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Review article

A comparative study between limb-salvage and amputation for treating osteosarcoma

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ABSTRACT

Purpose: Osteosarcoma is an aggressive malignant neoplasm, and conflicting findings have been reported on the survival and function recovery in osteosarcoma patients experiencing limb salvage or amputation. In the present study, we compared clinical outcomes regarding limb salvage surgery vs. amputation for osteosarcoma patients by a meta-analysis.
Method: Literature search was conducted in CNKI, Medline, Embase, the Cochrane Database, and Web of Sciences, and the quality of included studies was evaluated based on Newcastle-Ottawa scale quality assessment. Odds ratio and 95% confidence interval of the local recurrence, 5-year overall survival, and metastasis occurrence were calculated.
Results: 17 articles were included according to selection criteria. There were 1343 patients in total derived from these studies. Our result showed that there was no significant difference between limb salvage surgery and amputation with respect to local recurrence, and patients with limb salvage surgery had a higher 5-year overall survival, and a lower metastasis occurrence.
Conclusions: The present study provided more comprehensive evidences to support limb salvage surgery as an optimal treatment of osteosarcoma patients.

Contents

Abbreviations: LSS, limb salvage surgery

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1. Introduction

Osteosarcoma is an aggressive bone neoplasm arising from primitive transformed cells of mesenchymal origin. It was such a fatal disease that "months to metastasis" rather than actual survival time, was used to measure the outcomes of treatment in studies of early stage. In the 1950s, there was no optional therapy that could significantly increase the survival rate, with a 5-year survival rate of 22% [1]. However, with the aid of effective chemotherapeutic drugs the survival rate of osteosarcoma has been significantly improved since the late 1970s [2,3]. Recently, the gold standard of osteosarcoma chemotherapy have been based on around 5 drugs; high-dose methotrexate (HDMTX) with leucovorin rescue, doxorubicin (adriamycin), cisplatin, ifosfamide, and etoposide [4]. Combinations of these drugs, mostly in the form of neoadjuvant as well as adjuvant MAP, are the current management for osteosarcoma [5], and various chemotherapy protocols are still under investigation. The experience with radiotherapy is limited, as osteosarcoma is long considered resistant to applicable doses of radiation. However, recent data suggest that the combined approach of irradiation with chemotherapy may be useful in patients who have microscopic residual tumor foci following intralesional resection [6].

With the advent of effective neoadjuvant chemotherapy in the 1970s, limb salvage surgery (LSS) has been taken as a potential treatment for osteosarcoma [7,8]. Usually, LSS has functional and physiological advantages over traditional amputative procedures when combined with neoadjuvant or adjuvant chemotherapy [9]. It is now generally accepted that LSS is indicative for localized osteosarcoma, while surgical amputation is adopted for high malignancy osteosarcoma. However, there are still some surgeons holding the view that immediate and aggressive removal of the tumor will prevent the progression of fracture-induced disease, and consequently amputation is considered to be a better option for osteosarcoma patients with pathologic fracture [10–13].

Conflicting findings have been reported on the survival and function recovery between treatments of LSS and amputation in patients with osteosarcoma. Toward this end, a meta-analysis of published clinical trials was performed to compare the clinical efficacy of LSS and amputation treatments in terms of local recurrence, 5-year overall survival rate, and metastatic occurrence. Several studies have attempted similar meta-analysis [14]; however, the included studies were much smaller, and their scopes were restricted to specific therapies compared with this meta-analysis. Through more extensive osteosarcoma literature, this meta-analysis tries to give a comprehensive conclusion on the outcomes in osteosarcoma patients receiving LSS and amputation. Such information will help us determine the most appropriate osteosarcoma-treating method.

2. Material and methods

2.1. Literature search

A comprehensive and complete search of Medline, Embase, Cochrane Database, Web of Sciences, and CNKI was performed from June 2014 to July 2014, using the search terms: "osteosarcoma", "limb salvage" and "amputation". There was no language or other restrictions. All articles with raw descriptive data were included, including original research, clinical trials, case reports, databases, letters, and reviews.

2.2. Included studies

Articles were included if they were (1) comparative study between LSS and amputation groups, (2) patients with osteosarcoma in their lower limb, (3) sufficient data was provide in terms of local recurrence, 5-year overall survival rate, or occurrence of metastasis. Exclusion criteria were as follows: (1) studies only reported data related to LSS or amputation groups without a comparison, (2) general case series with less than 20 total patients, (3) letters, case reports, editorials or reviews.

2.3. Data extraction

Outcome data were collected from the articles by two authors of our study. The authors used a structured sheet, and then gathered all the data into a database. Study characteristics included year of publication, number of patient with LSS and amputation, study period, gender, Enneking stage, response to chemotherapy, follow-up, etc. Any disagreement was resolved by continuing discussions until a consensus was reached.

2.4. Study quality

With the Newcastle–Ottawa scale (NOS) quality assessment as recommended by the Cochrane Observational Studies Method Working Group, the quality of included articles was evaluated by two independent reviewers. This scale has a maximum nine points concerning quality of selection, comparability, exposure, and outcome of study participants. Because of the variable quality of the observational studies, we took the criteria of 5 or more NOS scores as studies with good quality.

