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A meta-analysis of prognostic factors of osteosarcoma

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Abstract. – OBJECTIVE: To systemically evaluate the factors influencing the prognosis of osteosarcoma.

MATERIALS AND METHODS: Case-control studies (sample size>100) investigating the factors influencing the prognosis of osteosarcoma published from 1st January 1980 to 1st February 2019 were searched in the databases, including PubMed, Embase, and CBM. The meta-analysis was conducted within the Review Manager 5.3 software.

RESULTS: 22 studies were included. The 5-year overall survival (OS) of male patients was significantly lower than that of female patients (OR=0.84, 95% CI=0.76-0.93). There was no significant statistical difference in 5-year OS between the adolescent group (≤14 years old) and the adult group (>14 years old) (OR=0.88, 95% CI=0.68-1.14). Before standardized chemotherapy, which was started in 2000, the 5-year OS of patients receiving surgery and chemotherapy was significantly higher than patients only receiving surgery (OR=3.20, 95% CI=2.30-4.46). After 2000, the 5-year OS of patients receiving standardized chemotherapy was significantly higher than those undergoing non-standardized chemotherapy (OR=2.17, 95% CI=1.77-2.67). The 5-year OS of the limb-salvage surgery group was higher than that of the amputation surgery group (OR=2.17, 95% CI=1.77-2.67). The 5-year OS of patients with a good response to chemotherapy (Huvos III+IV) was higher than that of patients with poor response to chemotherapy (Huvos I+II) (OR=2.45, 95% CI=2.10-2.87). Patients without bone metastasis had significantly better 5-year OS than those with bone metastasis at initial diagnosis (OR=0.2, 95% CI=0.11-0.39).

CONCLUSIONS: The prognosis of male osteosarcoma patients was slightly worse than that of female patients. Surgery plus standardized chemotherapy can improve the 5-year OS of osteosarcoma patients. Patients who had undergone limb-salvage surgery had a better prognosis. Poor response to chemotherapy and bone metastasis had a negative influence on the prognosis of osteosarcoma.

Key Words:
Osteosarcoma, Prognostic, Meta-analysis.

Introduction

Osteosarcoma, originating from mesenchymal cells, is the most common primary bone malignancy in adolescents. It has an insidious onset, high malignancy, and rapid progression[1]. Previous studies[2] have found that 10 to 15 percent of patients with osteosarcoma had lung metastases that can be detected by routine examinations (such as lung CT examination) at the first diagnosis. In recent years, comprehensive treatment including preoperative chemotherapy, limb salvage surgery, and postoperative chemotherapy have been widely used. They have improved the survival rate of patients with osteosarcoma, reduced the rate of postoperative tumor metastasis, and recurrence and improved the quality of life of patients and their families[3].

A health survey of 3,482 patients with osteosarcoma between 1973 and 2004 in America revealed that there were two peaks of osteosarcoma in young and old adults (about 15 and 75-years old, respectively) with a male-to-female ratio of about 1.22:1[4]. Previous studies found that the limb salvage rate and osteosarcoma chemotherapy rate increase year by year and the 5-year overall survival (OS) is about 64.0%, but the development of osteosarcoma treatment entered into the plateau stage nearly a decade; even larger doses of chemotherapy drugs or new chemotherapy drugs were used for patients with osteosarcoma[5]. Therefore, it is necessary to study the related factors affecting the prognosis of patients with osteosarcoma, so as to achieve the goal of individualized treatment, further improve the cure rate and remission rate, and reduce the prevalence of complications.

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Previous investigations related to osteosarcoma were mostly retrospective studies, which lacked meta-analysis of large samples. Therefore, we searched large sample literature on the prognostic factors of osteosarcoma and evaluated the prognostic factors of patients with osteosarcoma by meta-analysis.

Materials and Methods

Search Strategy

PubMed, Embase, and China Biology Medicine disc (CBM) databases were searched. The search terms were "osteosarcoma" and "prognosis", and we limited the fields in the title and abstract. In order to increase the search efficiency, we also excluded the literature with keywords including "meta-analysis", "review", and "case report". The time of publication was January 1st, 1980 to February 1st, 2019. We also searched the reference list of acquired articles manually.

