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Research Article

Comparing the Outcomes of Neoadjuvant Versus Adjuvant Chemotherapy for Osteosarcoma Patients

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Abstract

Background: Neoadjuvant chemotherapy followed by surgery and subsequent adjuvant chemotherapy has been a mainstay of many osteosarcoma treatment protocols. However, the overall survival (OS) benefit over surgery and adjuvant chemotherapy is unclear. *Aims*: This study therefore directly compares the outcomes among these treatment groups using a large population in the National Cancer Database (NCDB). *Methods*: In a retrospective cross-sectional study, osteosarcoma patients in the NCDB (2004-2019) were stratified based on chemotherapy and surgery timing (neoadjuvant and adjuvant vs adjuvant-only chemotherapy). We used Kaplan-Meier curves to compare OS in the unmatched population and in a propensity score matched cohort that controlled for demographics, treatment, and tumor characteristic differences. Univariate and multivariate analyses were also used to predict the likelihood of positive margins among the population. Chi-square tests were used to compare 30- and 90-day mortality among treatment groups. P-values <0.05 were considered significant. *Results*: The study population included 4,659 patients: 3,733 neoadjuvant and 926 adjuvant-only chemotherapy regimens. Patients who underwent neoadjuvant therapy had significantly longer survival in the unmatched analysis ($p<0.001$), but this difference narrowed when controlling for covariates in the matched cohort ($p=0.67$). Mortality at 30 and 90 days was insignificant between treatment groups in both the full and matched cohorts ($p=0.3$ and $p=0.9$ respectively). Neoadjuvant chemotherapy regimens predominated with over 75% utilization, but this rate remained constant during the 15-year study period. Three- and five-year survival rates were relatively unchanged during this period at 75% and 62.5% respectively. Factors significantly associated with positive margins in the multivariate analysis included adjuvant-only chemotherapy (OR=1.6, $p<0.001$), older age (OR=1.01, $p<0.001$), female sex (OR=1.27, $p=0.04$), adjuvant radiation (OR=4.96, $p<0.001$), and stage IVB tumors (OR=2.11, $p<0.001$). *Conclusions*: These results indicate that neoadjuvant chemotherapy did not increase overall or short-term survival compared to adjuvant chemotherapy alone in our study. However, neoadjuvant therapy was associated with fewer positive margins at the time of surgery. These insights offer information to help clinicians evaluate osteosarcoma treatment regimens to maximize outcomes and limit treatment morbidity.

Keywords

Osteosarcoma, Chemotherapy, Survival Analysis, Margins of Excision, Morbidity, National Cancer Database (NCDB)

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1. Introduction

Osteosarcoma is a mesenchymal, osteoid-producing malignancy that is the most common cause of primary bone sarcoma in young patients [1, 2]. Males, African Americans, and Hispanics are disproportionately affected populations with an increased incidence of disease [1-4]. Osteosarcoma most commonly occurs in long bones but affects axial locations in approximately 10% of patients [5-8]. Around 12% of osteosarcoma patients present with metastatic disease, with the lungs being the primary site in over 85% of these cases [9]. Before the advent of multi-agent chemotherapy, over 90% of osteosarcoma patients died from sequelae of pulmonary metastasis [10].

Chemotherapy, along with adequate surgical resection, is now a mainstay of osteosarcoma treatment, which has resulted in improved survival [1, 7, 8]. Presently, patients treated with this combined regimen experience a median relapse time of 2.5 years [11, 12]. Among surgical options, limb salvage surgery has surpassed amputation in recent decades due to advancements in imaging, engineering, and chemotherapy regimens [13-15]. The subsequent addition of multi-agent chemotherapy regimens to surgery is highly effective against osteosarcoma, increasing disease-free survival (DFS) by over 40% compared to surgery alone, and therefore is the workhorse of treatment [16-19]. The MAP (methotrexate, doxorubicin, and cisplatin) chemotherapy regimen that began in the 1980s remains the most common multiagent chemotherapy treatment for osteosarcoma [19, 20]. A recent meta-analysis showed a small increase in overall survival among other chemotherapy regimens compared to MAP but failed to find a difference in event-free survival and noted a significant increase in adverse effects among patients treated with non-MAP regimens [20]. Immunotherapy, including immune checkpoint inhibitors and chimeric antigen receptor-T cell therapy, is also playing an increasing role in osteosarcoma management but further research is still needed on the safety and efficacy of this promising new avenue of treatment [21].

