Clinical Outcome Following Prolonged Neoadjuvant Chemotherapy and Delayed Surgery in Osteosarcoma Patients: An Evidence-based Clinical Review

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ABSTRACT

Background: *The incidence of osteosarcoma reached 16.8 cases annually at dr. Cipto Mangunkusumo Hospital in 1995-2008. Previous studies suggested that prolonged neoadjuvant chemotherapy followed by delayed surgery improves the clinical outcome. Prolonged neoadjuvant chemotherapy followed by delayed surgery commonly occurs in Indonesia, as diagnostic imaging and surgery waiting list will delay the surgery. The aim of this study is to observe the survival rate and the event-free survival rate of osteosarcoma patients with prolonged neoadjuvant chemotherapy and delayed surgery.* ***Methods:*** *This review included randomized controlled trials (RCTs), cohort studies, retrospective cohort studies, clinical trials, and reviews. Literature search was conducted through MEDLINE (PubMed search engine), Cochrane Central Register of Controlled Trial, and Scopus. The studies were screened and selected according to inclusion criteria by author and contributors independently.* ***Results:*** *Six studies were included in the qualitative synthesis of this study. Overall survival rate, event-free survival rate, histological response and recurrence as well as neoadjuvant chemotherapy duration, cycle and regiment were assessed in this study.* ***Conclusion:*** *Prolonged neoadjuvant chemotherapy and delayed surgery results in 5-years survival rate of 43.2% to 96.6% and 5-years event-free survival rate of 35.7% to 86.4%.*

Keywords**:** *prolonged chemotherapy, neoadjuvant chemotherapy, delayed surgery, osteosarcoma.*

INTRODUCTION

Osteosarcoma is a malignant bone tumor of mesenchymal origin produced in the bone stroma characterized histologically by spindle cells and osteoid production.[1,2] Osteosarcoma most frequently develops from the epiphyseal growth plate in distal femur or proximal tibia, where rapid bone growth occurs.[1] The alteration of mesenchymal stem cell differentiation to osteoblast is considered the most probable cause of osteosarcoma.[1] The definite cause of osteosarcoma has not been elucidated.[3] Several authors suggested that the germline mutation of TP53 gene in chromosome 17p13C in Li-Fraumeni syndrome (LFS) plays a role as a predisposing factor for osteosarcoma.[3] Microdeletion germline loss of RB1 gene in chromosome 13q14 in retinoblastoma is also associated with osteosarcoma in some degree.[3,4]

Osteosarcoma is the most common primary bone tumor with the global incidence of 2-3 cases/million/year in the general population, 8-11 cases/million/year in adolescent, and 2.5-5 cases/million/year in elderly.[1,5] The incidence of

osteosarcoma has bimodal distribution across age groups with the first peak in children and adolescents (<24 years old) and the second peak in the elderly (>60 years old) and it is commonly related to Paget's disease.[3,5,6] The incidence of osteosarcoma in Asia, including Indonesia, shows a similar epidemiological pattern with the incidence of 2.5-4.1 cases/million/year in adolescents and 2.4-3.1 cases/million/year in elderly.[5] A study conducted in Jakarta, Indonesia showed the incidence of osteosarcoma reached 16.8 cases annually at dr. Cipto Mangunkusumo General Hospital in 1995-2008.[7] Furthermore, in Indonesia the osteosarcoma patients usually receive delayed proper therapy due to social-economical condition, low education, strong belief in traditional medicine, geographical factor, long administrative process, and scarcity of oncologic orthopedic surgeons. Delayed treatment in osteosarcoma could lead to significant morbidity and mortality.[8] Previous study shows significant lower overall survival and event free survival in patients with delayed chemotherapy initiation and completion.[9]

Advancement of chemotherapy, surgery, and reconstruction options improves the clinical and functional outcomes of osteosarcoma in the last 50 years.[10] A study conducted in 1982 showed increased survival rate with preoperative chemotherapy (neoadjuvant) compared to immediate surgery.[3] Currently, osteosarcoma is treated by neoadjuvant chemotherapy followed by wide surgical resection and adjuvant chemotherapy.[10] Even with chemotherapy, the previous study showed that the survival rate of osteosarcoma had plateaued around 60% in 5-years survival.[11] However, a study in China suggested that a prolonged neoadjuvant chemotherapy followed with delayed surgery showed an improved clinical outcome with 2-years survival of 74.2%.[12] Moreover, prolonged neoadjuvant chemotherapy followed by delayed surgery commonly occurs in Indonesia, as diagnostic imaging and surgery waiting list will delay the surgery. Further investigation of prolonged neoadjuvant chemotherapy followed by delayed surgery is necessary to improve the clinical outcome of osteosarcoma. Reviewing the outcome of prolonged neoadjuvant chemotherapy followed by delayed surgery is important as a potential treatment to improve clinical outcomes in osteosarcoma patients..

