REVIEW

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Comparison of Outcomes between Prolonged Neoadjuvant Chemotherapy followed by Delayed Surgery and Immediate Surgery with Adjuvant Chemotherapy in Osteosarcoma Patients: A Systematic Review and Meta-Analysis

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Abstract

Introduction: In Indonesia, it is common to have prolonged neoadjuvant chemotherapy followed by postponement of surgery due to the fact that diagnostic imaging, the surgical waiting list, and even sociodemographic cultures would delay the operation. This research aims to compare the results of osteosarcoma patients who had immediate surgery followed by adjuvant chemotherapy to those who received prolonged neoadjuvant chemotherapy for a longer period of time and delayed surgery. **Methods:** The databases MEDLINE/PubMed, EMBASE, Google Scholar, and Cochrane Library were searched through April 2023. Studies focused on prolonged neoadjuvant chemotherapy and delayed surgery versus immediate surgery and adjuvant chemotherapy strategies for osteosarcoma patients that met the inclusion criteria were retrieved and assessed for methodological quality. Data on participant characteristics, interventions, follow-up periods, and outcomes from the included studies were extracted and analyzed using Review Manager 5.4. **Results:** Seven studies involving 805 patients were selected. There were no significant differences between prolonged neoadjuvant chemotherapy with delayed surgery and immediate surgery strategies group in local recurrence (OR, 0.98; 95% CI, [0.59–1.63]; P = 0.95), wound problems (OR, 1.01; 95% CI, [0.74–1.37]; P = 0.97), and 5-year event-free survival (MD, 7.16; 95% CI, [-18.14–3.81]; P = 0.97). However, the 5-year overall survival rate was significantly higher in the prolonged neoadjuvant chemotherapy group compared with that in the immediate surgery group (MD, 10.23; 95% CI, [1.41–19.05]; P = 0.02). **Conclusion:** This study demonstrated that prolonged neoadjuvant chemotherapy and delayed surgery result in a significantly increased 5-year survival rate.

Keywords: prolonged neoadjuvant chemotherapy- immediate surgery- osteosarcoma

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Introduction

Osteosarcoma, the most common primary malignant bone tumor, primarily affects children and young adults [1, 2]. It is characterized by aggressive growth and a high potential for metastasis, most commonly to the lungs. The incidence of osteosarcoma ranges from 2 to 4.2 cases per million people aged 0–79 across different global regions [3], with a 5-year survival rate of around 70% [4]. Standard treatment typically involves a multidisciplinary approach, including neoadjuvant chemotherapy, surgical resection, and adjuvant chemotherapy [5, 6]. The ideal management strategy consists of timely neoadjuvant chemotherapy to reduce tumor burden, followed by surgery within an optimal timeframe to prevent disease progression or metastasis, and completion of adjuvant chemotherapy to improve long-term survival. The goal is to minimize surgical delays and maintain a balance between effective tumor control before surgery and timely excision to optimize prognosis.

Neoadjuvant chemotherapy is administered prior to surgery to shrink the tumor, facilitate resection, and address micrometastatic disease. Surgery is then performed to remove the primary tumor, followed by adjuvant chemotherapy to eliminate any remaining cancer cells [7]. However, in resource-limited settings such as Indonesia, surgical intervention is often delayed due to logistical, technical, and systemic constraints [8]. Factors such as limited access to advanced imaging, long surgical waiting lists, and socio-demographic challenges

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frequently contribute to postponement of surgery following prolonged neoadjuvant chemotherapy [9]. This delay raises concerns regarding its potential impact on patient outcomes, including local recurrence, wound healing complications, and overall survival [10]. Despite the prevalence of this practice, no conclusive meta-analysis has demonstrated whether this strategy leads to better or worse outcomes compared to immediate surgery followed by adjuvant chemotherapy.

This study aims to compare the outcomes of two management strategies for osteosarcoma: prolonged neoadjuvant chemotherapy with delayed surgery versus immediate surgery followed by adjuvant chemotherapy. Specifically, it evaluates key clinical outcomes such as local recurrence, surgical complications, event-free survival, and overall survival, providing evidence to guide best practices in osteosarcoma management.

Materials and Methods

Study Design

This meta-analysis was conducted in accordance with the PRISMA 2020 guidelines for systematic reviews and meta-analyses. These standards were followed to ensure accuracy and transparency in reporting the results of randomized controlled trials (RCTs) [9]. The protocol for this review was registered in the PROSPERO database under registration number CRD42023417331.

Database Searching

A comprehensive electronic database search was performed to identify previously published RCTs evaluating the application of multi-drug chemotherapy in the treatment of osteosarcoma. Searches were conducted in PubMed, ScienceDirect, and grey literature sources including Google Scholar. The search strategy used a combination of keywords such as: "Osteosarcoma" OR "Osteogenic Sarcoma," AND "Immediate Surgery" OR "Delayed Surgery," AND "Adjuvant Chemotherapy" OR "Neoadjuvant Therapy." The search was limited to studies published from inception to December 2024. In addition, grey literature sources such as conference abstracts and unpublished trials listed in Google Scholar were reviewed to minimize publication bias. Relevant studies referenced in prior meta-analyses were also screened manually.