While the efficacy of chemotherapy is well-documented, a clear survival benefit of neoadjuvant chemotherapy has not been definitively established. There has been a long-thought advantage to neoadjuvant chemotherapy so that the treatment response of the tumor could be established pathologically and, perhaps, adjusted in poor responders in hopes of improving their prognosis. Unfortunately, clinical trials have yet to show improved survival based on this approach [22-25]. Additionally, certain histiotypes of osteosarcoma are considered less responsive to chemotherapy and could progress while on therapy, making surgery paradoxically more challenging. Previous studies comparing outcomes between neoadjuvant chemotherapy and adjuvant chemotherapy alone were performed over 25 years ago and consist of small samples of adjuvant-only treatment groups [9, 22, 26].

This study aimed to evaluate the survival and surgical outcomes of neoadjuvant and adjuvant-only chemotherapy regimens among the large, nationally representative population of the National Cancer Database. Overall survival was our primary outcome and our secondary outcomes included 30- and 90-day mortality, changes in treatment utilization rates, and risk factors for positive surgical margins.

2. Methods

2.1. Patient Population

Our study population was derived from the 2022 Participant User File of the National Cancer Database (NCDB). The NCDB is a joint project of the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society. The NCDB is a de-identified and publicly available database, gathering data from over 1500 CoC-accredited hospitals in the United States. This database accounts for over 70% of all cancer diagnoses nationwide and are reported according to standards established by the North American Association of Central Cancer Registries. This data includes patient demographic information, and data pertaining to cancer staging, tumor histology, treatments, short-term outcomes, and long-term outcomes. All data was de-identified and exempt from institutional review board approval.

2.2. Patient Cohort Selection

Patients with osteosarcoma in the National Cancer Database (2004-2019) were included in the initial cohort, corresponding to the following histology codes: 9180-7, 9192-5. As shown in Figure 1, only surgical patients with an initial and primary osteosarcoma diagnosis were included, and all patients with unknown long term survival information, unknown chemotherapy and surgical treatment details, or unknown/discordant tumor staging were excluded. 4,659 patients were included in the final analysis and were stratified based on chemotherapy and surgery timing (neoadjuvant vs adjuvant chemotherapy). The neoadjuvant treatment group included patients who received neoadjuvant therapy alone and those receiving both neoadjuvant and adjuvant chemotherapy.

