



## Review Article

## Does intensified chemotherapy increase survival outcomes of osteosarcoma patients? A meta-analysis



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## ABSTRACT

**Study Design:** Meta-analysis.

**Background:** Although some new insights have been offered for clinical and scientific relevance, minor progress has been made in osteosarcoma treatment after a dramatic survival improvement in the late 1980s with the addition of chemotherapy to surgery. Intensified chemotherapy strategies have been suggested to increase the survival rate of patients with osteosarcoma. We performed this study to access whether intensified chemotherapy strategies increased survival outcomes of osteosarcoma patients compared with conventional chemotherapy strategies.

**Methods:** MEDLINE/PubMed, EMBASE, BIOSIS Previews, and Cochrane Library were searched from database set up to October 2016. Randomized controlled trials (RCTs) and comparative clinical trials (CCTs) on intensified versus conventional chemotherapy strategies for osteosarcoma patients met the inclusion criteria, and the methodological quality standard were retrieved and reviewed. Data on participant characteristics, interventions, follow-up period, and outcomes were extracted from the included studies and analyzed by Review Manager 5.3. **Results:** 12 studies (8 RCTs and 4 CCT) involving 4112 patients were selected. There were no significant differences between intensified and conventional chemotherapy strategies group in 3-year event-free survival (OR, 1.01; 95% CI, [0.74–1.37];  $P = 0.97$ ), 5-year event-free survival (OR, 1.00; 95% CI, [0.86–1.17];  $P = 0.97$ ), and 5-year overall survival (OR, 1.04; 95% CI, [0.87–1.26];  $P = 0.64$ ), and good histologic response to preoperative chemotherapy (OR, 1.12; 95% CI, [0.78–1.60];  $P = 0.55$ ). Pooled analysis of local recurrence rate showed that local recurrence rate was significantly decreased in the intensified group compared with that in the conventional group (OR, 0.60; 95% CI, [0.42–0.85];  $P = 0.004$ ).

**Conclusions:** Intensified chemotherapy might not be a preferred treatment for all of the osteosarcoma patients.

## 1. Introduction

Osteosarcoma is the most common bone malignancy (incidence: 0.2–0.3/100,000/year) with a predilection for adolescents and young adults [1]. Osteosarcoma was considered to be an incurable disease before 1970s with 5-year survival rate approximately 10–20%, indicating very poor prognosis [2]. After the introduction of adjuvant chemotherapy, the cumulative 5-year survival has improved to 60–80%, indicating that adjuvant chemotherapy is vital for long-term survival of osteosarcoma.

Currently, the combination of surgical removal of the tumor and

systemic multidrug chemotherapy mainly consisting of methotrexate, adriamycin and cisplatin with or without ifosfamide, is the standard strategy to treat conventional osteosarcoma [3]. As a second-line chemotherapy strategy, combinations of gemcitabine with docetaxel seemed to show greater efficacy, with milder toxicity, when compared to pirarubicin-based chemotherapy for relapsed and refractory osteosarcoma [4]. Moreover, several investigators have demonstrated that caffeine, a DNA-repair inhibitor, improved 5-year event-free survival to 75%, when added to ADM- or CDDP-based chemotherapy in patients without metastasis at the initial examination [5]. Also, some promising novel agents, such as IGF-1R antibody or a mTOR inhibitor, are currently in Phase I/II clinical trials

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osteosarcoma [6]. IFN- $\alpha$  has been associated with activity against osteosarcomas in vitro, in animal models, and in patients with metastatic disease. Owing to its antiproliferative, differentiation-inducing, apoptotic, and antiangiogenic properties, and its clinical activity has been demonstrated in several cancers [7–9]. Muramyl tripeptide (MTP) phosphatidylethanolamine (MTP-PE) has been encapsulated in liposomes to deliver the agent selectively to monocytes and macrophages to activate them to become tumoricidal, and the effect of MTP has been confirmed in rodent xenograft models and in spontaneous canine OS [10]. The addition of novel agents to the standard MAP chemotherapy may provide improvements in outcome for patients with osteosarcoma.