2.5. Statistical analysis

The outcome of measurement used in our study was local recurrence, 5-year overall survival rate, and occurrence of metastasis, which were all dichotomous data. We used the software of the Cochrane Collaboration (Review Manager 5.2) to calculate OR and 95% CI for all outcomes. Statistical heterogeneity among the included studies was assessed by the Chi squared and I^2 tests. Statistically significant heterogeneity was defined as an I^2 value > 0.5. A random effects model was selected for heterogeneous data; otherwise, a fixed effect model was selected.

Funnel plots were used to test the possibility of publication bias, which exhibited the intervention effect from the individual study against the respective standard error. A symmetrical plot represents no bias, and any asymmetry of the plot suggests the existence of publication bias.

3. Results

3.1. Literature information

In the preliminary literature search, 137 potentially relevant articles were identified. However, according to the inclusion criteria, only 17 articles [15–31] were selected (Fig. 1; Table S1). All of the 17 research articles were retrospective studies. The publication dates ranged from 1996 to 2012. 1343 patients with osteosarcoma were comprised totally, of whom 617 patients received LSS and 726 received amputation. The results of quality assessment by NOS are shown in Table 1, and the detail information of patients in each articles were listed in Table 2. Among 5 of the studies

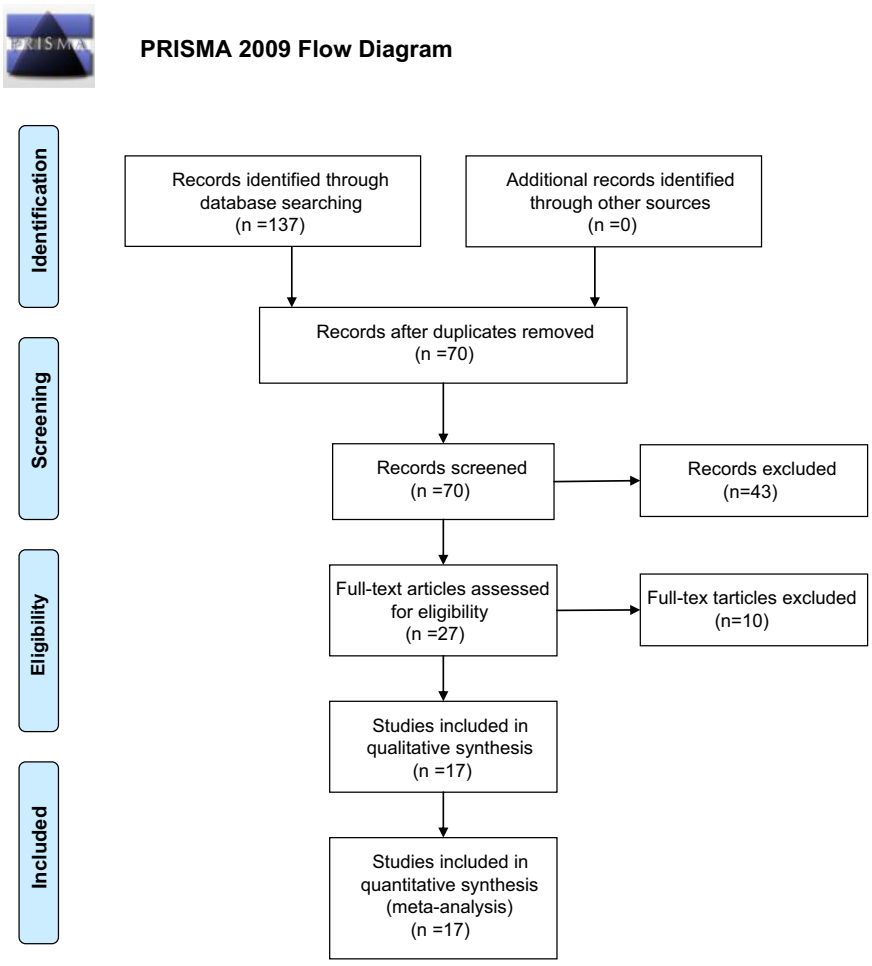

Fig. 1. Flow chart of studies included and excluded.

Table 1
Quality assessment for the 17 included articles based on Newcastle–Ottawa quality assessment scale.

Refs.	Selection			Comparability			Exposure			NOS
	Inclusion criteria	Sample size > 50	Endpoint	Anatomical location	Enneking stage	Chemotherapy	Local recurrence	5-year overall survival	Metastatic	
Abudu et al. [12]	*	–	*	*	*	*	*	*	*	8*
Bacci et al. [13]	*	–	*	*	*	*	*	–	–	6*
Bacci et al.[b] [14]	*	*	*	–	–	*	*	*	*	7*
Bramer et al. [15]	*	*	*	*	–	*	*	–	–	6*
Ferguson et al. [16]	*	–	*	*	–	*	*	–	–	5*
Guo et al. [17]	*	–	*	*	–	*	*	–	*	6*
Hegyi et al. [18]	*	*	*	–	–	*	*	*	*	7*
Jiang et al. [19]	*	*	*	*	*	*	*	–	–	8*
Kim et al. [20]	*	–	*	*	–	*	*	–	–	5*
Ma et al. [21]	*	*	*	*	–	*	–	*	–	6*
Mavrogenis et al. [22]	*	–	*	*	–	*	*	–	*	6*
Niu et al. [23]	*	–	*	*	*	*	*	*	*	8*
Robert et al. [24]	*	*	*	*	–	–	*	*	–	6*
Scully et al. [25]	*	*	*	*	*	*	*	*	–	8*
Xu et al. [26]	*	*	*	*	*	*	*	*	–	8*
Zhang et al. [27]	*	–	*	*	*	*	*	–	*	7*
Zhao et al. [28]	*	*	*	*	*	*	*	–	–	7*

[20,22,25,30,31] patients with Enneking Stage-IIA, and Stage-IIB osteosarcoma were both included. For other 5 studies [15,16,26,28,29], patients with Enneking Stage-IIB osteosarcoma were included. Histologic response to preoperative chemotherapy is reported to be a independent prognostic factor of osteosarcoma [32]. Among the included studies, 7 studies assessed the histologic response to preoperative chemotherapy [16,17,18,21,23,25,28].

