologic fractures and 118 patients without pathologic fractures. The 3-year OS rate in the pathologic fractures group was 66.7% and the 3-year OS rate in the non-pathologic fracture group it was 83%, and this difference was statistically significant [22]. Given the limited sample size of these single study, these conclusions are uncertain and conflicting. Therefore, a meta-analysis of the currently published studies to further evaluate the relationship between pathologic fractures and prognosis in patients with limb local osteosarcoma has guiding significance for clinical treatment.

The 15 retrospective cohort studies included in our study included 542 patients with a pathologic fracture and 3297 patients without. The quality evaluation results show that 3 studies scored 7 points, 10 scored 8 points, and 2 scored 9 points, indicating that the quality of these literature is high and the credibility of this study is good; the Begg's funnel plots analysis results shows that the funnel plot has good symmetry on both sides, and the Begg's test results shows that there is no obvious publication bias, so the conclusion is convincing. A meta-analysis of 5 articles about chemotherapy response shows that the selected studies were homogeneous and the invalid lines were crossed, indicating that there was no statistical difference in chemotherapy efficacy between the pathologic and non-pathologic fracture groups. This allowed us to further compare the outcomes of different surgical approaches under a relatively consistent condition [34].

Our study analysis results show that the selected studies are homogeneous, and the forest plot results are on the right side of the invalid line (3-year OS: OR = 1.71, P < 0.05; 5-year OS: OR = 1.57, P < 0.05), suggesting that there is a significant difference in the prognosis between