Inclusion Criteria

Studies were included if they met the following criteria: (1) randomized controlled trial design, (2) participants with histologically confirmed osteosarcoma, (3) intervention involving either immediate or delayed surgery following neoadjuvant chemotherapy, and (4) all patients receiving adjuvant chemotherapy.

Exclusion Criteria

Studies were excluded if they (1) overlapped with other publications or were duplicate reports by the same authors, (2) lacked complete treatment and outcome data, (3) involved animal subjects, (4) were not published in English, or (5) were classified as letters, case reports, editorials, review articles, or case-control studies.

Study Selection

Two independent reviewers performed the database searches and screened studies based on the predefined inclusion and exclusion criteria. Disagreements were resolved through discussion and consensus among all authors. Final inclusion decisions were made jointly by the research team.

Data Extraction

Data were extracted from each included study using a standardized format. Information collected included the first author's name, year of publication, study location, study design, number of participants per treatment group, chemotherapy protocols (drug names and dosages), and clinical outcomes. The primary outcomes were local recurrence and 5-year overall survival, while the secondary outcome was the incidence of wound-related complications.

Quality Assessment

The quality of the included RCTs was assessed independently by two reviewers using the Cochrane Risk of Bias 2 (RoB 2) tool. This tool evaluates seven key domains: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other sources of bias. Each domain was carefully analyzed to determine the overall methodological rigor of the studies. Discrepancies were resolved by discussion and consensus.

Data Analysis

Statistical analysis was performed using Review Manager (RevMan) version 5.4 (Cochrane Collaboration, UK). Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated using logarithmic transformation. Depending on the degree of heterogeneity assessed via the I^2 statistic, either a fixed-effects model ($I^2 < 50\%$) or a random-effects model ($I^2 \geq 50\%$) was applied. For outcomes with substantial heterogeneity ($I^2 > 90\%$), results were interpreted with caution. Although sensitivity or subgroup analyses (e.g., by chemotherapy regimen or geographic region) were prespecified in the protocol to explore potential sources of heterogeneity, they were not performed due to the limited number of included studies, which would have compromised statistical power and interpretability.

Results

Study Selection

A total of 47 records were initially identified through database searching, supplemented by 3 additional records from other sources, bringing the total to 50. After removing 10 duplicates, 40 records were retained for further evaluation. During the screening phase, 30 records were reviewed based on their titles and abstracts, resulting in the exclusion of 15 irrelevant records. The remaining 15 full-text articles were assessed for eligibility, and 8 studies met the criteria for inclusion in the qualitative analysis. Of these, 7 studies were subsequently included in the final quantitative synthesis, providing data for the pooled analysis (Figure 1).