Although some new insights have been offered for clinical and scientific relevance, minor progress has been made in osteosarcoma treatment after a dramatic survival improvement in the late 1980s with the addition of chemotherapy to surgery. Multiagent or intensified chemotherapy strategies have been suggested to improve the histological response of tumor cells, and finally increase the survival rate of patients with osteosarcoma as well as other malignancies [11,12].

Meanwhile, there are conflicting results reported when administering more-intensive agents in the process of chemotherapy. Dose intensification will bring more therapy toxicity and expense for osteosarcoma patients. Moreover, many researchers thought that the inherent sensitivity of tumor cells to chemotherapeutic drugs can not be changed by increasing chemotherapy dose, thus the chemotherapy-induced necrosis rate levels may be not increased in theory. A recently reported study displayed that dose intensification with high-dose chemotherapy did not increase the probability of survival [13].

By summarizing the evidence from randomized controlled trials (RCTs) and comparative observational studies (CCTs), we performed this meta-analysis and aimed to gain a better understanding of whether the high drug dosage can improve the histological response of tumor cells, thus improving the patient's survival compared with conventional-dose chemotherapy.

## 2. Methods

### 2.1. Search for eligible studies

We retrieved electronic databases of PubMed, Ovid, the Cochrane library, and CNKI using the following keywords: “osteosarcoma”, “chemotherapy”, “survival” (from database set up to October 2016 to identify the eligible articles. The reference lists of retrieved articles and relevant reviews were reviewed manually to find additional relevant studies.

### 2.2. Inclusion and exclusion criteria

Articles were selected if they met the following general criteria:

(1) Randomized controlled trials (RCTs) or comparative observational studies (CCTs); (2) subjects were diagnosed with osteosarcoma; (3) More intensified chemotherapy strategies in the treatment group than the control group administered conventional chemotherapy strategies; (4) clear survival rate.

Articles were excluded if there were: (1) Patients with metastases or history of cancer; (2) articles in non-English; (3) The study type of letters, case reports, editorials or reviews; (4) articles with incomplete raw data.

### 2.3. Data extraction

For included articles, two authors (...and...) independently extracted and collected data from full-text articles. If there was disagreement, another author (...) joined to reach an agreement. The following information of each included article was collected: first author, year of publication, country, research design, sample size, duration of chemotherapy, planned number of courses, cycles, and dosage of

each drug in the chemotherapy period, overall duration of chemotherapy and the evaluated outcomes.

### 2.4. Study quality

Two independent authors (... and ...) assessed the methodological quality of the included studies based on the physiotherapy evidence database (PEDro) scale [14]. This scale consists of a list of 11 criteria, covering aspects of randomization method, allocation concealment, blinding referring to the study subjects, investigators and outcome assessors, attrition bias and baseline conditions. The first criterion did not score, and the other criterion conferred 1 point to the total score of 10 points. Studies with PEDro score  $\geq 6$  were considered as being high quality.

### 2.5. Statistical analysis

Cochrane systematic review software RevMan 5.3 was used in this meta-analysis.  $\chi^2$  test was used to analysis heterogeneity among studies. The fixed effects model or random-effects model was used for the pooled analysis of data from trials without or with heterogeneity ( $I^2 > 50\%$ ). Sensitivity analysis was performed to find the source of heterogeneity. Primary outcomes were 3-year event-free survival, 5-year event-free survival, and 5-year overall survival. Secondary outcomes were histological response to preoperative chemotherapy (the percentage of tumor necrosis), local recurrence rate, and toxicity.

## 3. Results

### 3.1. Search result and characteristic of included studies

A total of 964 relevant titles were identified through database searching. Of these, 918 were excluded after reviewing abstracts or titles for an unrelated topic; not intensified chemotherapy; not osteosarcoma; or non-English writing. Finally, 46 articles were retrieved after full-text reviewing, and 12 studies met the inclusion criteria (Fig. 1). The obtained 12 studies were all comparative studies between intensified and conventional chemotherapy strategies. The characteristics