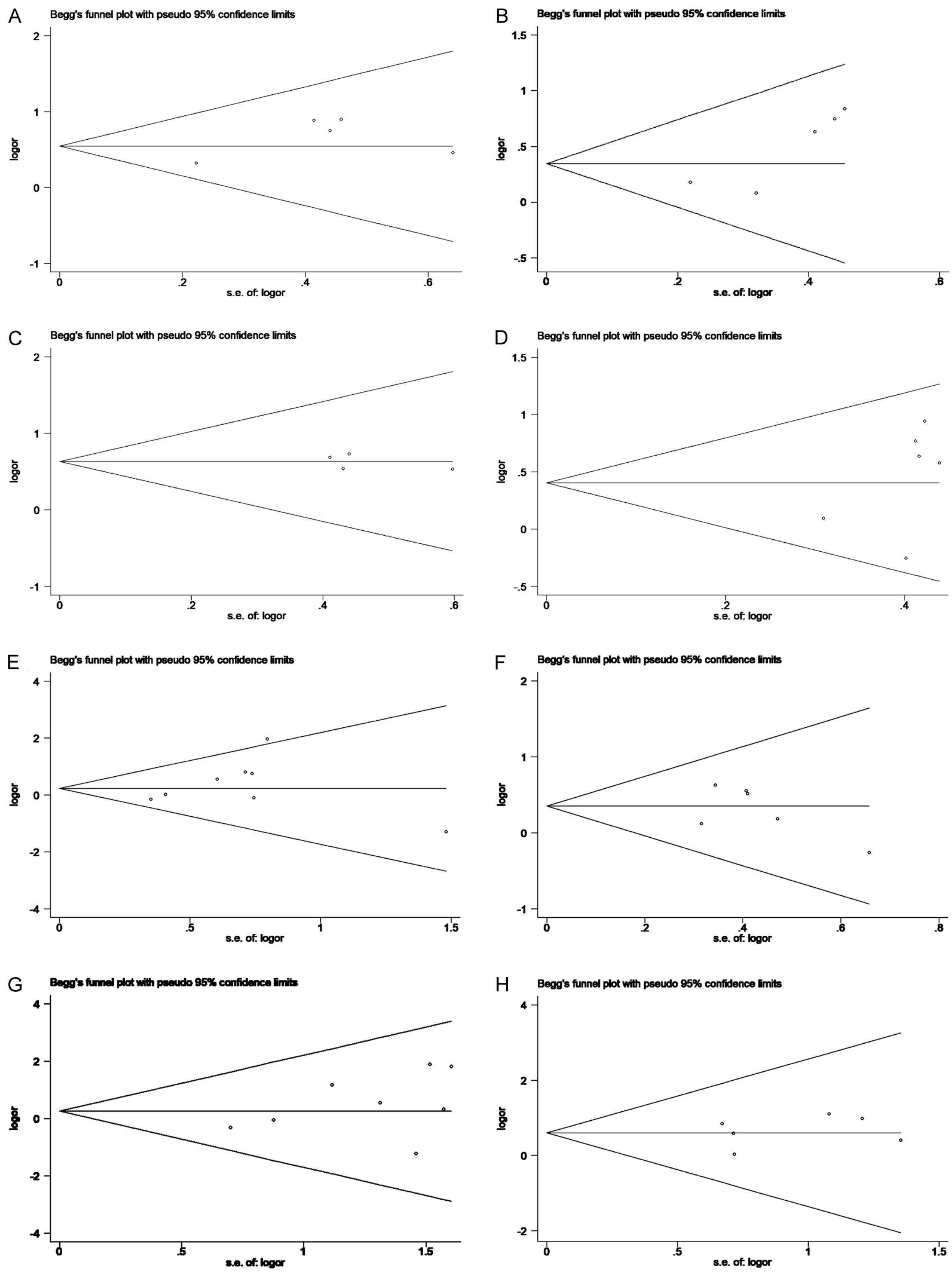

Figure 6. A, B. Begg's funnel plot for 3-year OS and 5-year OS analysis; C, D. Begg's Funnel plot for 3-year DFS and 5-year DFS analysis; E, F. Begg's Funnel plot for postoperative local recurrence rate and distant metastasis rate analysis; G, H. Begg's Funnel plot for local recurrence rate and distant metastasis rate analysis between amputation and limb salvage. As is shown in these figures, the studies we included were roughly symmetrical in funnel plots, suggesting the absence of publication bias and other biases.

patients with pathologic fractures and those without, and pathologic fractures can increase the mortality of patients with osteosarcoma. The results of DFS analysis also showed that there were significant differences in the 3-year and 5-year DFS between patients with pathologic fractures and those without. We found the OS rate and DFS rate of local osteosarcoma patients with pathologic fractures is significantly lower than those without, regardless of whether the cut-off point of survival was 3 years or 5 years. These results confirm that pathologic fracture is an independent negative factor affecting the prognosis of patients with limb local osteosarcoma. A basic research experiment on osteosarcoma found that pathologic fracture will further destroy the tissue around the tumor, affect the microcirculation, and make osteosarcoma cells more likely to spread [7]. This may be the reason for the relatively poor prognosis of osteosarcoma patients with pathologic fractures.

It is suggested that the lower OS and DFS rates in osteosarcoma patients with pathologic fractures are associated with postoperative distant metastasis. Our study analyzed the effect of pathologic fractures on local recurrence and distant metastasis of limb local osteosarcoma patients. The forest plot results of local recurrence shows that the invalid line was crossed, indicating that the effect of pathologic fracture on local recurrence of osteosarcoma is not statistically significant. Similarly, the influence of pathologic fractures on distant metastasis in patients with limb osteosarcoma was analyzed. The forest plot results are located on the right side of the invalid line, indicating that patients with pathologic fractures are at a significantly higher risk of distant metastasis after surgery than those without. The results proved the previous view that, in osteosarcoma patients with pathologic fractures, lower OS rate, and DFS rate were associated with distant metastasis after surgery rather than local recurrence. Therefore, pathologic fractures are more likely to cause distant metastasis of osteosarcoma, and then affect the prognosis of patients. In osteosarcoma patients with pathologic fractures, although no metastasis was found before operation, the metastasis rate in the later stage of treatment is still very high, especially lung metastasis. Therefore, improving the early detection rate of small metastases is particularly critical for the treatment of these patients [35].

The incidence of pathologic fractures in patients with osteosarcoma is about 5%-10% [5, 36]. Because of the poor prognosis of patients with pathologic fractures, pathologic fractures are regarded as contraindications to limb salvage treatment. In this meta-analysis, a subgroup analysis of the treatment methods of the pathologic fracture group showed that there was no significant difference in the LRR between the limb salvage group and the amputation group. In addition, the results of subgroup analysis of distant metastasis were consistent with the results of postoperative LRR, indicating no significant difference in DMR between the limb salvage group and the amputation group. Unfortunately, because there is not enough data on OS and DFS after amputation and limb salvage in patients with pathologic fractures, we cannot directly analyze whether there are differences between the two groups. Only from the perspective of no significant difference in LRR and DMR, the OS rate and DFS rate of two groups should be consistent. Therefore, although patients with a pathologic fracture have a higher risk of amputation, as long as they undergo standardized neoadjuvant treatment and meet the indications for limb salvage surgery, limb salvage will not increase the risk of local recurrence or distant metastasis after surgery [36].