Inclusion and Exclusion Criteria

Inclusion criteria: (1) the study was designed as a case control study; (2) the study was about prognostic factors of osteosarcoma; (3) relatively complete original data provided in the literature can be used to calculate the ratio (OR); (4) the follow-up period was more than 5 years; (5) the number of osteosarcoma cases was more than 100.

Exclusion criteria: (1) repeated published literature; (2) the literature did not provide relevant information; (3) the study lacked the control group.

Data Extraction and Quality Assessment

Literature screening and data extraction were performed independently by two researchers. Firstly, the related literature was selected by browsing the title and abstract of the article. After excluding the literature that did not meet the inclusion criteria, the full text of the literature that might meet the inclusion criteria was searched and read, and then screened again. Two researchers cross-checked the included literature. For the studies with differences and difficult to reach consensus, the third researcher was asked to decide.

The extracted data included: (1) basic information of the included literature, including author, publication time, country or region where the study was carried out, time of study implementation, type of study and sample size; (2) basic information of the subjects, including age and gender; (3) influencing factors and outcome indicators; (4) literature quality evaluation of the relevant information.

Two researchers evaluated the quality of the included literature according to the Newcastle Ottawa scale (NOS), and the third researcher evaluated the literature when the scores were inconsistent[6]. The full score of NOS score is 9 and the evaluation content includes the selection, comparability and exposure factors of the case control study between groups. The study with a score of more than 6 is divided into high-quality study.

Observed Indicator

Influencing factors included gender, age, metastasis or not at initial diagnosis, combined radiotherapy and chemotherapy or not, standard chemotherapy or not, limb salvage surgery or amputation, the curative effect of chemotherapy. Outcome indicator is 5-year OS.

Statistical Analysis

Statistical analysis was performed on the data by the software Review Manager5.3. Statistical heterogeneity was assessed by χ^2 and I^2, $p > 0.05$ or $I^2 < 50\%$ indicates low heterogeneity and fixed-effect model analysis was performed, whereas random effect model analysis was performed. The OR and its 95% confidence interval (CI) of the dichotomous data were calculated. The results were considered statistically significant when $p<0.05$.

Results

Study Selection and Study Characteristics

According to the inclusion and exclusion criteria of literature and the requirements of literature quality control, 22 studies were finally included[7-28]. The literature screening process and results are shown in Figure 1. The basic characteristics of the included studies are shown in Table I. All the included studies were retrospective studies with NOS scores above 7 (Table II).

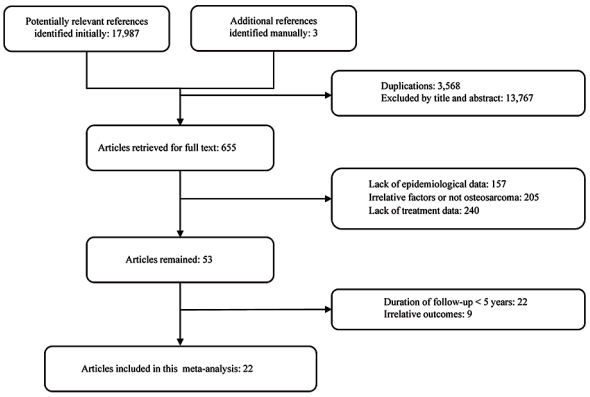

Figure 1. Study flow and selection diagram.

Influence of Gender on 5-Year OS in Patients with Osteosarcoma

A total of 12 studies were included, and there was no heterogeneity between the studies (p=0.54, I^2=0%). The fixed-effect model was applied. The results showed that the 5-year OS of male patients with osteosarcoma was significantly lower than that of female patients with osteosarcoma (OR=0.84, 95% CI=0.76-0.93) (Figure 2).

Influence of Age on 5-Year OS in Patients with Osteosarcoma

Most studies divide mindfulness into the adolescent group (≤14 years old) and adult group (>14 years old). A total of 7 studies were included. There was significant heterogeneity between the studies (p=0.002, I^2=71%), and the random effect model was used for analysis. There was no significant difference between the two groups (OR=0.88, 95% CI=0.68-1.14) (Figure 3).

