Prognostic Factors Associated with Resected Osteosarcoma: Efficacy of Adjuvant Setting, Real-World Experience

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ABSTRACT

Osteosarcoma is a curable tumor. Surgery is performed after neoadjuvant chemotherapy as the primary standard treatment, followed by adjuvant therapy again. However, it is seen in patients who have undergone surgery without neoadjuvant chemotherapy. Adjuvant treatment is always given in this group. However, it is controversial how many cycles of adjuvant treatment should be given. In our study, 42 patients with osteosarcoma who received only adjuvant treatment without neoadjuvant treatment were analyzed for the effects of epidemiologic factors, treatment regimens on overall survival and disease-free survival. Retrospectively, 42 osteosarcoma patients (5 centers) with a current age of 18years and older who were followed up between 2001-2022 were examined. Twenty-five (60.0%) were below 8 cm, and 16 (38.0%) were 8 cm and above. The median number of cycles of adjuvant chemotherapy was 4 (range; 1-6). The 4-year DFS rate was 50.2%. In patients with primary tumors smaller and larger than 8cm, the 4-year DFS rates were 66.1% and 22.2%, respectively. The 4-year DFS rates for patients with 4 or less and more than 4 cycles of adjuvant chemotherapy were 27.1% and 69.2%, respectively. The 4-year OS rate was 78.5% in patients with primary tumors smaller than 8 cm and 18.8% in patients with tumors larger than 8 cm. The 4-year OS rate was 24.3% in patients who received 4 or less adjuvant cycles and 79.5% in patients who received more than 4 cycles. We have demonstrated that the number of adjuvant therapy courses above 4 and the presence of primary tumors smaller than 8 cm are influential over overall and disease-free survival in the patients who did not receive neoadjuvant therapy. The number of postoperative adjuvant treatment cycles should be forced as much as possible in these patients who haven't had neoadjuvant therapy.

Keywords: Osteosarcoma, Disease-free survival, Overall survival, Adjuvant therapy

INTRODUCTION

Osteosarcoma is a rare malignant bone tumor characterized by an osteoid matrix produced by malignant cells.[1] It is the most common primary bone malignancy.[2,3] In the US, 1000 new patients are diagnosed with osteosarcoma each year, and 500 of these patients are children or adolescents under the age of 20.[2] It is most prevalent among children between the ages of 13 and 16 and among adults over the age of 65.[4,5] The disease predominates slightly more in men than in women (ratio: 1.4/1).[4,6,7] Conventional osteosarcoma is the most common type, accounting for roughly 90% of all osteosarcomas.[8,9] Conventional osteosarcoma is subdivided into osteoblastic (76-80%), chondroblastic (10-13%), and fibroblastic (10%) types.[9,10]

One of the most crucial prognostic factor is disease stage. Metastasis of osteosarcoma occurs most frequently to the lungs; then other bones comes as the second.[11] The prognosis is worse for adults with the primary tumor located in the pelvis.[4,12-15]

As a cure for osteosarcoma is possible, intensive chemotherapy and resection should be conducted in adult osteosarcoma patients.[15,16] For the majority of histologic subtypes, clinical outcome is primarily determined by the response to neoadjuvant chemotherapy.[17-24] Methotrexate plus doxorubicin and cisplatin (MAP) regimen is recommended for children.[25] For adults,the most frequently advised treatment regimen is doxorubicin plus cisplatin.[26-28]

Our aim was to determine the effects of epidemiological factors, histopathological features and treatment regimens on overall survival (OS) and disease-free survival (DFS) in patients diagnosed with osteosarcoma.

PATIENTS AND METHODS

In our study, 42 patients who received only adjuvant treatment without neoadjuvant were evaluated retrospectively between 2001-2022. The study was multicenter and included 5 centers. Four of these patients were diagnosed in the Pediatric Oncology outpatient clinic, their treatment was initiated, their follow-up and treatment were carried out by the adult Medical Oncology clinic since they were 18 years of age or older and they were included in the study.