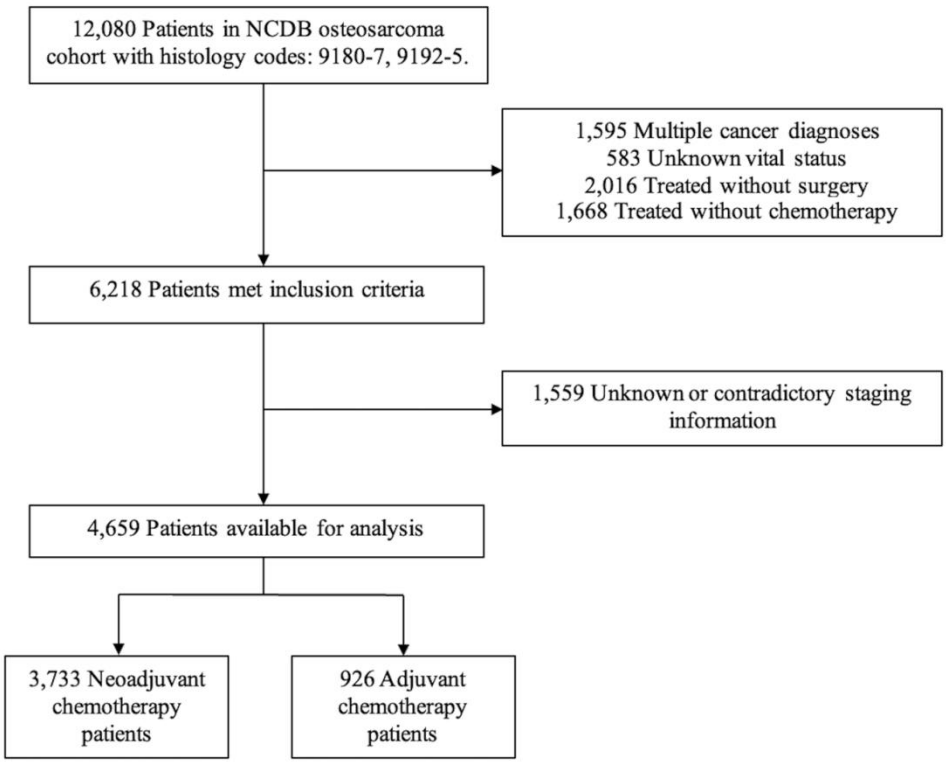

Figure 1. *STROBE based diagram showing patient selection for this study.*

2.3. Statistical Analyses

All statistical analyses were completed using R (version 2022.07.0; Posit). Initially, the patients were stratified into those receiving neoadjuvant or adjuvant chemotherapy, and compared based on demographic, tumor, and treatment factors. Data were presented as median [Q1, Q3] for numeric variables and count (%) for categorical variables. 1:1 nearest neighbor propensity score matching (MatchIt package in R) was used to control for relevant covariates, and the matched groups were compared using standardized mean difference (with >0.1 being considered a significant imbalance). Propensity score matching has been shown to minimize confounders and effectively estimate treatment effects in time-to-event analyses with little bias and was therefore selected as our analytical matching tool. [27] The diagnostic plot for the propensity score match can be found in the Supplementary Materials. Kaplan-Meier survival analysis with a log rank test were used to compare overall survival in the unmatched population and in the propensity score matched cohort. Univariate and multivariate analyses were also used to determine the patient factors associated with the likelihood of positive margins through the calculation of odd ratios (OR). Chi-square tests were used to compare 30- and 90-day mortality among neoadjuvant and adjuvant treatment groups in both an unmatched population and propensity score matched cohort. All provided p-values are derived from two-tailed tests. We also included a sensitivity analysis comparing patients who only received neoadjuvant chemotherapy or only adjuvant chemotherapy. Longitudinal trends were evaluated using a logistic regression model. The data used in the study are derived from a de-identified NCDB file. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytic or statistical methodology employed, or the conclusions drawn from these data by the investigator.

3. Results

3.1. Study Population Characteristics and Propensity Score Match

The neoadjuvant (NA) and adjuvant-only (AO) cohorts consisted of 3,733 patients and 926 patients, respectively. Demographic, facility, treatment, and tumor characteristics of the two cohorts are summarized in Table 1. The NA cohort was more likely to be younger (17 [13, 28] vs. 34 [20, 52]; P<0.001) and male (2,208/3,733, 59.1% vs. 510/926, 55.1%; P=0.027) and underwent radiation less commonly (3,501/3,733, 93.8% vs. 782/926, 84.4%; P<0.001). More of the tumors in the NA group were appendicular (3,290/3,733, 88.1% vs. 611/926, 66.0%; P<0.001) and limb salvage surgery was more common in the NA cohort (2,612/3,733, 70.0% vs. 525/926, 56.7%; P<0.001). Negative surgical margins were achieved in the NA group more than the AO group (3,250/3,733, 87.1% vs. 689/926, 74.4%; P<0.001). Further differences were noted with

ethnicity, insurance status, facility type, and 7th edition TNM clinical staging between the cohorts as shown in Table 1.

Table 1. *The following table shows the demographic, facility, treatment, and tumor characteristics for the patient cohort stratified by chemotherapy and surgery order.*

Characteristics	Neoadjuvant N = 3,733	Adjuvant N = 926	P-value
Age	17 [13, 28]	34 [20, 52]	<.001
Sex			.027
Male	2,208 (59.1)	510 (55.1)	
Female	1,525 (40.9)	416 (44.9)	
Race			.3
White	2,764 (74.0)	698 (75.4)	
Black	588 (15.8)	153 (16.5)	
Asian American and Pacific Islander (AAPI)	198 (5.3)	37 (4.0)	
Unknown	183 (4.9)	38 (4.1)	
Ethnicity			<.001
Non-Hispanic	3,039 (81.4)	772 (83.4)	
Hispanic	587 (15.7)	109 (11.8)	
Unknown	107 (2.9)	45 (4.9)	
Charlson-Deyo Comorbidity Index			.082
0	3,451 (92.4)	838 (90.5)	
1	243 (6.5)	72 (7.8)	
2+	39 (1.0)	16 (4.9)	
Insurance Status			<.001
Private	2,328 (62.4)	548 (59.2)	
Medicare	130 (3.5)	108 (11.7)	
Medicaid	937 (25.1)	182 (19.7)	
Other Government	86 (2.3)	14 (1.5)	
Uninsured	141 (3.8)	46 (5.0)	
Unknown	111 (3.0)	28 (3.0)	
Facility Type			.018
Non-Academic	836 (22.4)	230 (24.8)	
Academic	2,682 (71.8)	662 (71.5)	
Unknown	215 (5.8)	34 (3.7)	
Radiation			<.001
No Radiation	3,501 (93.8)	782 (84.4)	
Neoadjuvant	29 (0.8)	10 (1.1)	
Adjuvant	96 (2.6)	96 (10.4)	
Unknown	107 (2.9)	38 (4.1)	