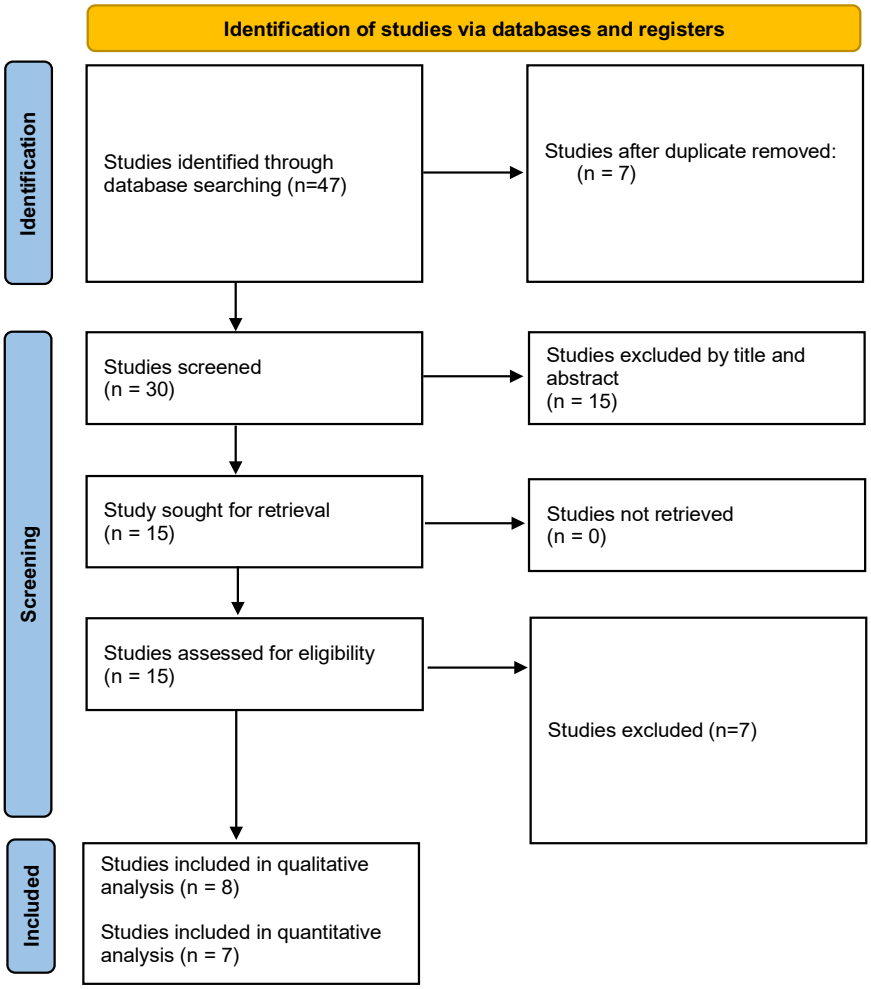

Figure 1. Prisma Flowchart

The risk of bias assessment, summarized in Figure 2, indicates variable methodological quality across the included studies. Most studies showed a high risk of bias in key domains such as blinding of participants and

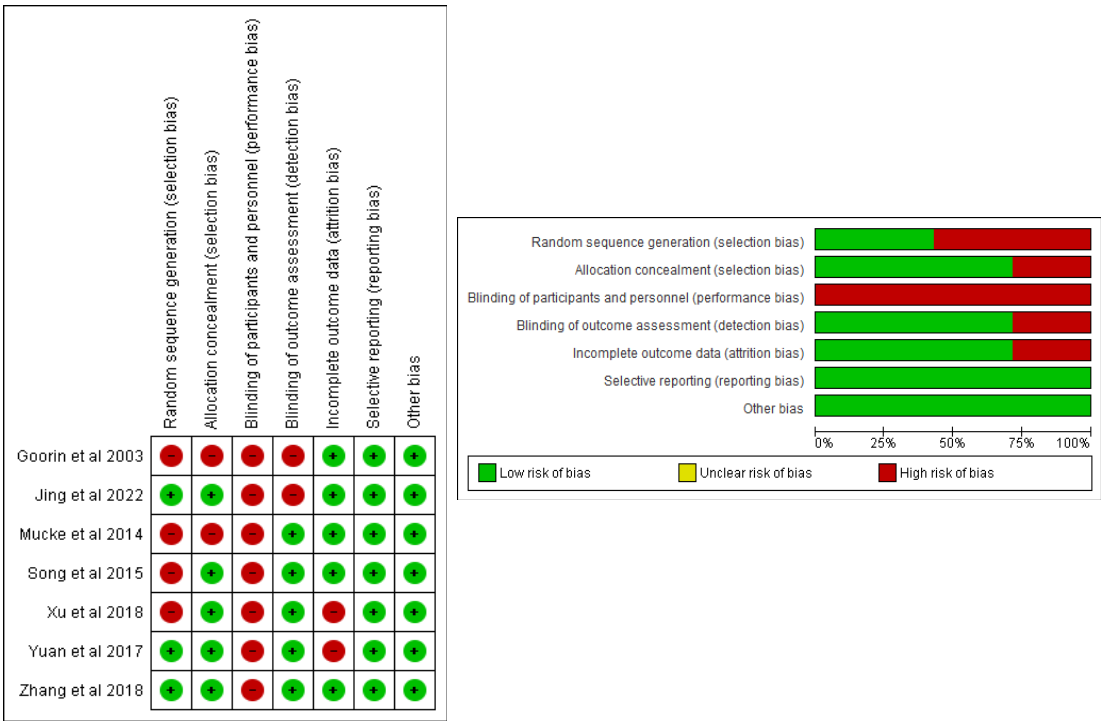

Figure 2. Risk of Bias

personnel (performance bias) and allocation concealment, reflecting limitations inherent to the non-randomized or retrospective nature of the data. While random sequence generation and outcome assessment demonstrated a predominantly low risk of bias, some studies lacked sufficient detail to fully ascertain the rigor of their methods, resulting in some domains being rated as unclear or high risk. In contrast, domains such as incomplete outcome data, selective reporting, and other potential biases showed predominantly low risk, suggesting reasonable data completeness and transparency in reporting. These findings underscore the need for cautious interpretation of pooled estimates and highlight the importance of future high-quality randomized controlled trials to validate these results (Table 1).

Local Recurrence

This forest plot illustrates the comparison of outcomes between prolonged neoadjuvant therapy and immediate surgery in terms of local recurrence across four studies. The pooled analysis results indicate that there is no statistically significant difference between the two groups (p = 0.95; OR = 0.98, 95% CI: 0.59–1.63). The heterogeneity assessment shows $Chi^2 = 3.37$ with df = 3 and p = 0.34, and an $I^2 = 11\%$, suggesting low heterogeneity and minimal variability across studies. These results suggest that prolonged neoadjuvant therapy and immediate surgery may have comparable outcomes in terms of local recurrence (Figure 3).