Influence of Metastasis at Initial Diagnosis on 5-Year OS in Patients with Osteosarcoma

In general, patients with osteosarcoma often have a poor prognosis when first diagnosed with tumor metastasis. A total of 6 studies were included. There was no heterogeneity between the studies (p=0.65, I^2=0%), and the fixed effect model was used for analysis. The results showed that the 5-year survival rate of the patients with tumor metastasis at initial diagnosis was significantly lower than that of the patients without metastasis (OR=0.2, 95% CI=0.11-0.39) (Figure 4).

Table I. Basic characteristics of included studies.

Studies	Region	Type	Time span	No. of patients (male/female)	Mean age	Outcomes
Bacci 1990	Italy	Single-Center	1983-1987	72/65	–	12
Bacci 2000	America	Multicenter	1986-1989	89/75	–	12
Bacci 2001	Italy	Multicenter	1983-1995	–	–	67
Bacci 2005	Italy	Multicenter	1972-1999	926/677	16.7	1567
Bacci 2006	Italy	Single-Center	1983/1999	449/334	–	1267
Cai 2000	China	Single-Center	1977-1992	112/58	21	46
Faisham 2017	Malaysia	Single-Center	2005-2010	107/56	–	1367
Ferrari 2018	European	Multicenter	2010-2014	136/82	51	13
Fukushima 2018	Japan	Single-Center	2006-2013	1930/1527	–	2
Guo 2004	China	Single-Center	1996-2002	65/48		7
Hung 2016	China	Single-Center	1995-2011	126/76	18.1	136
Joo 2015	Asia	Multicenter	–	116/116	50	35
Kim 2008	Korea	Multicenter	1985-2006	214/117	16.9	127
Lee 2015	Korea	Multicenter	1989-2009	192/128	11.8	1237
Li 1989	China	Single-Center	1964-1986	84/30	–	4
Nagano 2017	Japan	Single-Center	2006-2013	386/360	62	14
Ogura 2017	Japan	Single-Center	2006-2012	4581/3707	58.3	126
Sun 2002	China	Single-Center	–	111/57	24	4
Tan 2011	China	Single-Center	1998-2008	270/143	18.2	5
Tan 2012	China	Single-Center	1998-2008	206/105	18.6	1356
Wang 2018	China	Single-Center	1973-2013	244/213	41.9	1
Zhong 1991	China	Single-Center	1978-1988	102/57	-	4

1: gender; 2: age; 3: metastasis or not at initial diagnosis; 4: combine chemotherapy and surgery or not; 5: standard chemotherapy or not; 6: limb salvage surgery or amputation; 7: curative effect of chemotherapy.

Table II. NOS scores of included studies.

Studies	Selection	Comparability	Exposure	Total
Bacci 1990	4	2	3	9
Bacci 2000	4	2	3	9
Bacci 2001	4	2	3	9
Bacci 2005	4	1	2	7
Bacci 2006	4	2	3	9
Cai 2000	4	1	3	8
Faisham 2017	4	2	3	9
Ferrari 2018	4	2	3	9
Fukushima 2018	4	2	3	9
Guo 2004	4	1	3	8
Hung 2016	4	2	3	9
Joo 2015	4	2	3	9
Kim 2008	4	2	3	9
Lee 2015	4	2	3	9
Li 1989	4	1	3	8
Nagano 2017	4	2	3	9
Ogura 2017	4	1	3	8
Sun 2002	4	1	3	8
Tan 2011	4	1	3	8
Tan 2012	4	2	3	9
Wang 2018	4	2	3	9
Zhong 1991	4	1	3	8

Influence of Combining Chemotherapy and Surgery on 5-Year OS in Patients with Osteosarcoma

Before 2000, no conventional normative chemotherapy was carried out. During this period, the studies were mainly to compare the effects of surgical treatment and surgical treatment combined with chemotherapy on 5-years OS of patients with osteosarcoma. A total of 5 studies were included. There was no heterogeneity between the studies, and the fixed effect model was used for analysis (p=0.16, I^2=39%). The results showed that the 5-year OS of patients receiving surgery combined with chemotherapy was significantly higher than that of patients receiving surgery only (OR=3.20, 95% CI=2.30-4.46) (Figure 5).