3.2. Study heterogeneity and publication bias

The *P*-value for study heterogeneity was 0.26, 0.29, 0.80 for three outcomes including local recurrence, 5-year overall survival rate, and

Table 2
Characteristic of the 17 included studies.

Ref.	Abudu et al. [12]	Bacci et al. [13]	Bacci et al.[b] [14]	Bramer et al. [15]	Ferguson et al. [16]	Guo et al. [17]	Hegyi et al. [18]	Jiang et al. [19]	Kim et al. [20]
Country	England	Italy	Italy	UK	Canada	China	Hungary	China	Korea
Patient Number	40	46	560	56	31	21	122	64	37
LSS,	27	35	95	44	19	13	92	32	3
Amputation	13	11	465	12	12	8	30	32	4
Study period	1975–1994	1983–1999	1983–1995	1983–2003	1989–2006	1998–2008	1988–2006	2001–2011	–
Male	25	24	320	36	14	14	65	46	26
Female	14	22	240	20	17	7	57	18	11
Median age(range), years	18 (2–46)	11 (3–20)	–	16 (4–57)	30 (11–8)	14.5 (9–17)	13.8 ± 3.6a	18.4 ± 6.3 (12–30)	–
Enneking stage	Stage-IIB	Stage-IIB	–	–	–	Stage-IIA, Stage-IIB	–	Stage-IIA, Stage-IIB	–
Follow-up(range), months	55 (8–175)	132 (36–240)	22.6 (3–96)	117 (7–252)	–	38 (28–62)	–	8–42	43 (10–228)
Poor chemotherapy	–	12 (26%)	194 (35%)	43 (78%)	–	–	67 (55%)	–	23 (62%)
Local recurrence									
LSS	5	1	6	6	2	2	–	2	4
Amputation	0	1	20	2	0	–	–	2	0
5-year Survival									
LSS	17	–	60	–	–	9	58	25	–
Amputation	6	–	230	–	–	3	23	19	–
Metastatic occurrence									
LSS	12	–	–	–	–	1	–	–	–
Amputation	9	–	–	–	–	4	–	–	–

Ref.	Ma et al. [21]	Mavrogenis et al. [22]	Niu et al. [23]	Robert et al. [24]	Scully et al. [25]	Xu et al. [26]	Zhang et al. [27]	Zhao et al. [28]
Country	China	Italy	China	USA	USA	China	China	China
Patient Number	51	42	22	57	52	58	31	53
LSS,	32	23	12	33	30	43	17	37
Amputation	19	19	10	24	22	15	14	16
Study period	1991–1999	1985–2010	1992–2001	2007–2008	1977–1996	1992–2002	–	1996–2007
Male	35	23	15	20	28	30	26	–
Female	16	19	7	37	24	28	5	–
Median Age(range), years	22.3 (10–47) a	26 (7–78)a	18 (3–36)	33.8 (16.1–52)	23 ± 17.4a	20.26 (12–55)	17a	19.5 (5–45)a
Enneking stage	–	Stage-IIA, Stage-IIB	Stage-IIB	–	Stage-IIB	Stage-IIB	Stage-IIA, Stage-IIB	Stage-IIA, Stage-IIB
Follow-up(range), months	72 (60–144)	60 (8–288)	54.7 (8–146)	223.2 (39.6–338.4)	54 (6–152.4)	129.6 (72–192)	43.2	–
Poor chemotherapy	–	7 (17%)	–	–	29 (64%)	–	–	–
Local recurrence								
LSS	2	5	2	–	7	7	5	3
Amputation	–	2	1	–	4	1	12 (	1
5-year Survival								
LSS	12	–	8	–	19	19	6	19
Amputation	7	–	4	–	12	8)	1	
Metastatic Occurrence								
LSS	–	1	3	–	–	–		
Amputation	–	3	6	–	–	–		

metastatic occurrence. As a result of the true difference in terms of treatment effect, clinical characteristics, etc., the variability (I^2) across all studies was 18%, 16%, and 0% for three outcomes respectively. All the results above indicated that there was no heterogeneity among the included studies (Tables 3–5). Moreover, the funnel plots for all outcome measurements were symmetrical (Fig. 2A–C). All the spots representing individual studies fell evenly within the top of the inverted funnel, indicating that there was no publication bias.

3.3. Meta-analysis of local recurrence

1127 cases from 14 studies were selected for meta-analysis of local recurrence. The overall incidence of local recurrence in LSS and amputation group was 11.88% (57 of 480) and 7.73% (50 of 647), respectively. The results showed that there was no significant differences between LSS and amputation group (OR: 1.03 with 95% CI ranging from 0.65 to 3.30; $Z=0.14$, $P=0.89$) (Table 3; Fig. 3).