The aim of this evidence-based clinical review is to observe and evaluate the clinical outcome of prolonged neoadjuvant chemotherapy and delayed surgery in osteosarcoma patients. This review will answer these following questions: 1). What are the survival rate and the event-free survival rate of prolonged neoadjuvant chemotherapy and delayed surgery in osteosarcoma patients? 2) What is the ideal duration for neoadjuvant chemotherapy in osteosarcoma patients?

METHODS

In this review, we only included randomized controlled trials (RCTs), cohort studies, retrospective cohort studies, clinical trials, and reviews. Case reports, case series, and commentary were not included in this review. The characteristics of population in this review are patients with osteosarcoma in any age with or without metastatic disease. The interest of this study is interventions addressing prolonged neoadjuvant chemotherapy followed by delayed surgery defined as preoperative chemotherapy with three or more cycles of any chemotherapy regimens followed by surgical resection and adjuvant chemotherapy. There was no restriction by type of comparison of intervention in this review. The primary outcomes for this study were outcomes related to the survival of osteosarcoma patients such as overall survival rate and event-free survival rate. Other outcomes affecting the survival including histopathological pattern and recurrence rate were considered as a secondary outcomes. Primary and secondary outcomes were collected as reported from each study. The outcome were analyzed and graded.

Information Sources

Literature search strategy were developed using medical subject headings (MeSH) terms and any text words related to prolonged neoadjuvant chemotherapy in osteosarcoma cases. Literature search were conducted through MEDLINE (PubMed search engine), Cochrane Central Register of Controlled Trial, and Scopus

from 1970-2020. The literature search was not limited by language. Reference lists of included studies and relevant reviews provided by the electronic database were scanned to ensure literature saturation.

Search Strategy

Quantitative studies and qualitative studies were included in this study. An electronic database search engine was used to search the literatures. Specific search keywords were created by the primary author with input from other contributors. Search keywords were (((((osteosarcoma) OR osteogenic sarcoma) OR bone sarcoma)) AND ((((neoadjuvant chemotherapy) OR neo-adjuvant chemotherapy) OR preoperative chemotherapy) OR pre-operative chemotherapy)) AND ((((delayed surgery) OR prolonged chemotherapy) OR long course chemotherapy) OR multiple course chemotherapy) for MEDLINE and Cochrane database. Search keywords of (Osteosarcoma) AND (prolonged neoadjuvant chemotherapy) AND (delayed surgery) were used for Scopus database. Literature searching was conducted in January 24th 2020.

Study Records

Study titles and abstracts were screened and selected according to the inclusion criteria by author and contributors independently. Selected studies were matched among the contributors. Full-text articles were downloaded and reviewed by the author and contributors. Additional information from the study was sought if necessary. Disagreement among authors and contributors was solved by discussion.

Risk of Bias

To ascertain the validity of the selected studies, a pair of independent reviewers were selected to determine the randomization adequacy, blinding, concealment of data, data collection, drop-out subjects, and outcome assessment. Cochrane risk of bias for cohort study was used as risk of bias assessment tool. Reviewers were then concluded the risk of bias from the selected studies.

RESULTS

Systematic literature searching identified 130 relevant titles and abstracts with 109 articles from MEDLINE, 18 articles from Cochrane and 3 articles from Scopus. Eight abstracts were excluded after duplication screening of the titles. One-hundred twenty-two abstracts were reviewed and 98 abstracts were excluded due to study population, study design, and intervention incompatibility. Twenty-four full-text articles were reviewed and analyzed. Eighteen full-text articles was excluded from this study due to intervention incompatibility (neoadjuvant chemotherapy regimen shorter than 3 cycles, combined with radiotherapy, regional therapy, and early surgical intervention), unrelated outcomes (did not include overall survival rate nor event-free survival rate), and other considerations (no full-text available). Therefore, six studies were included in the qualitative synthesis of this study. A complete flowchart of the systematic literature search is outlined in **Figure 1**.