Influence of Standard Chemotherapy on 5-Year OS in Patients with Osteosarcoma

After 2000, neoadjuvant chemotherapy was gradually widely used and the research in this period focused on the comparison of the effects

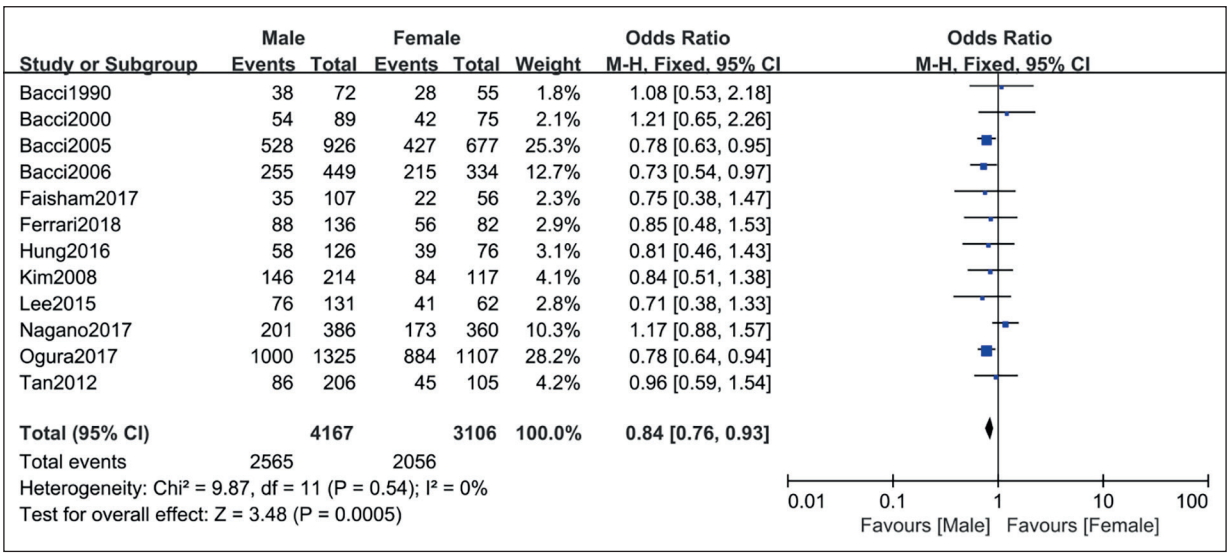

Figure 2. Meta-analysis on the influence of gender on 5-year OS in patients with osteosarcoma.

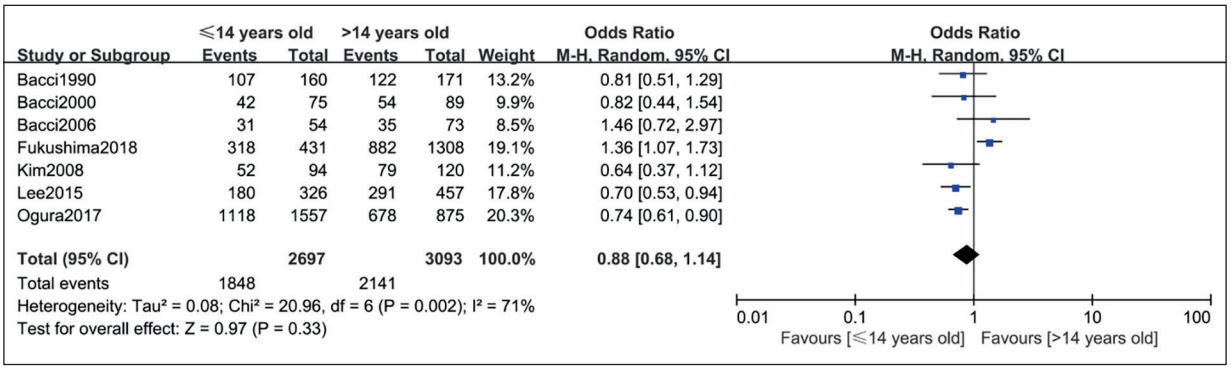

Figure 3. Meta-analysis on the influence of age on 5-year OS in patients with osteosarcoma.