3.4. Meta-analysis of 5-year overall survival

Totally, 1074 cases from 10 studies were analyzed for 5-year overall survival. The 5-year overall survival rate in LSS and amputation group was 58.60% (252 of 430) and 49.84% (321 of 644), respectively. In patients treated with LSS, the 5-year overall survival rate was significantly higner than those treated with amputation (OR: 1.47 with 95% CI ranging from 1.10 to 1.97; $Z=2.61$, $P<0.05$) (Table 4; Fig. 4).

3.5. Meta-analysis of metastasis occurrence

125 cases from 4 studies were analyzed for metastatic analysis. The overall incidence of metastasis occurrence in LSS and amputation group was 22.67% (17 of 75) and 44% (22 of 50), respectively. Patients treated with LSS had a significantly lower metastasis occurrence compared those with amputation (OR: 0.24 with 95% CI ranging from 0.10 to 0.60; $Z=3.05$, $P<0.05$) (Table 5; Fig. 5).

Table 3
Statistic summary of forest plot of comparison: local recurrence of LSS vs. amputation for the treatment of osteosarcoma.

Study	LSS		Amputation		Weight (%)	Odds Ratio
	Events	Total	Events	Total		M–H, Fixed, 95% CI
Abudu et al.	5	27	0	13	1.5	6.60 [0.34, 128.99]
Bacci et al.	1	35	1	11	4.2	0.29 [0.02, 5.14]
Bacci et al.[b]	6	95	20	465	17.9	1.50 [0.59, 3.84]
Bramer et al.	6	44	2	12	7.6	0.78 [0.14, 4.52]
Ferguson et al.	2	19	0	12	1.5	3.57 [0.16, 81.03]
Guo et al.	2	13	5	8	14.8	0.11 [0.01, 0.87]
Jiang et al.	2	32	2	32	5.3	1.00 [0.13, 7.57]
Kim et al.	4	33	0	4	2.1	1.37 [0.06, 30.04]
Mavrogenis et al.	5	23	2	19	4.8	2.36 [0.40, 13.84]
Niu et al.	2	12	1	10	0.0	1.80 [0.14, 23.37]
Scully et al.	7	30	4	22	10.0	1.37 [0.35, 5.41]
Xu et al.	7	43	1	15	3.5	2.72 [0.31, 24.19]
Zhang et al.	5	17	12	18	23.2	0.21 [0.05, 0.87]
Zhao et al.	3	37	1	16	3.6	1.32 [0.13, 13.79]
Total (95%) CI	57	480	50	647	100.0	1.03 [0.65, 1.64]

Heterogeneity: $\chi^2=14.47$, df=12 (P=0.26); $I^2=18\%$.
Test for over effect: $Z=0.14$ ($P=0.89$).

Table 4
Statistic summary of forest plot of comparison: 5-year overall survival of LSS vs. amputation for the treatment of osteosarcoma.

Study	LSS		Amputation		Weight (%)	Odds Ratio
	Events	Total	Events	Total		M–H, Fixed, 95% CI
Abudu et al.	17	27	6	13	4.0	1.98 [0.52, 7.58]
Bacci et al.[b]	60	95	230	465	38.5	1.75 [1.11, 2.76]
Guo et al.	9	13	3	8	1.5	3.75 [0.59, 23.94]
Hegyi et al.	58	92	23	30	17.2	0.52 [0.20, 1.34]
Jiang et al.	25	32	19	32	5.6	2.44 [0.82, 7.31]
Ma et al.	12	32	7	19	7.4	1.03 [0.32, 3.33]
Niu et al.	8	12	4	10	1.9	3.00 [0.52, 17.16]
Scully et al.	19	30	12	22	6.8	1.44 [0.47, 4.41]
Xu et al.	19	43	8	15	8.9	0.69 [0.21, 2.25]
Zhang et al.	6	17	1	14	1.0	7.09 [0.74, 68.24]
Zhao et al.	19	37	8	16	7.3	1.06 [0.33, 3.41]
Total (95%) CI	252	430	321	644	100.0	1.47 [1.10, 1.97]

Heterogeneity: $\chi^2=11.94$, df=10 (P=0.29); $I^2=16\%$.
Test for overall effect: $Z=2.61$ ($P=0.009$).

4. Discussion

With the improved efficacy of chemotherapy, the number of patients with osteosarcoma who received LSS instead of amputation has significantly increased recent years [33–37]. Moreover, LSS benefits not only malignant primary osteosarcoma patients, but also high-grade, localized osteosarcoma patients. However, there are substantial studies showing that the survival rate and local recurrence between LSS and amputation for osteosarcoma have been conflicting [25,38]. In this study, it was concluded that patients treated with LSS had a similar local recurrence and a lower metastasis occurrence compared with those treated with amputation, which was identical with that of Yin [14] but with more expansive literature included in our study. In addition, we found that 5-year overall survival rate of patients treated with LSS was higher than those treated with amputation. Therefore, our results provide more comprehensive evidence to support LSS for the treatment of osteosarcoma patients.

In the meta-analysis of local recurrence of LSS vs. amputation for the treatment of osteosarcoma, there was no significant difference in the two surgery methods (OR: 1.03 with 95% CI ranging from 0.65 to 3.30; $Z=0.14$, $P=0.89$) (Table 3; Fig. 3). In five of 17 articles, the local recurrence rate in patients undergoing LSS was dramatically higher than those receiving amputation [15,19,23,25,29]. The sample sizes of these five studies were relatively small. Differently from these studies, other included studies revealed similar local recurrence rates between the two surgery methods. Moreover, in a study of Bacci et al. [17] with more than 500 samples investigated, local recurrence rates were found to be similar between LSS and amputation, which offered solid evidence to evaluate the local recurrence of LSS for the treatment of osteosarcoma.