Characteristics	Neoadjuvant N = 3,733	Adjuvant N = 926	P-value
Surgery			<.001
Local Excision or Destruction	151 (4.0)	109 (11.8)	
Partial Resection	209 (5.6)	102 (11.0)	
Radical Excision and Limb Salvage	2,612 (70.0)	525 (56.7)	
Amputation	761 (20.4)	190 (20.5)	
Margins			<.001
Positive	239 (6.4)	120 (13.0)	
Negative	3,250 (87.1)	689 (74.4)	
Unknown	244 (6.5)	117 (12.6)	
Clinical TNM Staging			
7th Edition (’04-’17)			<.001
IA	310 (9.8)	111 (13.5)	
IB	293 (9.3)	56 (6.8)	
IIA	728 (23.0)	244 (29.7)	
IIB	1,229 (38.9)	261 (31.8)	
III	83 (2.6)	26 (3.2)	
IVA	346 (11.0)	346 (11.0)	
IVB	170 (5.4)	170 (5.4)	
8th Edition (’18-’19)			.07
IA	67 (11.7)	21 (20.0)	
IB	61 (10.6)	15 (14.3)	
IIA	142 (24.7)	26 (24.8)	
IIB	173 (30.1)	21 (20.0)	
III	21 (3.7)	3 (2.9)	
IVA	83 (14.5)	11 (10.5)	
IVB	27 (4.7)	8 (7.6)	
Tumor Location			<.001
Head	174 (4.7)	162 (17.5)	
Axial	240 (6.4)	136 (14.7)	
Appendicular	3,290 (88.1)	611 (66.0)	
Unknown	29 (0.8)	17 (1.8)	

Numeric variables are presented as a median [25th percentile, 75th percentile]; categorical variables are presented as count (%).

Table 2 shows the relevant demographic, facility, treatment, and tumor characteristics of the cohort after the propensity score match. Of the 926 possible matches, 872 (94.2%) patients were included in the final match.

Table 2. *The below table shows the results of the propensity score match stratified by chemotherapy timing.*

Characteristics	Neoadjuvant N = 872	Adjuvant N = 872	SMD
Age	31 [17, 51]	31 [19, 48]	0.019
Year of Diagnosis	2011 [2007, 2014]	2011 [2007, 2015]	0.038
Sex			0.007
Male	488 (55.5)	485 (55.2)	
Female	388 (44.5)	391 (44.8)	
Race			0.059
White	637 (73.1)	655 (75.1)	
Black	162 (18.6)	146 (16.7)	
AAPI	32 (3.7)	35 (4.0)	
Unknown	41 (4.7)	36 (4.1)	
Ethnicity			0.025
Non-Hispanic	728 (83.5)	722 (82.8)	
Hispanic	101 (11.6)	108 (12.4)	
Unknown	43 (4.9)	42 (4.8)	
Charlson-Deyo Comorbidity Index			0.018
0	789 (90.5)	787 (90.3)	
1	69 (7.69)	69 (7.9)	
2+	14 (1.6)	16 (1.8)	
Insurance Status			0.084
Private	511 (58.6)	518 (59.4)	
Medicare	77 (8.8)	91 (10.4)	
Medicaid	181 (20.8)	177 (20.3)	
Other Government	19 (2.2)	14 (1.6)	
Uninsured	50 (5.7)	45 (5.2)	
Unknown	34 (3.9)	27 (3.1)	
Facility Type			0.005
Non-Academic	211 (24.2)	209 (24.0)	
Academic	628 (72.0)	630 (72.2)	
Unknown	33 (3.8)	33 (3.8)	
Radiation			0.052
No Radiation	762 (87.4)	755 (86.6)	
Neoadjuvant	13 (1.5)	10 (1.1)	
Adjuvant	63 (7.2)	73 (8.4)	
Unknown	34 (3.9)	34 (3.9)	
Surgery			0.099
Local Excision or Destruction	77 (8.8)	88 (10.1)	

Characteristics	Neoadjuvant N = 872	Adjuvant N = 872	SMD
Partial Resection	80 (9.2)	91 (10.4)	
Radical Excision and Limb Salvage	496 (56.9)	507 (58.1)	
Amputation	219 (25.1)	186 (21.3)	
Margins			0.055
Positive	108 (12.4)	105 (12.0)	
Negative	677 (77.6)	665 (76.3)	
Unknown	87 (10.0)	102 (11.7)	
Clinical TNM Staging			0.082
7th Edition ('04-'17)			
IA	100 (11.5)	96 (11.0)	
IB	65 (7.5)	54 (6.2)	
IIA	218 (25.0)	229 (26.3)	
IIB	258 (29.6)	250 (28.7)	
III	21 (2.4)	22 (2.5)	
IVA	62 (7.1)	67 (7.7)	
IVB	48 (5.5)	52 (6.0)	
8th Edition ('18-'19)			
IA	17 (1.9)	19 (2.2)	
IB	16 (1.8)	15 (1.7)	
IIA	25 (2.9)	26 (3.0)	
IIB	17 (1.9)	21 (2.4)	
III	4 (0.5)	3 (0.3)	
IVA	14 (1.6)	11 (1.3)	
IVB	7 (0.8)	7 (0.8)	
Tumor Location			0.028
Head	129 (14.8)	137 (15.7)	
Axial	117 (13.4)	118 (13.5)	
Appendicular	612 (70.2)	604 (69.3)	
Unknown	14 (1.6)	13 (1.5)	

Numeric variables are presented as a median [25th percentile, 75th percentile]; categorical variables are presented as count (%). A standardized mean difference (SMD) was considered a significant imbalanced when >0.1.