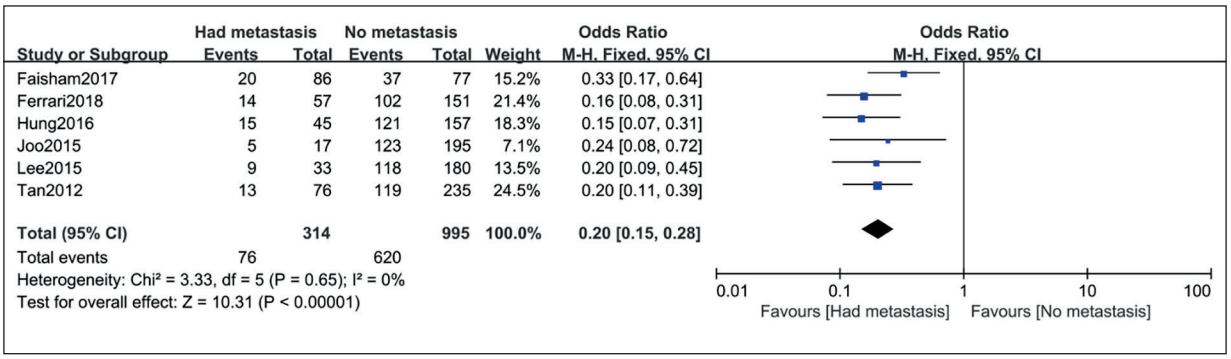

Figure 4. Meta-analysis on the influence of metastasis at initial diagnosis on 5-year OS in patients with osteosarcoma.

of standard chemotherapy and non-standard chemotherapy on OS in patients with osteosarcoma. A total of 4 studies were included. There was no heterogeneity between the studies (p=0.19, I^2=36%), and the fixed effect model was used for analysis. The results showed that the 5-year OS of patients in the standard chemotherapy group was significantly higher than that in the non-standard chemotherapy group (OR=2.17, 95% CI=1.77-2.67) (Figure 6).

Influence of Surgical Procedures on 5-Year OS in Patients with Osteosarcoma

Surgical methods for osteosarcoma can be divided into limb salvage surgery and amputation surgery. A total of 8 studies were included. There was significant heterogeneity between the studies (p<0.00001, I^2=80%) and random effect model was used for analysis. The results showed that the 5-year OS of patients in the limb salvage surgery group was significantly

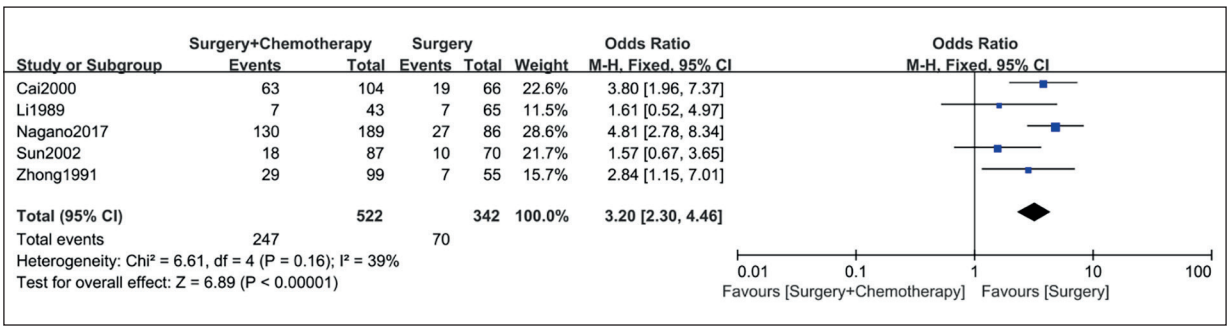

Figure 5. Meta-analysis on the influence of combining chemotherapy and surgery on 5-year OS in patients with osteosarcoma.