Our meta-analysis yielded meaningful results that may help clinicians make more appropriate decisions in the face of osteosarcoma patient complicated with pathologic fractures. However, it has several limitations and needs further improvement. First, our study considered only the effects of pathologic fractures while no further grouping analysis was conducted for other prognostic factors, such as histologic subtype [37], size [38, 39] and surgical margin [40, 41]. Second, relevant research in other languages is excluded because all publications included are written in English. Third, in our study, we analyzed only published data from existing studies, so unpublished data may influence the results. In addition, although we included more studies than in previous meta-analyses, the number of publications included is still limited. Considering these limitations, we believe that further large-scale studies should be performed to confirm our conclusion.

There is no authoritative standard guideline for the treatment of osteosarcoma with pathologic fracture, and the views of the current research are contradictory. Clinically, the appearance of pathologic fractures undoubtedly makes it difficult for surgeons to make treatment decisions. Our study found that pathologic fracture is a negative prognostic indicator in osteosarcoma, and its poor survival rates (OS and DFS) may be related to the higher rate of distant metastasis. For osteosarcoma patients with pathologic fractures who received standard treatment, there was no significant difference in the LRR and DMR between amputation and limb salvage surgery. Although patients with pathologic fractures have a higher risk of amputation, limb salvage surgery will not increase the risk of local recurrence or distant metastasis as long as they receive standardized neoadjuvant therapy and meet the indications for salvage.

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Disclosure of conflict of interest

None.

Abbreviations

NOS, Newcastle-Ottawa Scale; LRR, Local Recurrence Rate; DMR, Distant Metastasis Rate; OS, Overall Survival; DFS, Disease-free Survival; OR, Odds Ratio; CI, Confidence Intervals.

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References

[1] de Azevedo JWV, de Medeiros Fernandes TAA, Fernandes JV Jr, de Azevedo JCV, Lanza DCF, Bezerra CM, Andrade VS, de Araújo JMG and Fernandes JV. Biology and pathogenesis of human osteosarcoma. Oncol Lett 2020; 19: 1099-1116.

[2] Pingping B, Yuhong Z, Weiqi L, Chunxiao W, Chunfang W, Yuanjue S, Chenping Z, Jianru X, Jiade L, Lin K, Zhengdong C, Weibin Z, Chen F and Yang Y. Incidence and mortality of sarcomas in Shanghai, China, during 2002-2014. Front Oncol 2019; 9: 662.

[3] Zhang Y, Yao Y and Zhang Y. Three-dimensional bone extracellular matrix model for osteosarcoma. J Vis Exp 2019.

[4] Zhao X, Wu Q, Gong X, Liu J and Ma Y. Osteosarcoma: a review of current and future therapeutic approaches. Biomed Eng Online 2021; 20: 24.

[5] European Sarcoma Network Working Group. Bone sarcomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2014; 25 Suppl 3: iii113-123.

[6] Ebeid W, Amin S and Abdelmegid A. Limb salvage management of pathologic fractures of primary malignant bone tumors. Cancer Control 2005; 12: 57-61.

[7] Schultheiss M, Traub SE and v Baer A. Pathologic fractures due to malignant bone tumors. Unfallchirurg 2014; 117: 583-592.

[8] Scully SP, Ghert MA, Zurakowski D, Thompson RC and Gebhardt MC. Pathologic fracture in osteosarcoma: prognostic importance and treatment implications. J Bone Joint Surg Am 2002; 84: 49-57.

[9] Bacci G, Ferrari S, Longhi A, Donati D, Manfrini M, Giacomini S, Briccoli A, Forni C and Galletti S. Nonmetastatic osteosarcoma of the extremity with pathologic fracture at presentation: local and systemic control by amputation or limb salvage after preoperative chemotherapy. Acta Orthop Scand 2003; 74: 449-454.