3.2. Overall Survival and Short-Term Mortality

Kaplan-Meier curves comparing overall survival (OS) are shown in Figure 2. The unmatched population (Figure 2A) showed a significantly increased survival among the NA cohort (P<0.0001) over a five-year period. However, in a propensity score matched analysis controlling for demographic and clinical characteristics (Figure 2B), there was no significant difference in OS (P=0.67). 30- and 90-day mortality was evaluated among the unmatched and propensity score matched cohorts. There was no difference in short-term mortality between the treatment groups in either the full cohort (P=0.3) or the matched cohort (P=0.9). When compared

excluding those who also received adjuvant chemotherapy with neoadjuvant chemotherapy, we found no statistically significant difference in survival (P=0.5). We also compared these treatment regimens for only those patients with head and neck osteosarcoma and found no difference in overall survival (P=0.6).

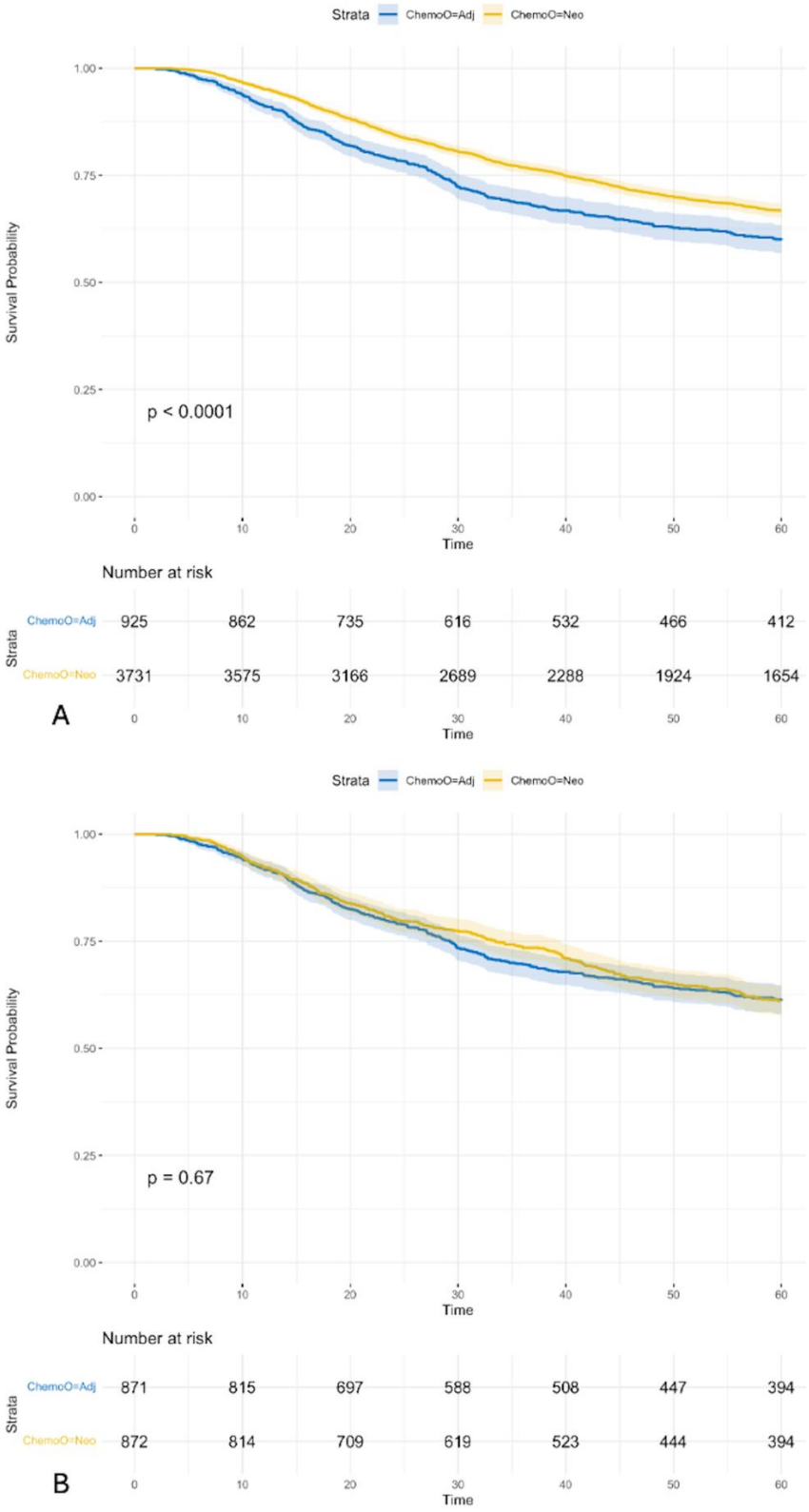

Figure 2. *The unmatched (A) and propensity score matched (B) survival comparisons based on chemotherapy timing. Time is measured in months.*

3.3. Survival and Treatment Trends

Annual treatment trends over the study period are shown in Figure 3. There were no significant changes in the use of NA chemotherapy (P=0.1) and AO therapy (P=0.1) with NA utilization ranging between 77.1% (year 2008, 195/253) and 85.5% (year 2011, 261/305) and AO therapy between 14.4% (44/305) and 22.9% (58/253) over the 15-year period. Three-year survival centered consistently around 75% (P=0.6) while five-year survival also remained steady around 62.5% (P=0.3) as shown in Figure 4.

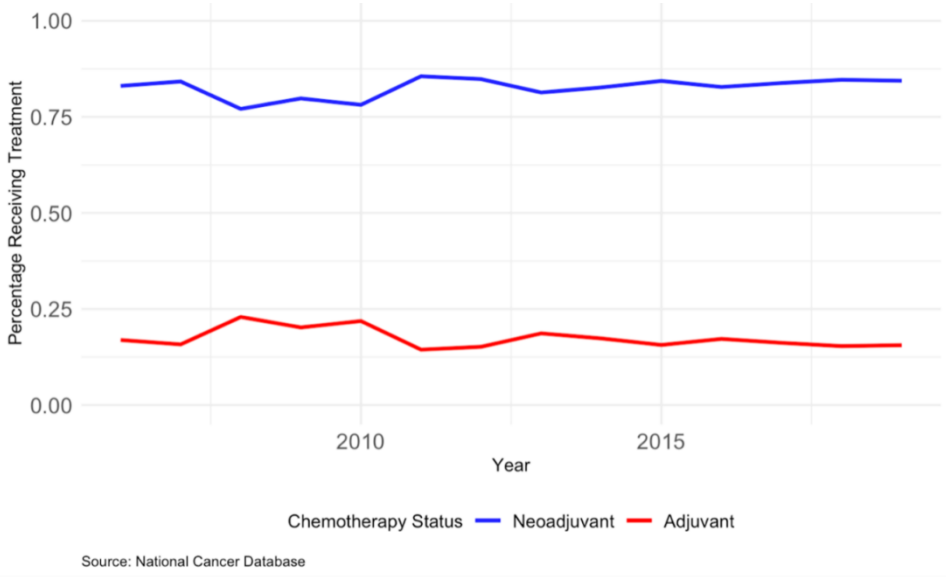

Figure 3. *The above figure shows the trends in treatment over time (annual basis) for neoadjuvant vs adjuvant chemotherapy.*

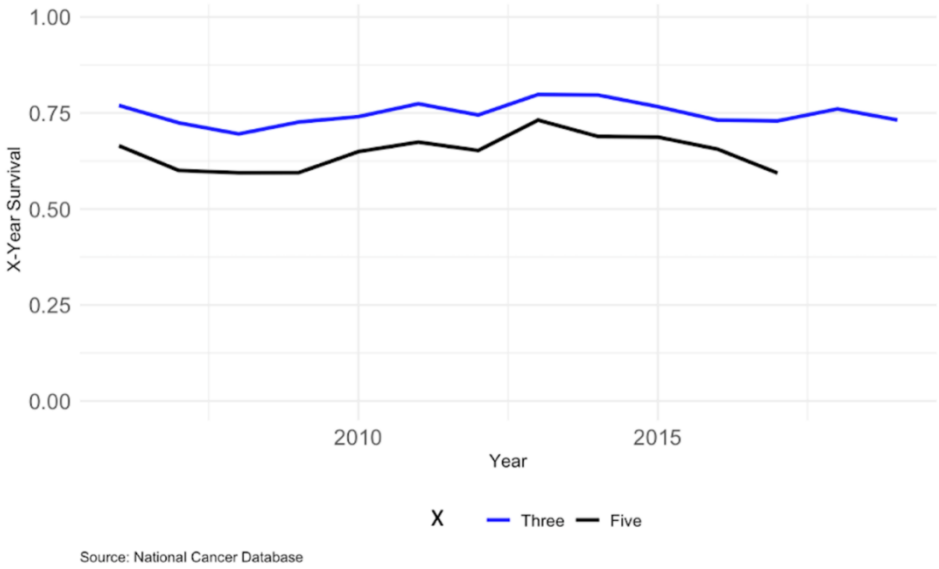

Figure 4. *The above figure shows the trends in 3- and 5-year survival over the study period.*