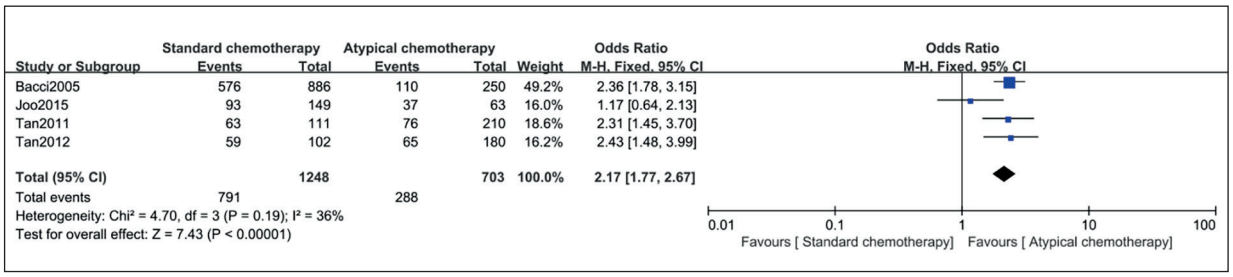

Figure 6. Meta-analysis on the influence of standard chemotherapy on 5-year OS in patients with osteosarcoma.

higher than that in the amputation surgery group (OR=2.39, 95% CI=1.63-3.51) (Figure 7).

Influence of Chemotherapy on 5-Year OS in Patients with Osteosarcoma

Chemotherapy effect evaluation was on the basis of tumor necrosis rate. Huvos tumor cell necrosis rate III, IV (tumor necrosis rate 90% or higher) referred to good chemotherapy group, I, II (tumor necrosis rate < 90%) for poor chemotherapy group. A total of 7 studies were included. There was no significant heterogeneity between the studies (p=0.02, I^2=62%) and the fixed effect model was used. The results showed that the 5-year OS of the patients with good chemotherapy response was significantly higher than that of the patients with poor chemotherapy response (OR=2.45, 95% CI=2.10-2.87) (Figure 8).

Publication Bias

Funnel plot was basically symmetrical in the studies included in this meta-analysis, suggesting that there was no significant deviation in the meta-analysis of gender, age, tumor metastasis at initial diagnosis, chemotherapy, and surgical methods. However, some analyses included few studies, resulting in atypical funnel plot (Figures 9A-9F). There was a publication bias in the studies included in the analysis of chemotherapy effect, but the bias was not evident and the articles that contributed to the bias had the lowest weight in the study, which was considered to be caused by a small number of cases (Figure 9G).

Discussion

Currently, it is one of the focuses of orthopedic surgeons to explore the factors affecting the prognosis of osteosarcoma, which is of great significance for guiding individualized treatment[29]. In this study, six factors including gender, age, tumor metastasis at first diagnose, adjuvant chemotherapy, surgical method, and chemotherapy effect were selected for meta-analysis, and the results showed that these factors had different effects on the prognosis of patients with osteosarcoma.

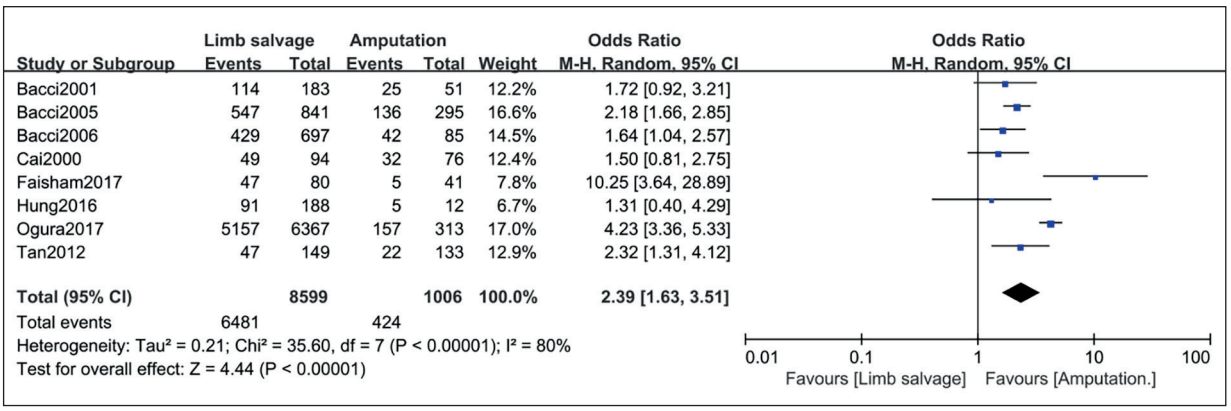

Figure 7. Meta-analysis on the influence of surgical procedures on 5-year OS in patients with osteosarcoma.