In this meta-analysis, the overall survival at 5 years was slightly better in those treated by LSS than those who had amputation(OR: 1.47 with 95% CI ranging from 1.10 to 1.97; $Z=2.61$, $P<0.05$)for treating osteosarcoma patients. Among the included studies, only two studies of Xu et al., Hegyi et al. [21,29] found that the amputation resulted in better 5-year survival. Abudu et al. [15] found that amputation didn't come with a prolonged overall survival, though it provide better eradication of local tumor than LSS. However, in another article which was not included in the meta-analysis [39], it was indicated that LSS did not affect the survival rate. Even through our analysis results were somewhat inconsistent with previous research, we still concluded that LSS had a similar 5-year overall survival rate to that of amputation.

The metastatic occurrence rate for patients treated with LSS was significantly lower than those treated with amputation (OR: 0.24 with 95% CI ranging from 0.10 to 0.60; $Z=3.05$, $P<0.05$) (Table 5; Fig. 5), which was identical with the results of Yin et al. [14]. However, only 4 of 17 studies reported the metastasis, including 125 patients. Abudu [15] found that the treatment of LSS or amputation influenced the development of metastases to some degree, 44% in patients with LSS and 69% in patients with amputation; Niu [26] reported that metastasis happened in 25% patients treated with LSS compared with 60% in patients treated with amputation; in the study of Mavrogenis et al. [22], one of 23 patients receiving LSS developed metastasis while 3 of 19 patients receiving amputation did; in another study, one of 13 patients undergoing LSS had metastatic occurrence and 4 of 8 patients undergoing amputation had metastatic occurrence [17]. Our analysis of metastatic occurrence was based on only four articles. There are some important prognostic factors of osteosarcoma, such as radical resectability of the tumor, extent of disease at diagnosis, initial tumor volume, and response to neoadjuvant chemotherapy[40], which makes the comparison of the two surgery methods complicate. Thus, additional high-quality, randomized

Table 5
Statistic summary of forest plot of comparison: metastatic occurrence in patients receiving LSS vs. amputation for the treatment of osteosarcoma.

Study	LSS		Amputation		Weight (%)	Odds ratio
	Events	Total	Events	Total		M–H, Fixed, 95% CI
Abudu et al.	12	27	9	13	34.8	0.36 [0.09, 1.44]
Guo et al.	1	13	4	8	23.6	0.08 [0.01, 0.98]
Mavrogenis et al.	1	23	3	19	16.2	0.24 [0.02, 2.55]
Niu et al.	3	12	6	10	25.3	0.22 [0.04, 1.37]
Total (95%) CI	17	75	22	50	100.0	0.24 [0.10, 0.60]

Heterogeneity: $\chi^2=1.02$, df=3 (P=0.80); $I^2=0\%$.
Test for overall effect: $Z=3.05$ ($P=0.002$).

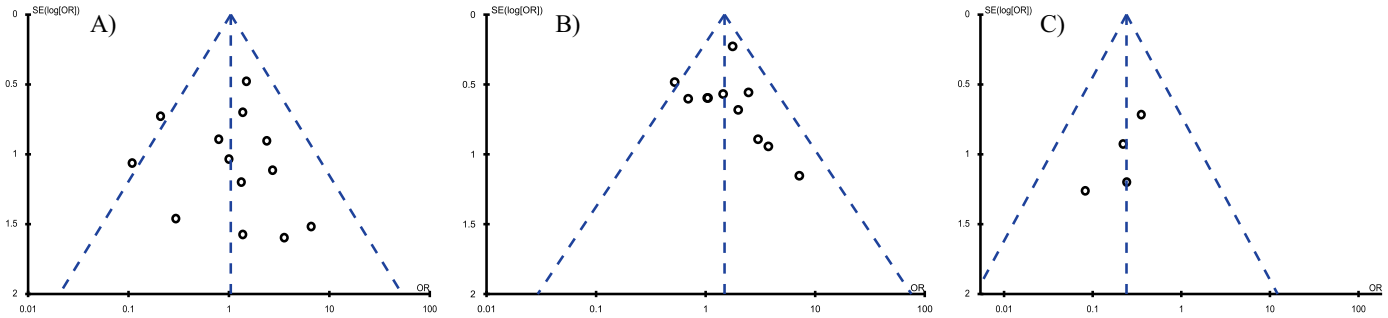

Fig. 2. Funnel plot of comparison. A: local recurrence of LSS vs. amputation; B: 5-year overall survival of LSS vs. amputation; C: metastatic occurrence of LSS vs. amputation.