The characteristics of the selected studies are outlined in **Table 1**. The studies were published between 1979-2019. The number of subjects in the study ranged from 31 to 300 osteosarcoma patients. Two of the studies obtained were published in China, two studies were published in the United States, and two studies was published in Europe. Five studies were retrospective studies and only one study was a prospective study. The neoadjuvant chemotherapy in these studies was followed by surgical intervention and various adjuvant chemotherapy.

Cycle and Duration

All studies had at least 3 cycles of neoadjuvant chemotherapy ranging from 3 – 10 courses of chemotherapy. One study administered 3 courses of chemotherapy with 36 days duration. One study administered 3-5 courses of chemotherapy with 13 weeks duration. Other studies administered 3-6 courses and 6 courses of chemotherapy with a duration of 52 and 50 weeks, respectively. Two studies administered 4 and 6-10 courses of chemotherapy without describing the duration of the therapy.

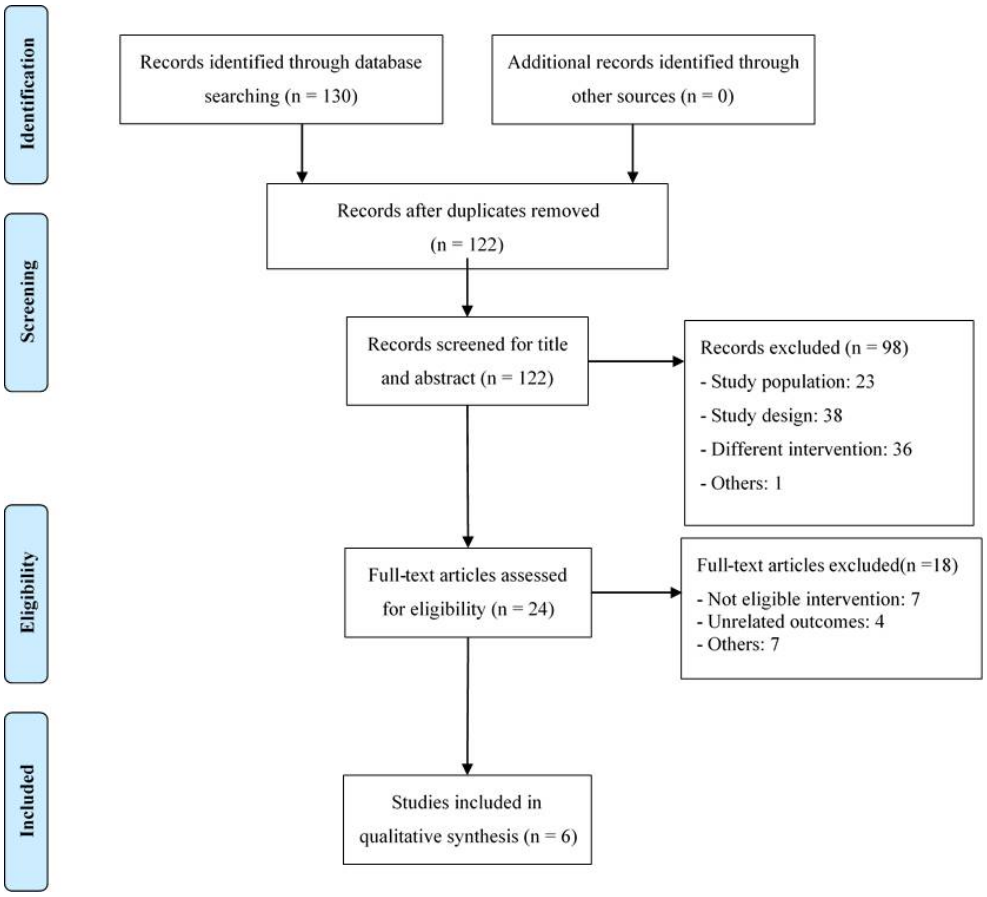

Figure 1. A flowchart of the study.

Regimen

Five of six studies included high-dose methotrexate (HD MTX) in the combination of neoadjuvant chemotherapy regimen, including HD MTX + ADR + IFO, HD MTX + DOX + IFO + CDDP, HD MTX + DOX + CDDP, HD MTX + CFR + ADR +VcR, and HDMTX + CDDP + ADR. Another study administered chemotherapy regimen without HD MTX with DOX + IA CDDP, and CDDP + ADR + IFO. We found no study administering monotherapy as prolonged neoadjuvant chemotherapy.