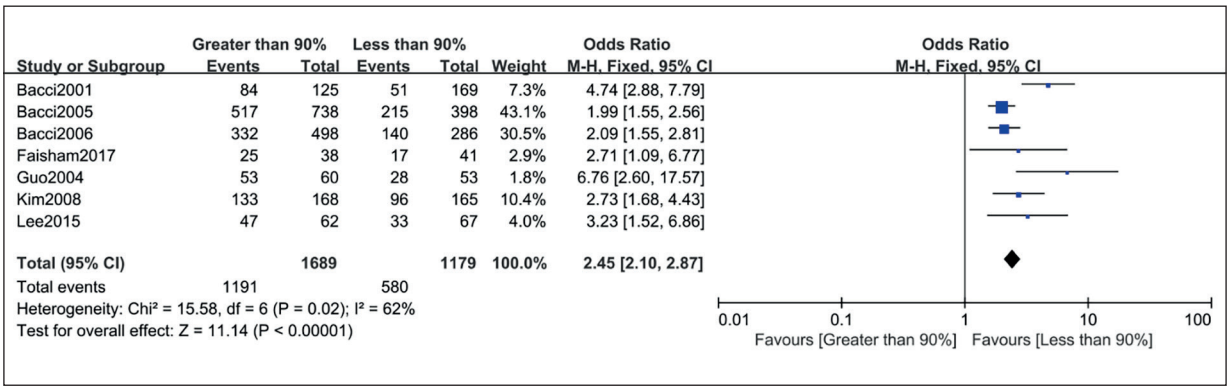

Figure 8. Meta-analysis on the influence of chemotherapy on 5-year OS in patients with osteosarcoma.

Osteosarcomas are more common in men, with a reported incidence of about 1.3:1[30]. The relationship between gender and prognosis of osteosarcoma has always been controversial. Some studies[31,32] have shown that the prognosis of male patients is worse than that of female patients, but most studies in recent years have shown that the gender of patients has no correlation with the prognosis of osteosarcoma. The meta-analysis results of this study showed that the 5-year OS of female patients was significantly higher than that of the male patients; whether this is due to data bias or tumor nature or gender differences required further study.

The correlation between age and prognosis of osteosarcoma has not been unified. Bacci et al[8] found that the 5-year OS among those under 14 years old was about 41.6 percent, lower than that