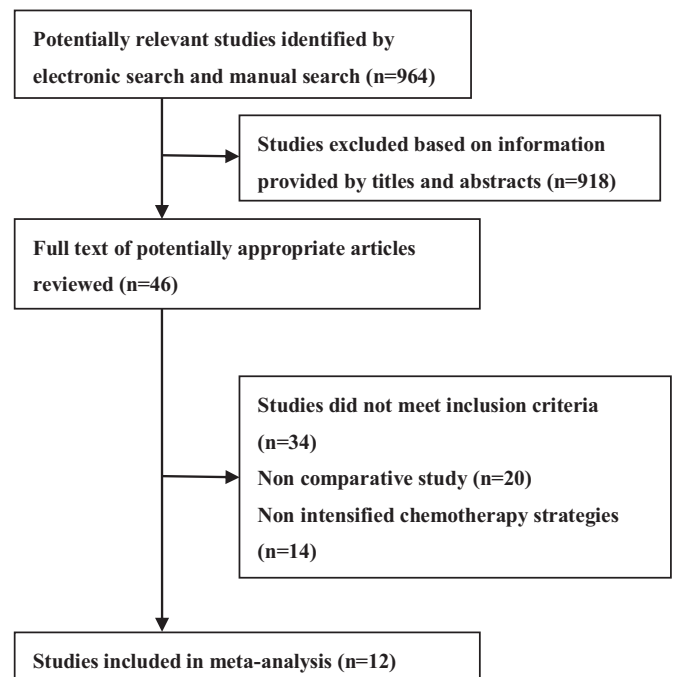


Fig. 1. The flow chart of screening included studies.

**Table 1**  
The characteristics of the 12 included studies.

References	Study location	Type of study	Duration (weeks)	No. of Patients Included	Age (years)	Timing of Surgery (weeks)	Outcome measure	Follow-up time (years)
Bacci G 1986	Italy	RCT	7:7	106	<50	NA	5-year disease free survival rate, histological response rate, 5-year overall survival rate, percentage of limb salvage rate, toxicity of therapy	2.5–5.5
Souhami RL 1997	UK	RCT	44:18	391	≤40	7:9	5-year disease free survival rate, local recurrence rate, histological response rate, 5-year overall survival rate, percentage of limb salvage rate, toxicity of therapy	5–6
Meyers PA 1998	USA	RCT	NA	73	≤36.4	11:7	5-year disease free survival rate, local recurrence rate, histological response rate, 5-year overall survival rate, toxicity of therapy	3.5–9
Bacci G 2003	Italy	CCT	NA	367	<50	13:11	5-year disease free survival rate, local recurrence rate, toxicity of therapy	7.5–10
Lewis IJ 2007	UK	RCT	15:21	497	<40	6:6	5 year disease free survival rate; 5 year overall survival rate; local recurrence rate, toxicity of therapy	9–10.5
Ferrari S 2012	Italy	RCT	34:44	246	≤40	11: 8	5-year disease free survival rate, 5 year overall survival, toxicity of therapy	6.3
Choeprasert W 2014	Thailand	CCT	36:31	66	≤18	NA	5-year disease free survival rate, 3-year disease free survival rate, 3-year overall survival rate, local recurrence rate	2.47
Meyers PA 2005	USA	RCT	31–38	677	<30	10	5-year disease free survival rate, 3-year disease free survival rate, toxicity of therapy	4.8
Schwartz CL 2016	Texas	CCT	36:28	242	<31	11	histological response rate, 3-year overall survival rate, toxicity of therapy	4.75
Bielack SS 2015	UK	RCT	29:67	716	≤40	11	Local recurrence, 5-year disease free survival rate, 5-year overall survival rate, 3-year disease free survival rate, 3-year overall survival rate, toxicity of therapy	3.67
Marina NM 2016	USA	RCT	40:29	618	≤40	NA	3-year disease free survival rate, 3-year overall survival rate, toxicity of therapy	5.17
Iwamoto Y 2009	Japan	CCT	NA	113	≤30	11	histological response rate, 5-year disease free survival rate, 5-year overall survival rate, toxicity of therapy	6.3

**Table 2**

The total scores for all included studies assessed by PEDro quality criteria.