Overall Survival Rate

Survival analysis was obtained in the forms of overall survival rate and event-free survival rate. Three of the studies reported 5-years survival rate ranging from 43.2% to 96.6%. Two studies reported 10-years survival rate ranged from 36.6% to 93.2%. One study reported 4-years survival rate of 77% and two studies did not report the overall survival rate. Event-free survival rate was reported in 5 studies within 5-10 years follow-up. Four studies reported 5 years of event-free survival rate ranging from 35.7% to 86.4%. One study reported 8-years event-free survival rate of 59% and two studies reported a 10-years event-free survival rate of 26.8% to 86.4%.

Histological Response and Recurrence

The histological response was reported in 5 of 6 studies included. Four studies reported good histological response as >90% tumor cell necrosis and one study reported good histological response as >90% reduction in tumor neovascularity. Studies reported >90% tumor cell necrosis ranged from 8% to 86% and reduction in tumor neovascularity of 87%. Local recurrence was described in 5 studies ranging from 0% to 41% local recurrence.

Risk of Bias Assessment

The risk of bias concluded from the assessment tool showed low risk of bias for study by Ferrari (2001). Moderate risk of bias were concluded from studies by Xu (2014), Xu (2018), Wilkins (2005), and Bacci (1993). Serious risk of bias was found from study by Rosen (1979) with poor confounding bias consideration and analysis method. Complete risk of bias assessment is presented in **Table 2**.

Table 1. Characteristics of included studies

Reference (year)	Study design	Cycle	Neoadjuvant chemotherapy duration	Neoadjuvant chemotherapy regimen	Surgical procedure
Xu et al.[13] (2014)	Retrospective study	6-10 courses	Not described	MMIA protocol (HD-MTX, ADR, IFO) and DIA protocol (CDDP, ADR, IFO)	Tumor resection and prosthetic replacement OR Tumor resection and autograft implantation OR Marginal tumor resection
Xu et al.[14] (2018)	Retrospective study	3-6 courses	1 year	DOX, HD MTX, IFO, CDDP	Not described
Ferrari et al.[15] (2001)	Retrospective study	4 courses	Not described	HD MTX, DOX, CDDP	Limb salvage, amputation, rotationplasty
Rosen et al.[16] (1979)	Retrospective study	6 courses	50 weeks	HD MTX, CFR, ADR, VcR	En bloc resection
Wilkins et al.[17] (2005)	Prospective study	3-5 courses	13 weeks	IA DOX, IA CDDP	Wide resection and endoprosthetic replacement
Bacci et al.[18] (1993)	Retrospective study	3 courses	36 days	HD MTX, CDDP, ADR	Limb salvage, amputation, rotationplasty

HD MTX: High-dose methotrexate, ADR: Adriamycin, IFO: Ifosfamide, CDDP: Cisplatin, DOX: Doxorubicin, CFR: Citrovorum factor, VcR: Vincristine, IA DOX: Intra-arterial Doxorubicin, IA CDDP: Intra-arterial Cisplatin

Table 2. Data extraction

Reference (year)	Cycle	Neoadjuvant chemotherapy regimen	Overall survival rate	Event-free survival rate	Histologic response	Recurrence
Xu et al.[13] (2014)	6-10 courses	MMIA protocol (HD-MTX, ADR, IFO) and DIA protocol (CDDP, ADR, IFO)	5-years survival rate = 61.8%	5 years = 57.7%	100% in 27 subjects (54%) >90% in 16 subjects (32%) 50-90% in 7 subjects (14%)	8.5% local recurrence
Xu et al.[14] (2018)	3-6 courses	DOX, HD MTX, IFO, CDDP	5-years survival rate = 43.2% 10-years survival= 36.6%	5 years = 35.7% 10 years = 26.8%	>90% in 4 subjects (8%) 60-90% in 23 subjects (45%) <60% in 24 subjects (47%)	30% local recurrence
Ferrari et al.[15] (2001)	4 courses	HD MTX, DOX, CDDP	Not described	8 years = 59%	>90% in 203 subjects (68%)	41% local recurrence
Rosen et al.[16] (1979)	6 courses	HD MTX, CFR, ADR, VcR	4-years survival rate = 77%	Not described	Not described	Not described
Wilkins et al.[17] (2005)	3-5 courses	IA DOX, IA CDDP	5- years survival rate = 96.6% 10-years survival rate = 93.2%	5 years = 86.4% 10 years = 86.4%	>90% in 54 subjects (87%)	No local recurrence
Bacci et al.[18] (1993)	3 courses	HD MTX, CDDP, ADR	Not described	5 years = 63.1%	>90% in 117 subjects (71.3%)	3% local recurrence