3.4. Surgical Margins

Factors significantly associated with positive margins in univariate and multivariate logistic regression analysis are shown in Table 3. Identified risk factors in multivariate analysis associated with positive margins included: adjuvant-only chemotherapy (OR=1.60; P<0.001), adjuvant-only radiation (OR=4.96; P<0.001), older age (OR=1.01; P<0.001), female sex (OR=1.27; P=0.04), and stage IVB cancer (OR=2.11; P<0.001). Factors inversely correlated with positive margins were Asian and Pacific Islander race (OR 0.37;

P=0.008) and academic facility type (OR=0.75; P=0.02).

Table 3. *The below table shows a univariate and multivariate analysis predicting the likelihood of positive margins.*

Characteristics	Univariate Analysis		Multivariate Analysis	
	OR	***P* value**	**OR**	***P* value**
Age	1.02	<0.001	1.01	<0.001
Sex				
Male	(Ref)	---		
Female	1.28	0.02	1.27	0.04
Race				
White	(Ref)	---		
Black	1.15	0.3		
Asian and Pacific Islander	0.41	0.01	0.37	0.008
Ethnicity				
Non-Hispanic	(Ref)	---		
Hispanic	0.80	0.2		
Charleson-Deyo Score				
0	(Ref)	---		
1	0.88	0.6		
2+	2.21	0.03	1.69	0.2
Insurance Status				
Private	(Ref)	---		
Medicare	1.97	0.001	0.94	0.1
Medicaid	0.93	0.6		
Other Government	1.74	0.07	1.70	0.8
Uninsured	1.02	0.9		
Facility Type				
Non-Academic	(Ref)	---		
Academic	0.74	0.02	0.75	0.02
Radiation				
No Radiation	(Ref)	---		
Neoadjuvant	1.72	0.3		
Adjuvant	7.55	<0.001	4.96	<0.001
Chemotherapy				
Neoadjuvant	(Ref)	---		
Adjuvant	2.37	<0.001	1.60	<0.001
Stage				
IA	(Ref)	---		
IB	0.77	0.3		
IIA	0.96	0.8		
IIB	0.67	0.03	0.81	0.1
III	0.69	0.4		
IVA	1.04	0.9		
IVB	2.24	<0.001	2.11	<0.001
Year of Diagnosis	0.99	0.7		

4. Discussion

The introduction of chemotherapy in osteosarcoma treatment began in the 1970s with Rosen et al. among the first to report a significant response to a chemotherapy regimen including methotrexate [28]. Several randomized control studies confirmed the effectiveness of adjuvant chemotherapy compared to surgery alone; chemotherapy improved both DFS and OS by over 30% and the relapse-free survival by nearly 50% [29, 30]. Chemotherapy regimens now often include high-dose methotrexate with leucovorin rescue, doxorubicin, cisplatin, and/or ifosfamide [22, 31]; with these regimens, the likelihood of DFS has increased by over 40% [19].

Chemotherapy has vastly improved outcomes in osteosarcoma since it was initially introduced as a postoperative adjuvant [14, 19, 28-31]. However, most protocols now use preoperative chemotherapy in addition to surgery and postoperative therapy [14, 19, 31]. The rationale for these protocols centers around treating microscopic disease, decreasing tumor size for easier surgical resection, allowing time for surgical and prothesis planning, and analyzing the tumor's histological response to chemotherapy to adjust adjuvant chemotherapy accordingly [26, 32-36]. However, the superiority of neoadjuvant protocols to improve survival outcomes over adjuvant-only regimens lacks scientific evidence and therefore warrants additional investigation [9, 19, 22, 26]. In the only randomized control trial comparing NA and AO chemotherapy regimens, Goorin et al. found there was no significant survival benefit to neoadjuvant therapy, however this study consisted of only 106 patients and was performed over 20 years ago [22]. Two retrospective studies from the Cooperative Osteosarcoma Study Group and Memorial Sloan Kettering Cancer Center found no significant improvement in survival among patients treated with neoadjuvant chemotherapy compared with adjuvant chemotherapy alone [9, 26].