Included studies	Item PEDro score											Total score
	1	2	3	4	5	6	7	8	9	10	11	
Bacci G 1986	+	+	-	+	-	-	-	+	+	+	+	6
Souhami RL 1997	+	+	-	+	-	-	-	+	+	+	+	6
Meyers PA 1998	+	+	+	+	-	-	-	+	+	+	+	7
Bacci G 2003	+	-	-	+	-	-	-	+	+	+	+	5
Lewis IJ 2007	+	+	-	+	-	-	-	+	+	+	+	6
Ferrari S 2012	+	+	+	+	-	-	-	+	+	+	+	7
Choeprasert W 2014	+	-	-	+	-	-	-	+	+	+	+	6
Meyers PA 2005	+	+	-	+	-	-	-	+	+	+	+	7
Schwartz CL 2016	+	-	-	+	-	-	-	+	+	+	+	6
Bielack SS 2015	+	+	+	+	-	-	-	+	+	+	+	8
Marina NM 2016	+	+	+	+	-	-	-	+	+	+	+	8
Iwamoto Y 2009	+	-	-	+	-	-	-	+	+	+	+	6

of the 12 included studies were listed in Table 1 [15–26], of which 8 studies were RCT and 4 studies were CCT. A total of 4112 patients were involved in this meta-analysis. In two studies, the administered chemotherapy scheme was identical for the treatment and control groups except that a higher dose was used in the treatment group. In seven study, chemotherapy combinations were added for the treatment group. In another three studies, the chemotherapy treatment was extended with the same chemotherapy combinations, equivalent to an increase in the cumulative dose. For the study of Meyers PA 2005, 2 × 2 factorial design was performed to evaluate the effect of addition of Ifosfamide and/or MuramylTripeptide to standard chemotherapy.

3.2. Assessing study quality

12 eligible studies were incorporated for study quality assessment. The total scores for all included studies assessed by PEDro quality criteria ranged from 5 to 8 (Table 2). Eleven studies were conferred with high quality (PEDro score ≥ 6), and one study was of low quality (PEDro score < 6). The two independent reviewers reached consensus on the scoring of all items without any disagreement. Nevertheless, the overall methodological quality was generally fair.

3.3. 3-year event-free survival

For 3 included studies, the data of 3-year event-free survival rates was reported. The 3-year event-free survival rate was 66.4% in the intensified group and 67.2% in the conventional group. Pooled analysis of 3-year event-free survival rate showed that there was no difference between the two groups (OR, 1.01; 95% CI, [0.74–1.37]; P = 0.97). As there was heterogeneity between the study estimates (I<sup>2</sup> = 64%), the random-effect model was used (Fig. 2).

3.4. 5-year event-free survival

For 8 included studies, the data of 5-year event-free survival rates was reported. The 5-year event-free survival rate was 53.7% in the intensified group and 53.4% in the conventional group. Pooled analysis of 5-year event-free survival rate showed that there was no difference between the two groups (OR, 1.00; 95% CI, [0.86–1.17]; P = 0.97). As there was no evidence of heterogeneity between the study estimates (I<sup>2</sup> = 49%), the fixed-effect model was used (Fig. 3).

3.5. 5-year overall survival

For 7 studies, the data of 5-year overall survival rates was reported. The 5-year overall survival rates was 63.1% in the intensified group, and 61.9% in the conventional group. Pooled analysis of 5-year overall

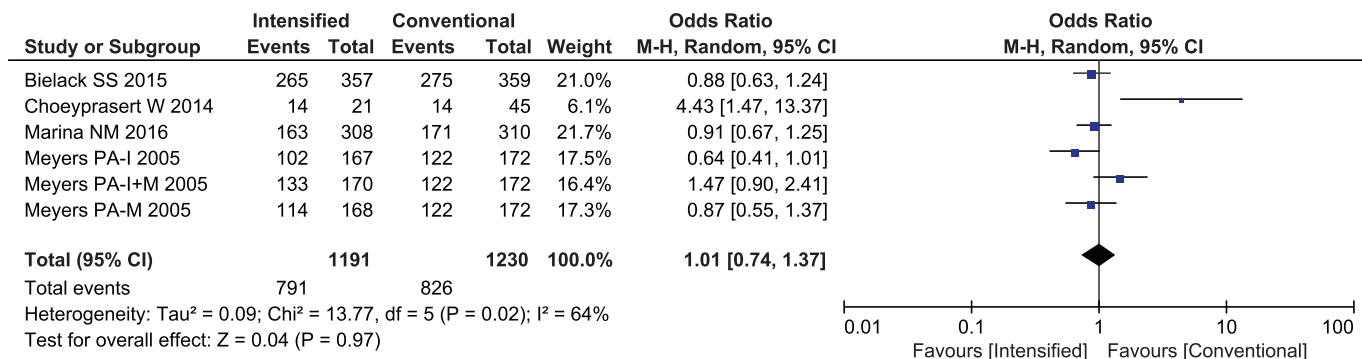


Fig. 2. Pooled analysis of 3-year event-free survival rate between intensified and conventional chemotherapy strategies.