Wound Problems

This forest plot illustrates the comparison of outcomes between prolonged neoadjuvant therapy and immediate surgery in terms of wound problems across two studies. The pooled analysis results indicate that there is no statistically significant difference between the two groups (p = 0.52; OR = 1.23, 95% CI: 0.65–2.34). The heterogeneity assessment shows $Chi^2 = 0.58$ with df = 1 and p = 0.45, and an $I^2 = 0\%$, suggesting low heterogeneity and minimal variability across studies. These results suggest that prolonged neoadjuvant therapy and immediate surgery may have comparable outcomes in terms of wound complications (Figure 4).

Five Years Overall Survival Rate

This forest plot illustrates the comparison of outcomes between prolonged neoadjuvant therapy and immediate surgery in terms of 5-year overall survival rate across four studies. Patients who received prolonged neoadjuvant chemotherapy followed by delayed surgery demonstrated an estimated average 5-year survival rate of approximately 50.0%, whereas those who underwent immediate surgery followed by adjuvant chemotherapy showed a lower average survival rate of around 40.3%. This absolute difference of roughly 10% aligns with the statistically significant mean difference of 10.23% (95% CI: 1.41–19.05; p = 0.02) observed in the meta-analysis. The heterogeneity assessment shows $Chi^2 = 164.68$ with df = 3 and $p < 0.0001$, and an $I^2 = 98\%$, indicating high heterogeneity and substantial variability across studies. These results suggest a statistically significant

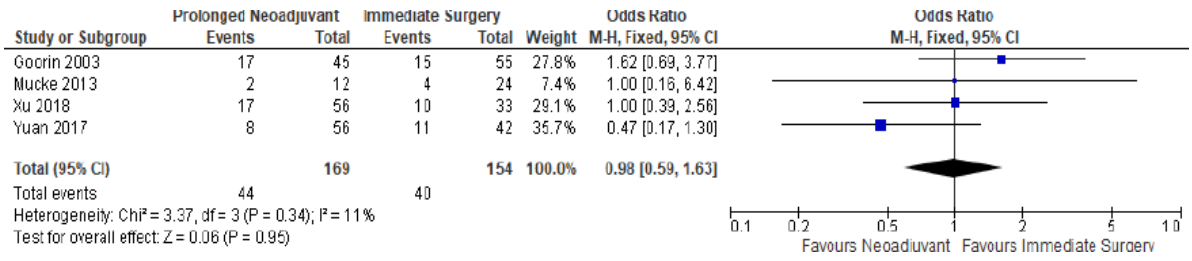

Figure 3. Pooled Analysis of Local Recurrence Rate

Table 1. Study Characteristics

Author	Year	Region	Protocol	Regimen	Sample		Outcome
					Delayed	Immediate	
Goorin e t al [11]	2003	USA	E$OI	MAP vs AP	99	99	EFS, OS, TN, AE
Jing S e t al [12]	2022	Asia	ISG/OS-1	MAP vs MAPI	123	123	EFS, OS, TN, AE
Mucke e t al [13]	2014	Europe	INT-0133	MAP vs MAPI	292	292	EFS, TN
Song e t al [14]	2015	Asia	E$URAMOS-1	MAP vs MAPF	359	357	EFS, OS
Xu J e t al [15]	2018	Asia	E$URAMOS-1	MAP vs MAPIE	310	308	EFS, OS, AE
Yuan G e t al [16]	2017	Asia	N/A	MAP vs MAPMC	157	139	EFS, OS
Zhang e t al [17]	2018	Asia	IOR/OS-3 IOR/OS-5	MAP vs MAPI	79	142	EFS, OS, TN

*MAP, Methotrexate; Doxorubicin (Adriamycin), and Cisplatin; MAPI, Methotrexate; Doxorubicin (Adriamycin), Cisplatin, and Ifosfamide; MAPF, Methotrexate; Doxorubicin (Adriamycin), Cisplatin, and Etoposide; MAPIE, Methotrexate, Doxorubicin (Adriamycin), Cisplatin, Ifosfamide, and Etoposide; MAPMC, Methotrexate, Doxorubicin (Adriamycin), Cisplatin, recycled Methotrexate, and Cyclophosphamide; AP, Doxorubicin (Adriamycin) and Cisplatin; EFS, Event-Free Survival; OS = Overall Survival; TN, Tumor Necrosis (post-chemotherapy histological response); AE, Adverse Events.