[10] Bramer JA, Abudu AA, Grimer RJ, Carter SR and Tillman RM. Do pathologic fractures influence survival and local recurrence rate in bony sarcomas? Eur J Cancer 2007; 43: 1944-1951.

[11] Deng ZP, Ding Y, Puri A, Wang EH, Gulia A, Durban C and Niu XH. The surgical treatment and outcome of nonmetastatic extremity osteosarcoma with pathologic fractures. Chin Med J (Engl) 2015; 128: 2605-2608.

[12] Xu M, Wang Z, Yu XC, Lin JH and Hu YC. Guideline for limb-salvage treatment of osteosarcoma. Orthop Surg 2020; 12: 1021-1029.

[13] Abudu A, Sferopoulos NK, Tillman RM, Carter SR and Grimer RJ. The surgical treatment and outcome of pathologic fractures in localised osteosarcoma. J Bone Joint Surg Br 1996; 78: 694-698.

[14] Jeon DG, Lee SY and Kim JW. Bone primary sarcomas undergone unplanned intralesional procedures - the possibility of limb salvage and their oncologic results. J Surg Oncol 2006; 94: 592-598.

[15] Longhi A, Errani C, De Paolis M, Mercuri M and Bacci G. Primary bone osteosarcoma in the pe-

diatric age: state of the art. Cancer Treat Rev 2006; 32: 423-436.
[16] Natarajan MV, Govardhan RH, Williams S and Raja Gopal TS. Limb salvage surgery for pathologic fractures in osteosarcoma. Int Orthop 2000; 24: 170-172.
[17] Godley K, Watts AC and Robb JE. Pathologic femoral fracture caused by primary bone tumour: a population-based study. Scott Med J 2011; 56: 5-9.
[18] Kim MS, Lee SY, Lee TR, Cho WH, Song WS, Cho SH, Lee JA, Yoo JY, Jung ST and Jeon DG. Prognostic effect of pathologic fracture in localized osteosarcoma: a cohort/case controlled study at a single institute. J Surg Oncol 2009; 100: 233-239.
[19] Cho WH, Song WS, Jeon DG, Kong CB, Kim MS, Lee JA, Yoo JY, Kim JD and Lee SY. Differential presentations, clinical courses, and survivals of osteosarcomas of the proximal humerus over other extremity locations. Ann Surg Oncol 2010; 17: 702-708.
[20] Xie L, Guo W, Li Y, Ji T and Sun X. Pathologic fracture does not influence local recurrence and survival in high-grade extremity osteosarcoma with adequate surgical margins. J Surg Oncol 2012; 106: 820-825.
[21] Zuo D, Zheng L, Sun W, Hua Y and Cai Z. Pathologic fracture does not influence prognosis in stage IIB osteosarcoma: a case-control study. World J Surg Oncol 2013; 11: 148.
[22] Liu Y, Xu Y, Lin N, Jiang S, Wang Y and Ye Z. High-dose methotrexate (HD-MTX) used as an adjunct with other chemotherapeutics for the treatment of osteosarcoma. Cell Biochem Biophys 2015; 71: 1097-1104.
[23] Poudel RR, Tiwari V, Kumar VS, Bakhshi S, Gamanagatti S, Khan SA and Rastogi S. Factors associated with local recurrence in operated osteosarcomas: a retrospective evaluation of 95 cases from a tertiary care center in a resource challenged environment. J Surg Oncol 2017; 115: 631-636.
[24] Glasser DB, Lane JM, Huvos AG, Marcove RC and Rosen G. Survival, prognosis, and therapeutic response in osteogenic sarcoma. The Memorial Hospital experience. Cancer 1992; 69: 698-708.
[25] Scully SP, Temple HT, O'Keefe RJ, Mankin HJ and Gebhardt M. The surgical treatment of patients with osteosarcoma who sustain a pathologic fracture. Clin Orthop Relat Res 1996; 227-232.
[26] Ferguson PC, McLaughlin CE, Griffin AM, Bell RS, Deheshi BM and Wunder JS. Clinical and functional outcomes of patients with a pathologic fracture in high-grade osteosarcoma. J Surg Oncol 2010; 102: 120-124.