survival rates showed that there was no statistically significant difference between the two chemotherapy treatments (OR, 1.04; 95% CI, [0.87–1.26]; P = 0.64). As there was no evidence of heterogeneity between the study estimates (I<sup>2</sup> = 10%), the fixed-effect model was used (Fig. 4).

3.6. Local recurrence rate

For 6 studies, the data of local recurrence rate was reported with a follow-up of 5 years. The local recurrence rate was 6.25% in the intensified group and 10.4% in the conventional group. Pooled analysis of local recurrence rate showed that local recurrence rate was significantly decreased in the intensified group compared with that in the conventional group (OR, 0.60; 95% CI, [0.42–0.85]; P = 0.004). As there was no evidence of heterogeneity between the study estimates (I<sup>2</sup> = 38%), the fixed-effect model was used (Fig. 5).

3.7. The effect of histologic response to preoperative chemotherapy on survival

For 8 studies, the data of rate of good histologic response to preoperative chemotherapy (90% tumor necrosis and above) was reported. The rate of good histologic response was 45.5% in the intensified group, and 41.0% in the conventional dose group. Pooled analysis of good histologic response showed that there was no statistically significant difference between the two chemotherapy treatments (OR, 1.12; 95% CI, [0.78–1.60]; P = 0.55), suggesting that the intensified chemotherapy strategies did not increase good histological response rate of tumor to the chemotherapy which was highly correlated with longer survival. As there was heterogeneity between the study estimates (I<sup>2</sup> = 64%), the random-effect model was used (Fig. 6).

3.8. Toxicity

The data of toxicity of therapy was reported in 10 studies, while the detail was not available in two studies. We displayed the occurrence rate of Grade 3 or greater toxicity during protocol chemotherapy in the intensified and conventional group in Table 3. Among those studies, two studies [27,28] performed statistical analysis, and showed that there was an significant increase in the occurrence of leucopenia, thrombocytopenia, RBC transfusion, PLT transfusion, neutropenic fever, and neutropeniain the intensified group compared with that of conventional group (P < 0.001).

4. Discussion

Neoadjuvant chemotherapy, as a major therapeutic modality, is essential for long-term survival in the treatment of osteosarcoma [29]. However, optimal chemotherapy protocol regarding the best chemotherapy regimen and the optimal intensity, remains unclear. Amounts of studies have shown that administrated dose of chemotherapy agents is closely related to the survival of patients with osteosarcoma [30,31]. To find the correlation between the chemotherapy intensity and patient survival, we performed this meta-analysis to access the intensified chemotherapy strategies on survival outcomes of osteosarcoma patients compared with conventional chemotherapy strategies. In this meta-analysis, we identified 12 clinical trials involving 4112 patient sex perienching chemotherapy for osteosarcoma. No significant differences were observed between intensified and conventional chemotherapy group in good histologic response rate to preoperative chemotherapy, 3-year event-free survival, 5-year event-free survival, and 5-year overall survival. While local recurrence rate was significantly decreased in the intensified group compared with that