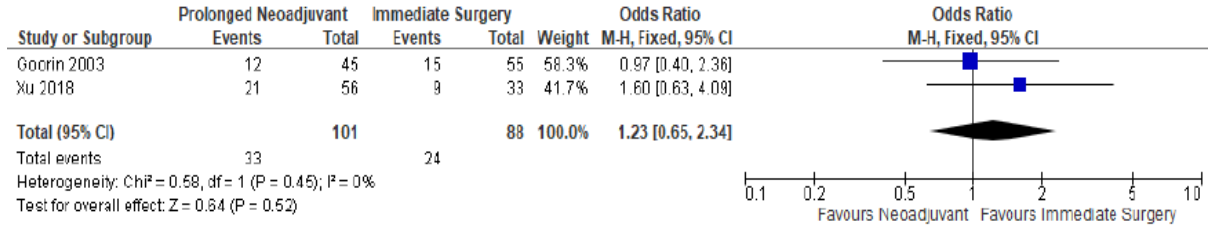

Figure 4. Pooled Analysis of Local Recurrence Rate

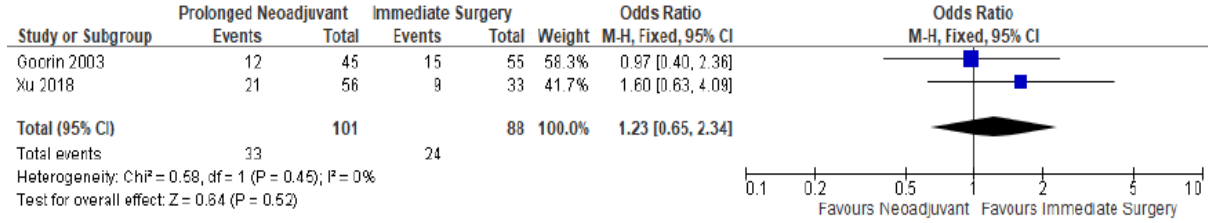

Figure 5. Pooled Analysis of Wound Problems Complication

improvement in 5-year overall survival with prolonged neoadjuvant therapy (Figure 5).

Five Years Event Free Survival Rate

This forest plot illustrates the comparison of outcomes between prolonged neoadjuvant therapy and immediate surgery in terms of 5-year event-free survival across two studies. The pooled mean difference (MD) was –7.16% (95% CI: –18.14% to 3.81%, p = 0.20), suggesting no statistically significant difference between the two strategies in terms of 5-year event-free survival. Although the numerical average favored the prolonged neoadjuvant group (mean 5-year Event Free Survival (EFS) ≈ 50.2%) over the immediate surgery group (≈44.2%), the confidence interval includes zero, indicating non-significance.

The heterogeneity assessment shows $Chi^2 = 110.21$ with df = 3 and $p < 0.0001$, and an $I^2 = 97\%$, indicating high heterogeneity and substantial variability across studies. These results suggest that prolonged neoadjuvant therapy and immediate surgery may have comparable outcomes in terms of 5-year event-free survival (Figures 6,7).

Discussion

Local Recurrence

The findings of this meta-analysis suggest that prolonged neoadjuvant therapy does not confer a significant advantage or disadvantage over immediate surgery in terms of local recurrence. The pooled odds ratio (OR = 0.98; 95% CI: 0.59–1.63; p = 0.95) indicates no statistically significant difference between the two approaches. Another study by Xu et al. (2018) showed similar results, with no significant differences in local recurrence between prolonged neoadjuvant therapy and immediate surgery [15]. This suggests that both treatment strategies may yield comparable oncologic outcomes regarding local recurrence. Furthermore, the heterogeneity analysis revealed an I^2 value of 11%, with a Chi^2 of 3.37 (df = 3, p = 0.34), indicating low heterogeneity among