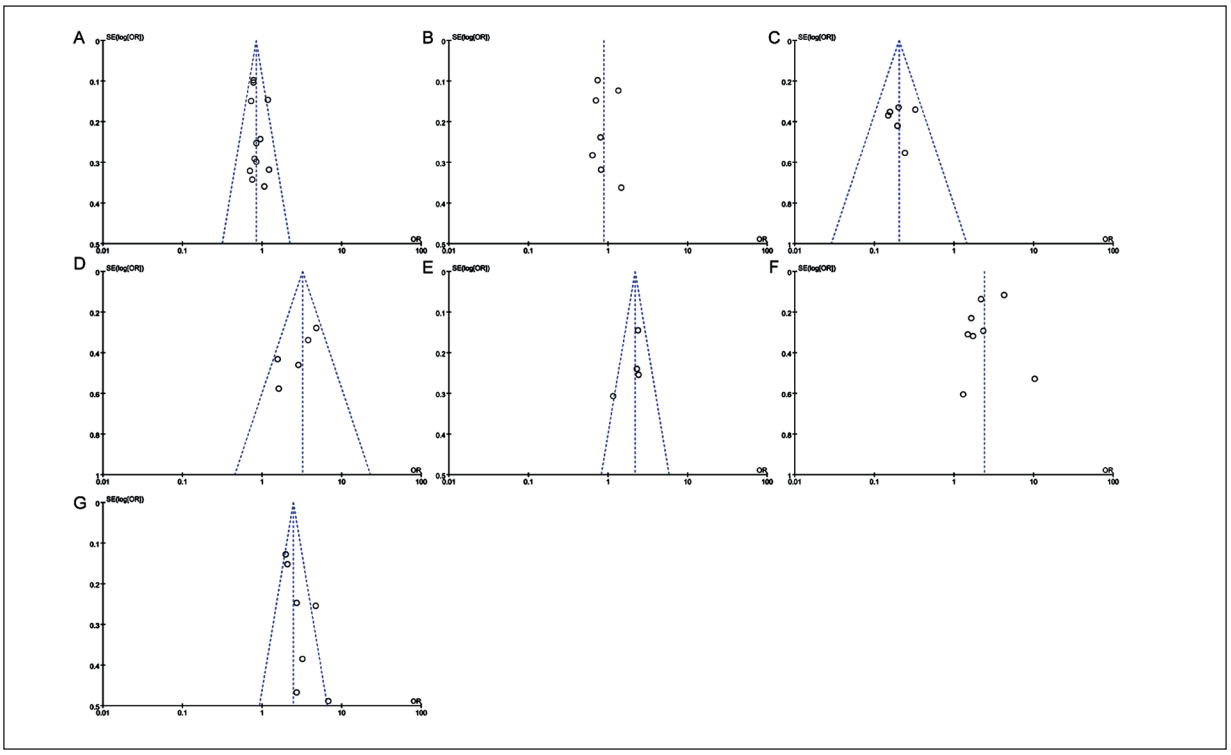

Figure 9. Funnel plots for publication bias assessment. **(A)** gender; **(B)** age; **(C)** metastasis or not at initial diagnosis; **(D)** combine chemotherapy and surgery or not; **(E)** standard chemotherapy or not; **(F)** limb salvage surgery or amputation; **(G)** curative effect of chemotherapy.

in other age groups. Meta-analysis results of this study showed that there was no statistical difference in the 5-year OS between the two groups. However, recent literature has pointed out that age is correlated in univariate analysis, but meaningless in multivariate analysis. Therefore, the relationship between age and prognosis remained to be further studied.

Through meta-analysis, Bramer et al[33] found that tumor response to chemotherapy was the most reliable independent risk factor for osteosarcoma prognosis. Studies[34] have shown that before the application of neoadjuvant chemotherapy, surgery combined with chemotherapy can improve the 5-year OS of patients with osteosarcoma. After the application of neoadjuvant chemotherapy, the 5-year OS in the standard chemotherapy group was higher than that in the non-standard chemotherapy group. Our meta-analysis also found that the 5-year survival rate in the standard chemotherapy group was significantly higher than that in the non-chemotherapy group, suggesting that the standard chemotherapy could significantly improve the survival rate of patients with osteosarcoma.

With the emergence of neoadjuvant chemotherapy, the development of imaging technology, and the continuous improvement of surgical techniques, the rate of limb salvage surgery in patients with osteosarcoma has gradually increased and the indications of limb salvage surgery are also expanding[35]. The scholars[36] think that not only patients of Enneking I phase and phase II are suitable for limb salvage surgery, but also by preoperative chemotherapy patients with IIB phase and even IIIB phase can also be suitable for limb salvage surgery. In recent years, most scholars believe that limb salvage surgery patients have a better prognosis. Our meta-analysis reached the same conclusion. However, we believed that sufficient surgical margins must be ensured during the operation, so the selection of surgical methods should be considered from various aspects, and the high limb salvage rate is not necessary.

Among the evaluation indexes of chemotherapy effect, the tumor necrosis rate has the advantage of being able to be accurately evaluated and with good sensitivity[37]. There is a significant correlation between tumor necrosis rate and prognosis of osteosarcoma. The results of this study also showed that the tumor necrosis rate was used to evaluate the effect of chemotherapy and the prognosis of patients with good effects of chemotherapy was better.

However, there still remain some limitations in our meta-analysis. Due to the large number of literature related to prognostic factors of osteosarcoma in the retrieved database, it is difficult to complete the retrieval. Therefore, only large sample studies with the number of cases greater than 100 were selected in this paper and the remaining studies were not included, which may cause data deviation. In addition, most of the studies included in the analysis were published 10 years ago, which may be different from the current situation. Therefore, further research will be needed to illuminate the prognostic factors of osteosarcoma.

Conclusions

The prognosis of male osteosarcoma patients was slightly worse than that of female patients. Surgery plus standardized chemotherapy can improve the 5-year OS of osteosarcoma patients. Patients who undergone limb-salvage surgery had a better prognosis. Poor response to chemotherapy and bone metastasis had a negative influence on the prognosis of osteosarcoma.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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