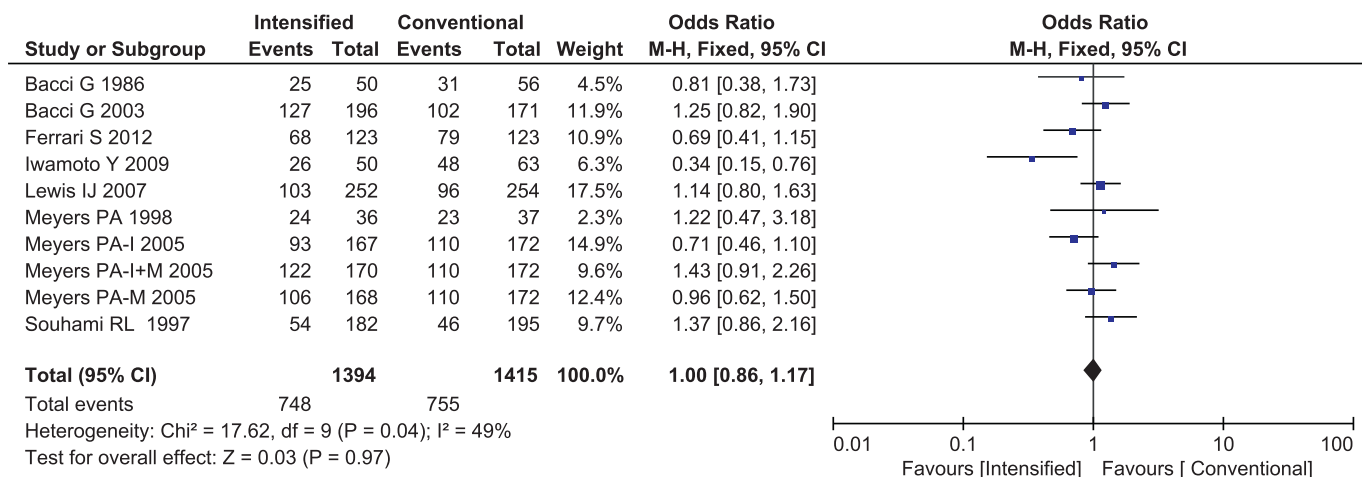


Fig. 3. Pooled analysis of 5-year event-free survival rate between intensified and conventional chemotherapy strategies.

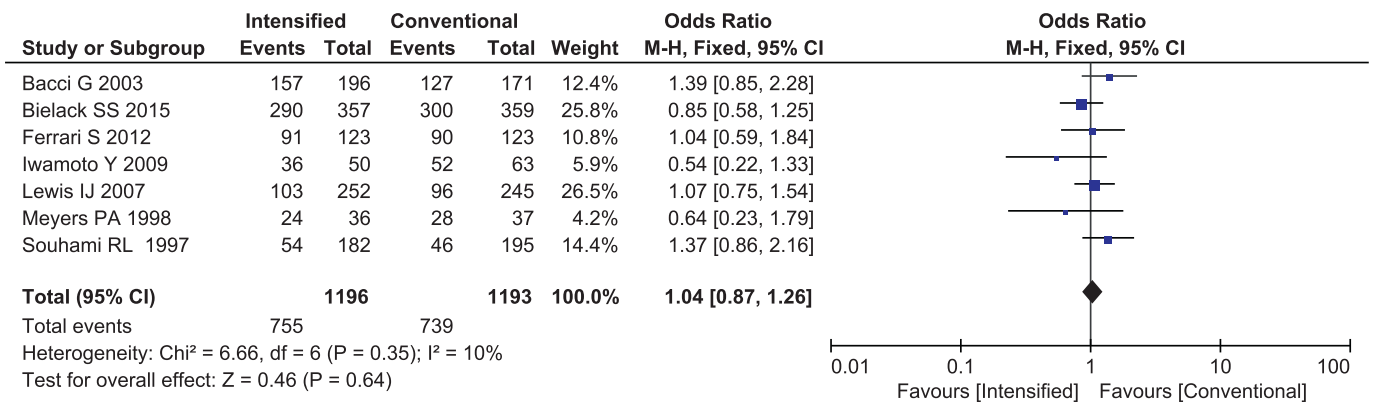


Fig. 4. Pooled analysis of 5-year overall survival rates between intensified and conventional chemotherapy strategies.