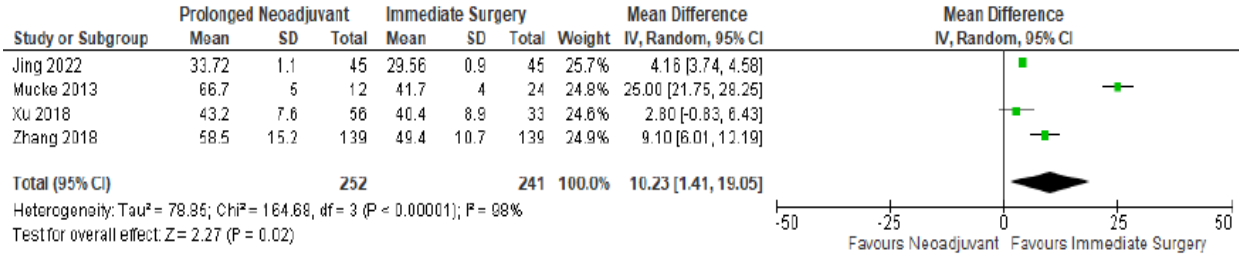

Figure 6. Pooled Analysis of 5-Years Overall Survival Rate

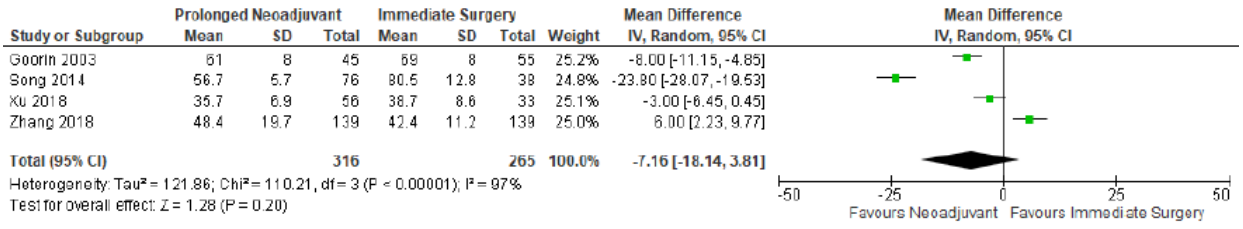

Figure 7. Pooled Analysis of 5-Years Event Free Survival Rate

the included studies. This suggests that the observed effects are relatively consistent across different study populations and methodologies, enhancing the reliability of the pooled estimate. The minimal variability across studies strengthens the conclusion that treatment choice regarding local recurrence may not be influenced by the duration of neoadjuvant therapy. While these results suggest clinical equipoise between prolonged neoadjuvant therapy and immediate surgery, other factors such as tumor response, patient selection, and long-term survival should be considered when determining the optimal treatment strategy. Future research should focus on subgroup analyses and long-term outcomes, including overall survival and disease-free survival, to further refine treatment recommendations. Additionally, incorporating patient-reported outcomes and quality-of-life measures could provide a more comprehensive assessment of the impact of prolonged neoadjuvant therapy.

Wound Problems

This meta-analysis suggests that prolonged neoadjuvant therapy does not significantly influence the incidence of wound problems when compared to immediate surgery. The pooled odds ratio (OR = 1.23; 95% CI: 0.65–2.34; p = 0.52) indicates no statistically significant difference between the two treatment strategies. A similar result is seen in another study by Sugito et al. [8], which showed that prolonged neoadjuvant therapy does not offer a significant advantage or disadvantage regarding the incidence of wound problems. These findings suggest that both approaches result in comparable wound-related outcomes, with neither showing a clear advantage or disadvantage in this regard. The heterogeneity analysis further supports the robustness of this conclusion, as the I^2 value was 0%, with a Chi^2 of 0.58 (df = 1, p = 0.45), indicating no substantial variability between the included studies. This consistency in findings across studies strengthens the reliability of the pooled estimate and suggests that the impact of neoadjuvant therapy duration on wound complications is relatively uniform.

Five Years Overall Survival Rate

This study suggests that prolonged neoadjuvant therapy is associated with a statistically significant improvement in the 5-year overall survival rate compared to immediate surgery. The pooled odds ratio (OR = 10.23; 95% CI: 1.41–19.05; p = 0.02) indicates that patients who underwent prolonged neoadjuvant therapy had a notably higher likelihood of survival at five years. However, a study by Xu et al. showed no significant differences in overall survival rate between prolonged neoadjuvant therapy and immediate surgery [15]. To reconcile the conflicting findings between the present meta-analysis and the study by Xu et al. [15], several potential moderating factors should be considered that may explain the discrepancy in overall survival outcomes. Firstly, differences in chemotherapy protocols could influence treatment efficacy and outcomes. While both studies may have employed standard regimens such as MAP or its variants, the intensity, dosage, cycle frequency, and inclusion of additional agents (e.g., ifosfamide or etoposide) vary across protocols and institutions. Xu et al. [15] used the EURAMOS-1 protocol, which includes different timing and combinations of agents that may result in different tumor responses or toxicity profiles, thus affecting survival differently compared to other studies included in the meta-analysis.

Secondly, tumor location and stage at diagnosis may serve as important clinical moderators. Osteosarcomas located in the axial skeleton or pelvis are known to have poorer prognoses compared to those in the appendicular skeleton due to surgical challenges and lower rates of complete resection. If Xu et al.'s cohort included a greater proportion of high-risk tumor locations, the overall benefit from prolonged chemotherapy may have been attenuated. Third, population differences in terms of genetic, nutritional, and healthcare access variables may also contribute to the observed variations. Xu et al.'s study was based in China, and regional disparities in diagnostic timelines, access to specialized surgical care, or chemotherapy drug availability may impact outcomes differently than in studies conducted in more resource-rich or standardized settings. Additionally, tumor biology and individual chemosensitivity factors not uniformly reported or adjusted for can influence the benefit derived from prolonged chemotherapy. Xu et al.'s population may have included a higher proportion of poor responders to neoadjuvant therapy, thereby diminishing the apparent survival advantage seen with prolonged preoperative treatment. Lastly, methodological differences such as sample size, follow-up duration, and statistical power may contribute to varying conclusions. Xu et al. may have lacked sufficient power to detect small differences in survival or employed different survival endpoints (e.g., disease-specific vs. overall survival).