These studies are based on patients that were now treated over 25 years ago with a limited number of patients treated with adjuvant-only chemotherapy. More recent literature evaluated the effects of total neoadjuvant chemotherapy and a review by Brito et al. evaluated outcomes in nonmetastatic appendicular osteosarcoma treated with neo-adjuvant or adjuvant-only chemotherapy and found no differences in survival with either study [24]. Even head and neck osteosarcoma, a less common subtype of osteosarcoma that is predominately treated with surgical resection alone, has seen an increase in chemotherapy utilization despite uncertainty of its survival benefit [37].

4.1. Overall Survival and Short-Term Mortality

Our current study analyzing survival and surgical outcomes from a large, nationally representative database supports the previously mentioned studies. We failed to find a significant difference in overall survival among patients treated with neoadjuvant chemotherapy compared to adjuvant therapy alone. The NA cohort showed significantly better overall survival in the unmatched analysis, but this was likely due to differences in clinical characteristics, as in the propensity score matched analysis, the difference in survival was insignificant. This analysis identified no difference in short-term survival among the treatment groups in either the full or matched cohorts.

4.2. Survival and Treatment Trends

Despite the unproven survival or short-term mortality benefit among patients treated with neoadjuvant chemotherapy, over 75% of osteosarcoma patients were treated consistently with this regimen over the study period. One possible explanation for this could be that many patients treated over the study period were enrolled on clinical trials on which this treatment paradigm was required. The consistency of three and five-year survival during the study period further demonstrates the difficulty of advancing outcomes among osteosarcoma patients. Interestingly, while radiation is not routinely used in the treatment of osteosarcoma, it did have a higher usage in patients with positive margins.

4.3. Surgical Margins

Patients treated in the AO chemotherapy cohort were at higher risk of positive surgical margins in multivariate analysis. As alluded to earlier, more favorable margins in the NA cohort may explain the wide-spread use of this treatment approach as surgeons find NA treated tumors well-demarcated and technically easier to operate on [38]. However, increased time to surgery may complicate resection if tumor progression would compromise the ability to resect a tumor with clear margins. Due in part to the inherent limitations of a database study, it is unclear why this association exists, and the authors do not assert a causative role of neoadjuvant chemotherapy in reducing the risk of positive margins at the time of surgery.

4.4. Limitations

As a database study, there are several limitations. Compared to the NA cohort, the AO arm had a relatively small size, echoing sample distributions in previous studies. Lack of clinical and histologic information including osteosarcoma subtypes, clinical presentation, tumor volume, and percent necrosis after NA therapy, among others, limit conclusions as well. We were unable to randomize cohorts or control for a single treatment variable and instead were limited to distilled categorical variables. Specifics of the chemotherapy regimens were unavailable for comparison including the type of agents, number of cycles, regimen changes after neoadjuvant therapy, and adverse effects that prematurely ended or paused chemotherapy treatment, which could limit the scope of conclusions. Surgical specifics including level of resection (R0, R1, R2), intra-operative adjuvants or type of limb salvage reconstruction (e.g. endoprosthetic, allograft, allograft-prosthetic composite, etc) may play a role in outcomes but are also unavailable in the database. Additional less tangible limitations inherent to large database research may further impact the quality of the interpretation of the data, such as coding bias and being restricted to in-hospital data. Finally, as with any study comparing treatments which occur over different time horizons, we are at risk of immortal time bias when comparing survival. However, given 1-year survival for resectable osteosarcoma is relatively high, we believe this difference due to said bias is not considerable enough to significantly affect the outcomes [39].

5. Conclusions

This database study adds to the current literature, looking at trends in neoadjuvant chemotherapy utilization over time, impact on survival, and margins among a large, representative population. While neoadjuvant chemotherapy is not shown to increase survival, there may be other rationale for its use such as enabling safer surgical resection and/or limb-salvage. The treatment of osteosarcoma with neoadjuvant chemotherapy was initially based on clinical advantages with no scientific evidence to prove its superiority over adjuvant chemotherapy alone. Despite this fact, it has remained a mainstay of osteosarcoma treatment protocols. This study found no differences in short-term or overall survival among NA and AO cohorts and the causality of a relationship between a decreased rate of positive margins and NA therapy could not be verified. These findings offer information to help clinicians critically evaluate current paradigms to personalize treatment and limit overall treatment-related morbidity in osteosarcoma patients. The results of this study add to the growing sentiment that sarcoma care providers should not feel shackled to the neoadjuvant chemotherapy treatment approach.

Abbreviations

OS	Overall Survival
NCDB	National Cancer Database
DFS	Disease-free Survival
CoC	Commission on Cancer
NA	Neoadjuvant
AO	Adjuvant-only
AAPI	Asian American and Pacific Islander
OR	Odds Ratio
SMD	Standardized Mean Difference
MAP	Methotrexate, Doxorubicin, and Cisplatin

Author Contributions

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Conflicts of Interest

The authors declare no conflicts of interest.

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