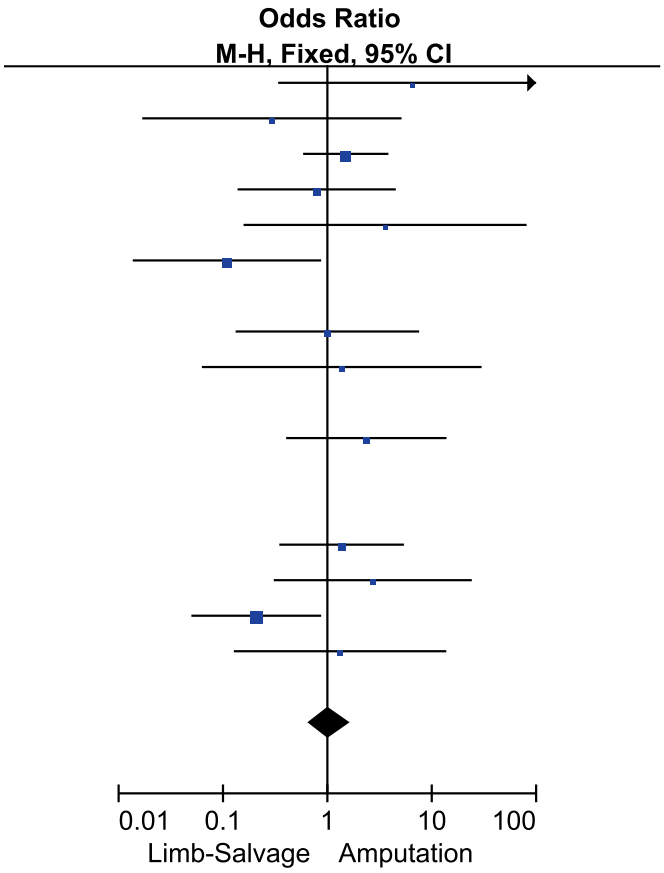

Fig. 3. Forest plot of comparison, local recurrence of LSS vs. amputation for the treatment of osteosarcoma.

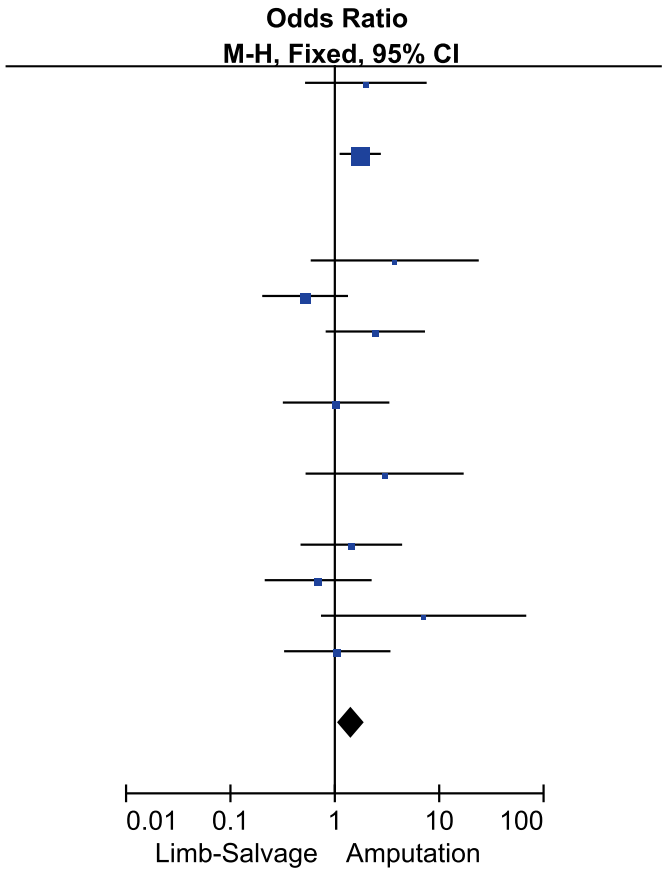

Fig. 4. Forest plot of comparison, 5-year overall survival of LSS vs. amputation for the treatment of osteosarcoma.

controlled studies are needed to confirm the conclusions.

5. Conclusions

In conclusion, our meta-analysis highlighted that LSS can be safely used in localized osteosarcoma patients with lower metastatic occurrence and better survival, which won't increase the risk for local recurrence. And our meta-analysis supported the conclusions proposed by Yin et al. and provided more comprehensive evidence to support application of LSS for the treatment of osteosarcoma patients.

6. Limitation

In our study, all the articles were retrospective designed, and most of the included studies had small sample sizes that were subjected to systematic and random bias. The small sample size here was more likely to be the main reason for the failure in detecting heterogeneity in articles if it did exist, as the test power of heterogeneity was low in this situation. Moreover, the number in some studies of events for the outcome measurement was very low. Finally, the details of Enneking Stage and response to preoperative chemotherapy were missing for some studies. Therefore, even our study represented more comprehensive evidence compared with previous studies, the conclusions should be confirmed by high-quality, randomized-controlled, large-sample studies.