HD MTX: High-dose methotrexate, ADR: Adriamycin, IFO: Ifosfamide, CDDP: Cisplatin, DOX: Doxorubicin, CFR: Citrovorum factor, VcR: Vincristine, IA DOX: Intra-arterial Doxorubicin, IA CDDP: Intra-arterial Cisplatin

Table 3. The risk of bias in cohort studies assessment tool

Reference	Bias due to confounding	Bias in selection of participant into the study	Bias in classification of interventions	Bias due to deviation from intended interventions	Bias due to missing data	Bias in measurement of the outcome	Bias in selection of the reported result	Conclusion
Xu et al. (2014)	Moderate risk	Low risk	Low risk	Low risk	Moderate risk	Low risk	Moderate risk	Moderate risk of bias
Xu et al. (2018)	Moderate risk	Low risk	Low risk	Low risk	Moderate risk	Low risk	Low risk	Moderate risk of bias
Ferrari et al. (2001)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk of bias
Rosen et al. (1979)	Serious risk	Moderate risk	Low risk	Low risk	Low risk	Low risk	Low risk	Serious risk of bias
Wilkins et al. (2005)	Moderate risk	Low risk	Low risk	Low risk	Moderate risk	Low risk	Low risk	Moderate risk of bias
Bacci et al. (1993)	Moderate risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Moderate risk of bias

DISCUSSION

Nowadays, neoadjuvant chemotherapy followed by wide surgical resection and additional adjuvant chemotherapy has been the main treatment of osteosarcoma.[10,19,20] Studies showed that administration of neoadjuvant chemotherapy has increased the 5-years survival rate of osteosarcoma to 50%-60% compared to 20% with surgery alone.[10,21] Furthermore, neoadjuvant chemotherapy theoretically could optimize the surgical result by treating micro-metastases early, allowing histological assessment of chemotherapy, and adjusting the adjuvant chemotherapy.[21] Common chemotherapeutic agents used as neoadjuvant chemotherapy are high-dose methotrexate (HD MTX), Doxorubicin (DXR), Cisplatin (CDDP), and Ifosfamide.[21,22] Other chemotherapeutic agents such as Vincristine (VcR), Bleomycin, and Dactinomycin have also been used for neoadjuvant chemotherapy.[22] Recent trials still used HD MTX as the backbone of neoadjuvant chemotherapy.[19] However, 5-years survival rate of osteosarcoma has remained stagnant in the past 25 years despite various attempt to improve survival.[23]

Prolonged neoadjuvant chemotherapy and delayed surgery have been around since the discovery of neoadjuvant chemotherapy for osteosarcoma patients.[14] Prolonged neoadjuvant chemotherapy aims to improve the histological response leading to the improvement of survival in osteosarcoma patients. Previous studies have shown a significant increase of event-free survival rate and overall survival rate in osteosarcoma patients with good histopathological response following neoadjuvant chemotherapy.[19,24,25] Prolonged neoadjuvant chemotherapy could also be used as a waiting therapy for osteosarcoma patients with delayed surgery in the case of long waiting time for prosthetic development. However, studies have shown various outcomes following prolonged neoadjuvant chemotherapy and delayed surgery.

Overall survival rate and event-free survival rate of most studies included in this review showed similar survival to previous studies with standard neoadjuvant chemotherapy, in which the 5-years survival rate ranged from 50%-60%.[19,22,23] The longest course of neoadjuvant chemotherapy cycle (6-10 cycles) shown by Xu et al. in 2014 reported 5-years survival rate of 61.8%.[12] However, a study conducted by Wilkins et al. in 2005 showed surprisingly high 5-years and 10-years survival rate with good histological response.[17] Direct evaluation of histological response (reduction in neovascularity) by using angiography in this study could be one of the factors improving the overall survival rate.[17] This could also explain the high rate of histological response reported in this study. On the contrary, a study by Xu et al. in 2018 showed particularly low overall survival rate and histological response to prolonged neoadjuvant

chemotherapy.[14] A long interval of neoadjuvant chemotherapy (up to 1 year) and higher risk of bias in this study could affect the outcome.[14] However, this study included an older patient with high infiltration rate to local tissue which could affect the outcomes.[14] The incidence of local recurrence in the studies included showed various results of up to 41%. Older age, tumor volume, aggressive tumor, no surgical resection, metastasis, poor histological response, and poor postoperative chemotherapy compliance are the prognostic factors for worse outcomes in osteosarcoma patients.[26–30] However, the chemotherapy regimen does not associate with the outcomes in osteosarcoma patients.[26]