Hospitals' automation system and the patient files in the Medical Oncology archive were used to obtain patient data. The date of the bone tru-cut biopsy report in non-operated patients and the date of the primary tumor operation pathology report were used to assign the date of diagnosis. Age, body mass index (BMI), Eastern Cooperative Oncology Group (ECOG) performance score, primary tumor site, tumor size, surgical margin, metastasis data, treatments administered and treatment results, type of progression (local recurrence and/or metastasis), and death date were retrospectively scanned through the patient file.

The primary outcome, DFS, was defined as the time between diagnosis and first progression, death or last disease-free visit. OS was calculated as the time from diagnosis to death or last visit.

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by Marmara University Faculty of Medicine (number: 1553 – date: December 08, 2023).

Statistical Analysis:

SPSS 23.0 software was used for analysis of all data. Univariate and multivariate analysis was conducted. The symbol for standard deviation was expressed as (±). The independent variable t test was used to compare parametric variables between groups. The chi-square test was used to evaluate nonparametric variables. Multivariate analysis was carried out using Cox Regression. For survival analysis, the Kaplan-Meier test was employed. The confidence interval was assigned at 95%. A p value of < 0.05 was deemed significant.

RESULTS

42 patients who received only adjuvant therapy without neoadjuvant were included in this study, patients with a current age of 18 years and above-who were monitored between 2001 and 2022. Clinical characteristics of the patients who only received adjuvant treatment without neoadjuvant treatment included; the gender distribution of the patients was 26 (61.9%) men and 16 (38.1%) women. The median age of patients at diagnosis was 36 (range, 12-75) years.While 30 patients (71.4%) had an ECOG-performance score of 0, twelve patients (28.6%) had a score of 1-2. Body surface area of the patients (BSA, m2) had a mean and standard deviation of 3.4 ± 0.83.

In this group, the median primary tumor size was 7 cm (range: 1.5-18.0). Of these tumors, 16 (38.0%) were 8 cm or higher and 25 (60.0%) were below 8 cm. There were 1 patient (2%), whose primary tumor size was unknown. For primary tumors located outside the pelvis, the median primary tumor size was 7.5 cm (range: 1.5-18.0). There were 16 patients (41.0%) with T2 (8 cm and above) and 22 patients (56.4%) with T1 (below 8 cm) tumors. The median primary tumor size of primary tumors

located in the pelvis was 5.5 cm (5.5-7.0). There were three (100%) patients with T1a (less than 8 cm) tumor but no T1b (8 cm or larger) tumor was involved.

The adjuvant regimen distribution for this cohort was cisplatin + doxorubicin in 26 patients (69.0%), MAP in 6 patient (14.3%), and ifosfamide plus doxorubicin in 7 patients (16.7%). The median number of cycles of adjuvant cisplatin was 4 (range; 1-6). In this group, the number of patients with negative surgical margins (R0) before adjuvant treatmentwas 33 (78.6%), the number of patients with positive margins (R1/2) was 7 (16.7%), and the surgical margin status of 2 (4.8%) patient was unknown. Recurrence or progression was present in 19 (45.2%) of 42 patients who received only adjuvant therapy. The clinical characteristics of the patients receiving adjuvant therapy are shown in Table 1.

The median follow-up period of the patients was 57.7 (95% CI: 36.5-78.9) months. The median overall survival time was 49.3 months. The 4-year overall survival rate is 53.6% and disease-free survival was 50.2%. A univariate analysis of factors associated with 4-year DFS and OS in patients is shown in Table 2. The 4-year DFS rate was 54.5% in those under the age of 30, and this rate was 49.1% at the age of 30 and above. The 4-year DFS rate was 48.1% in men who received only adjuvant therapy, while it was 53.0% in women. In this group, the 4-year DFS rate was 66.1% for those with a primary tumor size less than 8 cm, while the rate was 22.2% for those with a primary tumor size of 8 cm or more.