[27] Malagelada F, Tarrago LT, Tibrewal S, Ibanez AP, Jeyaseelan L and Alegria IG. Pathologic fracture in osteosarcoma: is it always an indication for amputation? Ortop Traumatol Rehabil 2014; 16: 67-74.
[28] Sheng G, Gao Y, Yang Y and Wu H. Osteosarcoma and metastasis. Front Oncol 2021; 11: 780264.
[29] Ayerza MA, Farfalli GL, Aponte-Tinao L and Muscolo DL. Does increased rate of limb-sparing surgery affect survival in osteosarcoma? Clin Orthop Relat Res 2010; 468: 2854-2859.
[30] Liu Z, Yin J, Zhou Q, Yang J, Zeng B, Yeung SJ, Shen J and Cheng C. Survival after pulmonary metastasectomy for relapsed osteosarcoma. J Thorac Cardiovasc Surg 2022; 163: 469-479.
[31] Chung LH, Wu PK, Chen CF, Weng HK, Chen TH and Chen WM. Pathologic fractures in predicting clinical outcomes for patients with osteosarcoma. BMC Musculoskelet Disord 2016; 17: 503.
[32] Mialou V, Philip T, Kalifa C, Perol D, Gentet JC, Marec-Berard P, Pacquement H, Chastagner P, Defaschelles AS and Hartmann O. Metastatic osteosarcoma at diagnosis: prognostic factors and long-term outcome -- the French pediatric experience. Cancer 2005; 104: 1100-1109.
[33] Zhu J, He T, Wei Z and Wang Y. Retrospective analysis of the effect of treatment of osteosarcoma complicated by pathologic fracture by neoadjuvant chemotherapy combined with limb salvage surgery. J BUON 2018; 23: 1809-1815.
[34] Papagelopoulos PJ, Mavrogenis AF, Savvidou OD, Benetos IS, Galanis EC and Soucacos PN. Pathologic fractures in primary bone sarcomas. Injury 2008; 39: 395-403.
[35] Seher K, Saeed H, Kareem T, Baqari AS, Niazi I and Wali RM. Indeterminate pulmonary nodules in osteosarcoma are associated with increased risk of pulmonary metastasis. J Pediatr Hematol Oncol 2021; 43: e826-e831.
[36] Haynes L, Kaste SC, Ness KK, Wu J, Ortega-Laureano L, Bishop M, Neel M, Rao B and Fernandez-Pineda I. Pathologic fracture in childhood and adolescent osteosarcoma: a single-institution experience. Pediatr Blood Cancer 2017; 64: 10.
[37] Kelley LM, Schlegel M, Hecker-Nolting S, Kevric M, Haller B, Rössig C, Reichardt P, Kager L, Kühne T, Gosheger G, Windhager R, Specht K, Rechl H, Tunn PU, Baumhoer D, Wirth T, Werner M, von Kalle T, Nathrath M, Burdach S, Bielack S and von Lüttichau I. Pathologic fracture and prognosis of high-grade osteosarcoma of the extremities: an analysis of 2,847 consecutive Cooperative Osteosarcoma Study Group (COSS) patients. J Clin Oncol 2020; 38: 823-833.

[38] Bispo Júnior RZ and Camargo OP. Prognostic factors in the survival of patients diagnosed with primary non-metastatic osteosarcoma with a poor response to neoadjuvant chemotherapy. Clinics (Sao Paulo) 2009; 64: 1177-1186.
[39] Song WS, Jeon DG, Kong CB, Cho WH, Koh JS, Lee JA, Yoo JY, Jung ST, Shin DS and Lee SY. Tumor volume increase during preoperative chemotherapy as a novel predictor of local recurrence in extremity osteosarcoma. Ann Surg Oncol 2011; 18: 1710-1716.
[40] Grimer RJ, Taminiau AM and Cannon SR. Surgical outcomes in osteosarcoma. J Bone Joint Surg Br 2002; 84: 395-400.
[41] Nathan SS, Gorlick R, Bukata S, Chou A, Morris CD, Boland PJ, Huvos AG, Meyers PA and Healey JH. Treatment algorithm for locally recurrent osteosarcoma based on local disease-free interval and the presence of lung metastasis. Cancer 2006; 107: 1607-1616.