The histological response of prolonged neoadjuvant chemotherapy showed various results ranging from 8% to 86% of >90% local tumor necrosis and 87% of >90% reduction of tumor neovascularity.[14,17,18] As aforementioned above, the histological response to neoadjuvant chemotherapy is one of the most important prognostic factors in osteosarcoma patients.[24,25,31–33] A previous study showed that a good histological responder to neoadjuvant chemotherapy had long-term survival of 70% to 80% compared to that of 15% in poor responders.[25,31] Studies included in this review shows a similar tendency towards high overall survival rate in good histological response. The poor histological response shown by Xu et al. (2018) translates to low overall survival rate compared to other studies with better histological response.[14]

The histological response of neoadjuvant chemotherapy in osteosarcoma depends on several factors, e.g. osteosarcoma type, various chemotherapy regimens, and drug resistance. The degree of necrosis in response to neoadjuvant chemotherapy varies between osteosarcoma type.[25] Telangiectatic osteosarcoma generally shows a good response to neoadjuvant chemotherapy (80-90%).[31] Incompatibility to chemotherapy regimen and prolonged waiting duration could also affect the histological response of osteosarcoma.[14] High-intensity neoadjuvant chemotherapy also shows a significant association with the histological response but not with overall survival rate in osteosarcoma patients.[34] High-intensity neoadjuvant chemotherapy might not increase the histological response high enough to affect the overall survival rate in osteosarcoma.[34] Furthermore, increased risk of adverse effects in high-intensity neoadjuvant chemotherapy, e.g. thrombocytopenia and mucositis, might also affect the overall survival rate.[34] Chemotherapy drug-resistant clone has been described in a previous study with poor response to neoadjuvant chemotherapy and increased risk of metastasis.[32]

Local recurrence after complete therapy in osteosarcoma patients is identified as a poor prognostic factor, especially the early local recurrence and positive margin at the time of initial surgery.[35–38] In this study, local recurrence ranged from 0% to 41% local recurrence.[15,17] A previous study showed 6% to 9% local recurrence with 60% of them occurring early (24 months).[39] Prognostic factors for local recurrence are good quality of surgical margin and good histological response to chemotherapy.[37] Improved survival after local recurrence could be achieved by wide surgical resection of osteosarcoma. Prognostic factors for survival after local recurrence are gender, metastasis, treatment of local recurrence, length of resection margin, alkaline phosphatase level, tumor volume, histologic subtypes, chemotherapy protocol.[36,40–42] Recurrence rate following prolonged neoadjuvant chemotherapy and delayed surgery showed similar recurrence rate, except for two studies with 41% and 30% local recurrence.[14,15] However, as aforementioned above, the local recurrence in osteosarcoma patients is highly affected by surgical procedure and histological response to chemotherapy.[37]

This review describes variable chemotherapy regimen, duration, and survival outcomes following prolonged neoadjuvant chemotherapy and delayed surgery. A limited amount of studies that controlled the duration of neoadjuvant chemotherapy and the quaility of the studies hinder the ability to conclude the optimal duration of neoadjuvant chemotherapy in this study. Therefore, we could not assess the effectivity of prolonged neoadjuvant chemotherapy and delayed surgery for the clinical outcomes nor the ideal duration of prolonged neoadjuvant chemotherapy in osteosarcoma patients. To

further address the outcomes of prolonged neoadjuvant chemotherapy and delayed surgery in osteosarcoma patients, a comparative study with a controlled duration of neoadjuvant chemotherapy models should be considered.

CONCLUSION

Studies have shown that prolonged neoadjuvant chemotherapy and delayed surgery results in 5-years survival rate of 43.2% to 96.6% and 5-years event-free survival rate of 35.7% to 86.4%. The ideal duration of neoadjuvant chemotherapy could not be concluded in this study.

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