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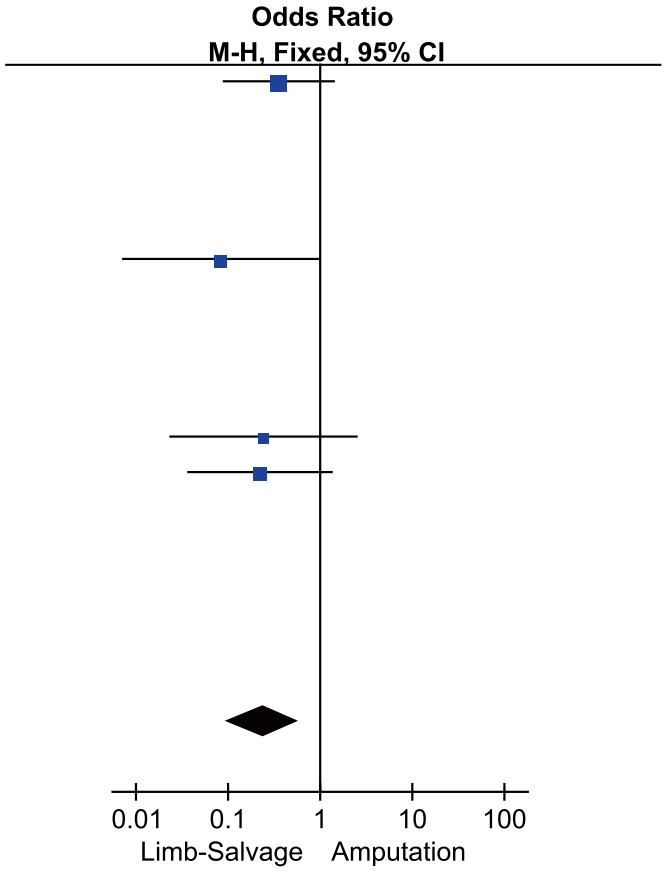

Fig. 5. Forest plot of comparison, metastatic occurrence of LSS vs. amputation for the treatment of osteosarcoma.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.jbo.2016.01.001.