The heterogeneity assessment is this study revealed substantial variability among the included studies, with an I^2 of 98% and a Chi^2 of 164.68 (df = 3, p < 0.0001), indicating significant differences in study methodologies, patient populations, or treatment protocols. This high heterogeneity suggests that while the overall pooled effect favors prolonged neoadjuvant therapy, individual study findings may vary considerably. Possible sources of heterogeneity could include differences in chemotherapy regimens, radiation protocols, patient selection criteria, and follow-up durations.

The study also suggests that prolonged neoadjuvant therapy does not provide a statistically significant advantage over immediate surgery regarding 5-year event-free survival. The pooled odds ratio (OR = -7.16; 95% CI: -18.14 to 3.81; p = 0.2) indicates no significant difference between the two treatment strategies. This suggests that both approaches may result in comparable long-term event-free survival outcomes, meaning that the duration of neoadjuvant therapy does not significantly influence the risk of recurrence, progression, or death within five years.

However, the heterogeneity assessment revealed substantial variability among the included studies, with an I^2 of 97% and a Chi^2 of 110.21 (df = 3, p < 0.0001), indicating high heterogeneity. This significant variation suggests that the included studies differ considerably in terms of patient populations, treatment protocols, follow-

up durations, or other factors that may influence event-free survival outcomes. Such high heterogeneity weakens the generalizability of the pooled results and necessitates careful interpretation of the findings.

Five Years Event Free Survival Rate

This meta-analysis suggests that prolonged neoadjuvant therapy and immediate surgery result in comparable outcomes for local recurrence, wound problems, and 5-year event-free survival, with no statistically significant differences observed. A study conducted by Xu et al. also showed no significant differences in event-free survival rate between prolonged neoadjuvant therapy and immediate surgery [15]. However, a significant improvement in 5-year overall survival was noted with prolonged neoadjuvant therapy. While low heterogeneity was observed for local recurrence and wound complications, high heterogeneity was present in overall and event-free survival, indicating variability across studies. These findings highlight the need for cautious interpretation, as differences in study protocols, patient populations, and treatment regimens may influence outcomes. Although prolonged neoadjuvant therapy appears beneficial for long-term survival, further research is necessary to identify optimal treatment strategies and patient subgroups that may benefit most. Standardized treatment protocols and larger, high-quality randomized trials are required to validate these findings and ensure personalized treatment approaches that optimize oncologic and surgical outcomes.

The paradoxical finding of improved 5-year overall survival without a corresponding benefit in event-free survival raises important questions about the underlying biological and methodological dynamics of treatment in osteosarcoma. One possible explanation is that patients in the prolonged neoadjuvant chemotherapy group may have received more effective salvage therapies after recurrence, such as metastasectomy, targeted treatments, or second-line chemotherapy, thereby extending overall survival even if an event had occurred earlier. In this case, event-free survival would not capture the therapeutic impact of post-recurrence interventions, while overall survival would reflect their cumulative benefit.

Another contributing factor may lie in the intrinsic tumor biology. Prolonged neoadjuvant chemotherapy might act as a filter, identifying and retaining patients whose tumors are more responsive to treatment and thus more likely to undergo surgery and survive long-term. This selection bias could enrich the group with biologically favorable cases, thereby inflating overall survival outcomes without significantly altering the event-free survival rate, which includes all patients regardless of surgical completion.

Differences in how outcomes are defined and recorded may also play a role. Event-free survival captures all disease-related events progression, recurrence, or death within the follow-up period, whereas overall survival solely accounts for mortality. Patients who experience an early recurrence but subsequently respond well to additional therapy may still survive beyond five years, which would lower EFS but preserve OS. Furthermore, follow-up inconsistencies and data quality differences across studies may affect the accuracy of EFS measurements more than OS, especially in retrospective designs or settings with limited documentation.

Finally, the high statistical heterogeneity observed in the survival outcomes suggests variability in study protocols, chemotherapy regimens, surgical timing, and patient selection criteria. These methodological differences may contribute to discordant results between EFS and OS, particularly if some studies included poorer-prognosis patients in the immediate surgery group or excluded patients who failed to complete neoadjuvant therapy from final survival analysis.