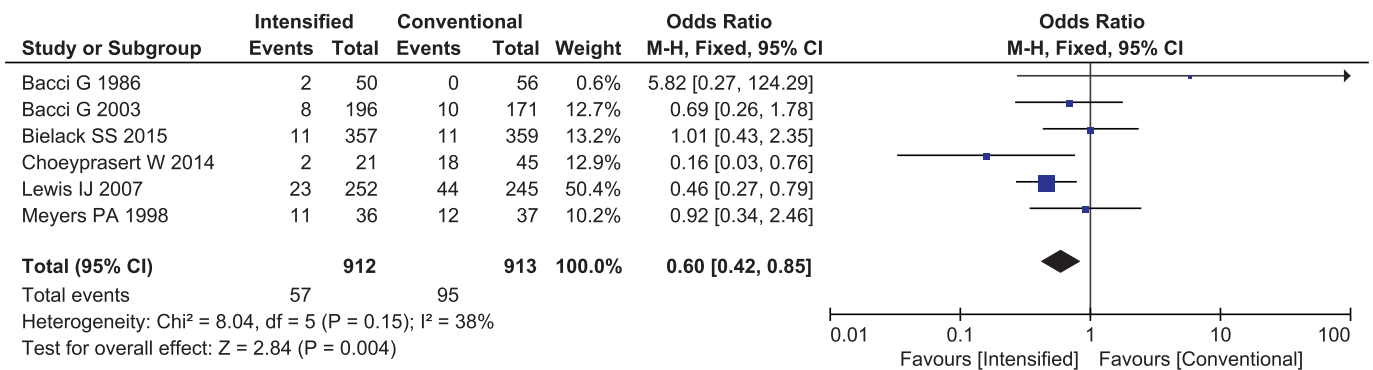


Fig. 5. Pooled analysis of local recurrence rate between intensified and conventional chemotherapy strategies.

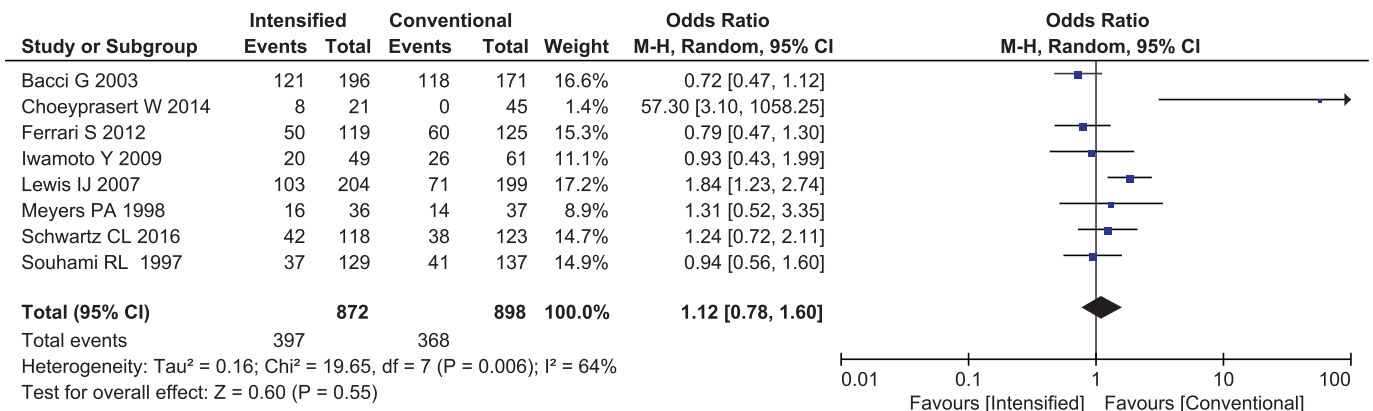


Fig. 6. Pooled analysis of the rate of good histologic response to preoperative chemotherapy between intensified and conventional chemotherapy strategies.

in the conventional chemotherapy group.

The influence of chemotherapy dose and dose intensity on survival of patients with malignant disease has been studied in various settings [32–34]. Early in vitro and in vivo experiments both revealed that increases in dose intensity consistently associated with higher response rates, as well as more potential for cure [35]. A meta-analysis also showed that increased dose intensity is correlated with superior remission rates in advanced-stage intermediate-grade lymphoma [36]. However, recently some clinical trials of increased drug doses have shown inconsistent results, generally providing no prolong in survival while considerably increasing toxicity [37,38], emphasizing that intensified chemotherapy may not be as important as previously considered.