References

[1] M.B. Coventry, D.C. Dahlin, Osteogenic sarcoma: a critical analysis of 430 cases, J. Bone Jt. Surg. 39 (1957) 741–758.
[2] M.M. Sampo, M. Tarkkanen, A.H. Kivioja, M.H. Taskinen, R. Sankila, et al., Osteosarcoma in Finland from1971 through 1990: a nationwide study of epidemiology and outcome, Acta Orthop. 79 (2008) 861–866.
[3] R.M. Wilkins, J.W. Cullen, L. Odom, B.A. Jamroz, P.M. Cullen, et al., Superior survival in treatment of primary nonmetastaticpediatric osteosarcoma of the extremity, Ann. Surg. Oncol. 10 (2003) 498–507.
[4] H.T. Ta, C.R. Dass, P.F. Choong, D.E. Dunstan, Osteosarcoma treatment: state of the art, Cancer Metastasis Rev. 28 (2009) 247–263.
[5] A. Luetke, P.A. Meyers, I. Lewis, H. Juergens, Osteosarcoma treatment-where do we stand? A state of the art review, Cancer Treat. Rev. 40 (4) (2014) 523–532.
[6] T. Ozaki, S. Flege, M. Kevric, et al., Osteosarcoma of the pelvis: experience of the Cooperative Osteosarcoma Study Group (COSS), J. Clin. Oncol. 21 (2003) 334–341.
[7] P.J. Messerschmitt, R.M. Garcia, F.W. Abdul-Karim, E.M. Greenfield, P.J. Getty, et al., Osteosarcoma, J. Am. Acad. Orthop. Surg. 17 (2009) 515–527.
[8] C.P. Carty, I.C. Dickinson, M.C. Watts, R.W. Crawford, P. Steadman, Impairment and disability following limb salvage procedures for bone sarcoma, Knee 16 (2007) 405–408.
[9] S. Ferrari, E. Palmerini, Adjuvant and neoadjuvant combination chemotherapy for osteogenic sarcoma, Curr. Opin. Oncol. 19 (2007) 341–346.
[10] W. Ebeid, S. Amin, A. Abdelmegid, Limb salvage management of pathologic fractures of primary malignant bone tumors, Cancer Control 12 (2005) 57–61.
[11] M.V. Natarajan, R.H. Govardhan, S. Williams, G.T.S. Raja, Limb salvage surgery for pathological fractures in osteosarcoma, Int. Orthop. 24 (2000) 170–172.
[12] Q. Cui, D.F. Li, C. Liu, J. Guo, S.B. Liu, Y.S. Liu, et al., Two case-reports of the limb salvage treatment of osteosarcoma consolidated with obvious pathological fractures, Pathol. Oncol. Res. 17 (2011) 973–979.
[13] K. Godley, A.C. Watts, J.E. Robb, Pathological femoral fracture caused by primary bone tumour: a population-based study, Scott. Med. J. 56 (2011) 5–9.
[14] K. Yin, Q.D. Liao, D. Zhong, J. Ding, B. Niu, et al., Meta-analysis of limb salvage versus amputation for treating high-grade and localized osteosarcoma in patients with pathological fracture, Exp. Ther. Med. 4 (2012) 889–894.
[15] A. Abudu, N.K. Sferopoulos, R.M. Tillman, S.R. Carter, R.J. Grimer, The surgical treatment and outcome of pathological fractures in localised osteosarcoma, J. Bone Jt. Surg. Br. 78 (1996) 694–698.
[16] G. Bacci, S. Ferrari, A. Longhi, D. Donati, M. Manfrini, S. Giacomini, et al., 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. 74 (2003) 449–454.
[17] G. Bacci, S. Ferrari, S. Lari, M. Mercuri, D. Donati, A. Longhi, et al., Osteosarcoma of the limb: amputation or limb salvage in patients treated by neoadjuvant chemotherapy, J. Bone Jt. Surg. Br. 2002 (84) (2002) 88–92.
[18] J.A. Bramer, A.A. Abudu, R.J. Grimer, S.R. Carter, R.M. Tillman, Do pathological fractures influence survival and local recurrence rate in bony sarcomas? Eur. J. Cancer 43 (2007) 1944–1951.
[19] P.C. Ferguson, C.E. McLaughlin, A.M. Griffin, R.S. Bell, B.M. Deheshi, J. S. Wunder, Clinical and functional outcomes of patients with a pathologic fracture in high-grade osteosarcoma, J. Surg. Oncol. 102 (2010) 120–124.
[20] X.J. Guo, D.K. Zhou, Z.J. Zhu, Therapeutic analysis of combined treatment and amputation therapy for osteosarcoma in children and adolescent patients 2011, J. Appl. Clin. Pediatr. 26 (2011) 1804–1805, In Chinese.
[21] M. Hegyi, A.F. Semei, Z. Jakab, I. Antal, J. Kiss, S. Miklos, et al., Good prognosis of localized osteosarcoma in young patients treated with limb-salvage surgery and chemotherapy, Pediatr. Blood Cancer 57 (2011) 415–422.
[22] H. Jiang, X.F. Chi, D. Yang, Effect of limb salvage surgery on 32 cases of osteosarcoma, J. Jilin Med. 33 (2012) 1832, In Chinese.
[23] M.S. Kim, S.Y. Lee, T.R. Lee, W.H. Cho, W.S. Song, S.H. Cho, et al., Prognostic effect of pathologic fracture in localized osteosarcoma: a cohort/case controlled study at a single institute, J. Surg. Oncol. 100 (2009) 233–239.
[24] C. Ma, X.C. Sun, Effects of operation combined with chemotherapy for osteogenic sarcoma, J. Southeast Univ. 23 (2004) 406–408.
[25] A.F. Mavrongenis, C.N. Abati, C. Romagnoli, P. Ruggieri, Similar survival but better function for patients after limb salvage versus amputation for distal tibia osteosarcoma, Clin. Orthop. Relat. Res. 470 (2012) 1735–1748.
[26] X.H. Niu, Y. Ding, The surgical treatment and outcome of nonmetastatic osteosarcoma of the extremity with pathologic fractures, Zhonghua Wai Ke Za Zhi 46 (2008) 1730–1733, In Chinese.
[27] R.S. Robert, G. Ottaviani, W.W. Huh, S. Palla, N. Jaffe, Psychosocial and functional outcomes in long-term survivors of osteosarcoma: a comparison of limb-salvage surgery and amputation, Pediatr. Blood Cancer 54 (2010) 990–999.
[28] S.P. Scully, M.A. Ghert, D. Zurakowski, R.C. Thompson, M.C. Gebhardt, Pathologic fracture in osteosarcoma: prognostic importance and treatment implications, J. Bone Jt. Surg. Am. 84 (2002) 49–57.
[29] B. Xu, Z.D. Cai, Z.R. Chen, Z.J. Yao, G.J. Zhang, A preliminary evaluation of limb salvage surgery for osteosarcoma around knee joint, PLoS One 7 (2012) e33492.
[30] H.Y. Zhang, X.Z. Luo, Z.Y. Wang, Limb salvage and amputation in osteosarcoma: report of 31 cases, Chin. J. Surg. 35 (1997) 556–557.
[31] Y.J. Zhao, The limb-salvage treatment of limb osteosarcoma a clinical outcome study study at a single institute, J. Surg. Oncol. 100 (2008) 233–239.
[32] J.A. Bramer, J.H. van Linge, R.J. Grimer, et al., Prognostic factors in localized extremity osteosarcoma: a systematic review, Eur. J. Surg. Oncol. 35 (2009) 1030–1036.
[33] G. Bacci, S. Ferrari, M. Mercuri, A. Longhi, R. Capanna, A. Tienghi, et al., Neoadjuvant chemotherapy for extremity osteosarcoma: preliminary results of the Rizzoli's 4th study, Acta Oncol. 37 (1998) 41–48.
[34] N. Delepine, G. Delepine, S. Alkallaf, et al., Local relapses following limb sparing salvage surgery for osteosarcoma: prognostic factors and influence of chemotherapy, ASCO Proc. 15 (1996) 526.
[35] G. Saeter, T. Wiebe, T. Wiklund, O. Monge, Y. Wahlqvist, K. Engstrom, et al., Chemotherapy in osteosarcoma: the Scandinavian sarcoma group experience, Acta Orthop. Scand. Suppl. 285 (1999) 74–82.
[36] H. Tsuchiya, K. Tomita, Prognosis of osteosarcoma treated by limbsalvage surgery: the ten-year intergroup study in Japan, Jpn. J. Clin. Oncol. 22 (1992) 347–353.
[37] K. Winkler, P. Bieling, S. Bielack, et al., Local control and survival from the co-operative osteosarcoma study group studies of the German Society of Pediatric Oncology and the Vienna Bone Tumour Registry, Clin. Orthop. 270 (1991) 79–86.
[38] D.C. Allison, S.C. Carney, E.R. Ahlmann, A. Hendifar, S. Chawla, A. Fedenko, et al., A meta-analysis of osteosarcoma outcomes in the modern medical era, Sarcoma 2012 (2011) 1–10.
[39] F. Zeifang, D. Sabo, V. Ewerbeck, Pathological fracture in primary malignant bone tumors 2000, Chirurg, 71, (2000) 1121–1125, In German.
[40] A.M. Davis, R.S. Bell, P.J. Goodwin, Prognostic factors in osteosarcoma: a critical review, J. Clin. Oncol. 21 (1994) 423–431.