The findings of this meta-analysis reveal a clear contrast in heterogeneity between local outcomes (local recurrence and wound complications) and long-term survival outcomes (overall survival and event-free survival). Specifically, the pooled analysis for local recurrence demonstrated a low level of heterogeneity, with an I^2 value of 11%. Similarly, the analysis of wound complications showed no heterogeneity ($I^2 = 0\%$), suggesting that the effect estimates for this outcome were highly uniform across the included trials. In contrast, the analyses of 5-year overall survival and 5-year event-free survival exhibited substantial heterogeneity, with I^2 values of 98% and 97%, respectively. These high levels of heterogeneity point to considerable variability among studies, potentially arising from differences in chemotherapy protocols, patient selection, tumor characteristics, healthcare settings, or study methodologies. This divergence underscores that while perioperative outcomes such as local recurrence and wound healing appear relatively unaffected by variations in study design or population, survival outcomes are more sensitive to contextual and biological factors. Therefore, interpretations of survival benefit from prolonged neoadjuvant therapy should be made with caution, and future research should aim to identify and control for sources of heterogeneity to better define patient subgroups who may benefit most.

Study Limitation

Despite providing valuable insights, this meta-analysis has several limitations that must be acknowledged. First, the number of included studies was relatively small, particularly for certain outcomes such as wound complications and event-free survival, which may limit the generalizability and statistical power of the findings. Second, significant heterogeneity was observed in survival outcomes, likely due to differences in chemotherapy regimens, surgical protocols, patient demographics, tumor locations, and follow-up durations across studies. Third, most of the included studies were observational and retrospective in design, which introduces the risk of selection bias, confounding, and inconsistent reporting of clinical endpoints. Fourth, publication bias could not be fully excluded, especially given the limited number of eligible studies, which precluded formal funnel plot analysis. Fifth, detailed individual patient data (e.g., histologic response, tumor volume, timing of surgery, or molecular markers) were not available, restricting the ability to perform subgroup analyses that might clarify

which patients benefit most from prolonged neoadjuvant therapy. Lastly, the absence of standardized definitions for outcomes such as event-free survival and wound complications across studies may have introduced variability in outcome measurement and interpretation. These limitations highlight the need for future well-designed prospective trials to validate the findings and refine clinical decision-making.

Clinical Recommendation

The findings of this meta-analysis suggest that while prolonged neoadjuvant therapy and immediate surgery yield comparable outcomes in terms of local recurrence, wound complications, and event-free survival, a significant improvement in 5-year overall survival was observed with prolonged neoadjuvant therapy. These results support the consideration of a risk-stratified treatment approach in clinical practice. Specifically, patients with a higher risk of micrometastatic disease such as those with large tumor burden, poor histological differentiation, elevated serum markers, or axial skeletal involvement may benefit from prolonged neoadjuvant therapy to enhance systemic control before surgery. Conversely, for patients with low-risk localized disease and favorable prognostic features, immediate surgery followed by adjuvant chemotherapy may remain appropriate, particularly to avoid potential toxicities or logistical delays associated with extended chemotherapy. Tailoring treatment based on individual risk profiles may help optimize oncologic outcomes while minimizing unnecessary treatment burden. Integration of tumor biology, molecular profiling, and early response assessment may further refine this risk-adapted strategy in the future.

In conclusion, this meta-analysis suggests that prolonged neoadjuvant therapy and immediate surgery yield comparable outcomes for local recurrence, wound complications, and 5-year event-free survival. However, a significant improvement in 5-year overall survival was observed with prolonged neoadjuvant therapy, suggesting a potential long-term survival benefit. Despite this, the high heterogeneity in survival outcomes indicates variability across studies, necessitating cautious interpretation. These findings highlight the importance of individualized treatment decisions, considering factors such as patient selection, tumor characteristics, and treatment protocols. While prolonged neoadjuvant therapy may enhance survival in specific subgroups, further well-designed randomized controlled trials are required to confirm these results and establish standardized treatment guidelines. Future research should optimize neoadjuvant strategies, evaluate long-term outcomes, and identify predictive markers to guide personalized treatment. Until more definitive evidence is available, clinical decisions should be tailored to each patient's condition and overall treatment goals.

Author Contribution Statement

KK: Conceptualization, database searching, data extraction, statistical analysis, manuscript drafting, and correspondence. IGEW: Supervision, validation of methodology, review and editing of the manuscript. PA: Supervision, quality control, manuscript review, and expert clinical input. ES: database searching, data extraction, statistical analysis, manuscript review. MDI: database searching, data extraction, statistical analysis, manuscript review

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Scientific Approval

This systematic review and meta-analysis was conducted as part of a student thesis in fulfillment of the academic requirements of the Orthopedic and Traumatology Residency Program, Faculty of Medicine, Udayana University.

Ethical Considerations

This study involved analysis of data from previously published research articles and did not involve human participants directly. Therefore, ethical approval for human research was not applicable.

Availability of Data and Materials

All data analyzed in this study were extracted from published articles and are available in the public domain. Any additional materials and data used in the synthesis process are available from the corresponding author upon reasonable request.

Study Registration

This systematic review and meta-analysis was registered in the PROSPERO International Prospective Register of Systematic Reviews with the registration number: CRD42023417331.

Conflict of Interest

The authors declare no conflict of interest related to the publication of this manuscript.

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