Histologic response rate to preoperative chemotherapy was an independent prognostic factor in osteosarcoma. Previous researches reported that patients with good histologic response would have higher

survival rate [39]. In two of our included studies [16,17], intensified preoperative chemotherapy resulted in modest increases in favorable histologic response rate, no improvement in 5 year disease-free or overall survival was observed. However, pooled analysis of all included studies did not display any difference in good histologic response rate to preoperative chemotherapy. A possible explanation for this result is that chemotherapy response may be mainly dependent on intrinsic tumor biology and not the intensity of chemotherapeutic agents.

Local recurrence, an indicator of poor survival, was significantly decreased in dose-intensive group compared with that in dose control group, while this did not translate into a demonstrable survival benefit in this meta-analysis. This may be explained by that intensified chemotherapy would cause greater tumor cell kill, and the amount of tumor cell remains a low level in short term, so the local recurrence was lower, however, the long-term survival was not affected for the unchanged malignancy of the tumor.

**Table 3**  
Grade 3 or greater toxicity during protocol chemotherapy.

Toxicity of therapy	Bacci G 1986	Souhami RL 1997	Bacci G 2003	Lewis IJ 2007	Ferrari S 2012	Meyers PA 2005	Bielack SS 2015	Marina NM 2016
Hearing loss		2%:0%		3%:0%		11%		1%:3%
Leucopenia		73%:75%			95%:64%(P < 0.001)			7%:4%
Thrombocytopenia		28%:46%	21%:7%		84%:49%(P < 0.001)			83%:78%
Nausea and vomiting		66%:74%		53%:48%				
Mucositis		14%:20%		35%:27%		30%:33%		
Alopecia		90%:86%						
Renal impairment		3%:2%			3.4%:2.4%			
Liver		12%:1%						
Infection		18%:21%		25%:27%				53%:36%
Skin effects		2%:1%						
Neurotoxicity		1%:1%	3%:0%	1%:0%				
Pulmonary		1%:0%						
Delayed excretion					8.2%:7.6%			
RBC transfusion					78%:35%(P < 0.001)			
PLT transfusion				77%:58%(P < 0.001)	64%:25%(P < 0.001)			
Neutropenic fever			14%:2%		71%:42%(P < 0.001)			73%:50%
Neutropenia			48%:15%	76%:92%(P < 0.001)				90%:89%
Cardiotoxicity	11%	2%:0%	0.5%:1.2%	1%:3%	3.4%:5.6%		4%:4%	1.3%:1%
Any toxicities	□	□	□	96%:97%	□	□	□	94%:95%

Importantly, the chemotherapy treatment of OS is associated with short and long term collateral toxic effects [40]. Acute-toxicities such as alopecia, myelosuppression, mucositis, and nausea and vomiting are common complications of most cytotoxic chemotherapy regimens [41]. The major causes of rare cases of toxic deaths have been early or late cardiac failure due to doxorubicin toxicity and sepsis following febrile neutropenia. Among those studies we extracted, there was a significant increase in the occurrence of leucopenia, thrombocytopenia, RBC transfusion, PLT transfusion, neutropenic fever, and neutropenia in the intensified group compared with that of conventional group. Combinations of gemcitabine with docetaxel seemed to show greater efficacy, with milder toxicity, when compared to pirarubicin-based chemotherapy for relapsed and refractory osteosarcoma [4].

There were some limitations in this meta-analysis. There is considerable heterogeneity among different studies. Firstly, osteosarcoma is consisted of various histopathologic subtypes. The administered chemotherapy agents or schemes differed, influence of drug dosage and intensity on outcomes for patients might display intrinsic differences for different drugs. Further RCTs with high quality were needed to provide more reliable evidence. Despite these limitations, this meta-analysis can still provide some value for clinical practice.

In conclusion, although the intensified chemotherapy decreased the local recurrence rate, long-term prognosis was similar between intensified and conventional chemotherapy in patients with osteosarcoma. Considered the higher cost or toxicity, there is no need to perform the intensified chemotherapy. Given that the survival rate of osteosarcoma could not be increased by intensified chemotherapy, it is expected to develop new therapeutic drugs for osteosarcoma in the future clinical investigation. Another direction the clinical investigation is heading for is to optimize the use of the active drugs, facilitating a possible personalized chemotherapy approach.

**Conflict of interest**

The authors declared that there is no conflict of interests in this work.

**Supplementary materials**

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jbo.2018.04.001.

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