While the 4-year DFS was 66.7% for those with a primary location in the pelvis, this rate was 48.2% for those with a primary location outside the pelvis. While the rate of 4-year DFS was 42.5% in those who received cisplatin plus doxorubicin as adjuvant treatment regimens, 71.4% in those who received ifosfamide plus doxorubicin and 50.0% in those who received MAP. While the 4-year DFS rate was 27.1% in those who received 4 or less adjuvant cycles, the rate was 69.2% in those who received more than 4 cycles. The 4-year DFS rate was 53.9% in patients with negative surgical margins and 28.6% in patients with positive margins.

Table 1. Clinical features of patients receiving only adjuvant therapy

Age at diagnosis, year	
Median (min-max)	36 (12-75)
Gender, n (%)	
Male	26 (61.9)
Female	16 (38.1)
ECOG score, n (%)	
0	30 (71.4)
1-2	
12 (28.6)	
BSA, m^2	
Mean±SD	3,4±0.83
Primary tumor size, cm	
Median (min-max)	7 (1.5-18.0)
< 8	
25 (60.0)	
≥ 8	
16 (38.0)	
Unknown	1 (2.0)
Extra-pelvic location	
Median (min-max)	7.5 (1.5-18.0)
T1 (< 8)	22 (56.4)
T2 (≥ 8)	16 (41.0)
Unknown	1 (2.6)
Pelvic	
Median (min-max)	5.5 (5.5-7.0)
T1a (< 8)	3 (100)
T1b (≥ 8)	–
Adjuvant treatment, n (%)	
Cisplatin+doxorubicin	29 (69.0)
Ifosfamide+doxorubicin	7 (16.7)
Methotrexate+doxorubicin and cisplatin	6 (14.3)
Adjuvant x cycle	
Median (min-max)	4 (1-6)
Surgical margin, n (%)	33 (78.6)
R0	7 (16.7)
R1/2	2 (4.8)
Unknown	
Recurrence or progression, n (%)	19 (45.2)

While the rate of 4-year OS was 54.2% for those under the age at diagnosis of 30, this rate was 54.0% for those aged at diagnosis 30 and above. While the rate of 4-year OS in men was 46.3%, it was 65.8% in women. In this cohort, while the 4-year OS rate of those with a primary tumor size less than 8 cm was 78.5%, the rate of those with a primary tumor size of 8 cm or more was 18.8%.

Table 2. Factors associated with 4-year DFS and OS in patients receiving only adjuvant treatment - Univariate analysis

	DFS[a] 4-years DFS (%)	OS[b] 4-years OS (%)
General (n= 42)	50.2	53.6
Age at diagnosis		
< 30	54.5	54.2
≥ 30	49.1	54.0
Gender		
Male	48.1	46.3
Female	53.0	65.8
Primary tumor size		
< 8 cm	66.1	78.5
≥ 8 cm	22.2	18.8
Bone location		
Extra-pelvic	48.2	51.7
Pelvic	66.7	66.7
Adjuvant treatment		
Cisplatin+doxorubicine	42.5	48.1
Ifosfamide+doxorubicine	71.4	68.6
Methotrexate+ doxorubicin+ cisplatin	50.0	50.0
Number of adjuvant cycle		
≤ 4	27.1	24.3
5-6	69.2	79.5
Surgical margin		
R0	53.9	50.1
R1/2	28.6	51.4

[a] PFS: progression free survival, time from frst progression to second progression
[b] OS: overall survival, time from frst progression to last control or death

Similarly, the 4-year OS rate of patients with a primary location in the pelvis was 66.7% but the rate of patients with a primary location outside the pelvis was 51.7%. While the rate of 4-year OS was 48.1% in those who received cisplatin plus doxorubicin as adjuvant treatment regimens, 68.6% in those who received ifosfamide plus doxorubicin, and 50.0% in those who received MAP. While the 4-year OS rate is 24.3% in those who received 4 or less adjuvant cycles, the rate is 79.5% in those who received more than 4 cycles. In this group, the 4-year OS rate was 50.1% in patients with negative surgical margins, and 51.4% in patients with positive margins.

Table 3. Factors associated with 4-years overall survival in patients receiving only adjuvant treatment -Univariate and Multivariate analysis

	Univariate HR (95%CI)	p
Age at diagnosis		
< 30 vs > 30	0.98 (0.37-2.60)	0.97
Gender		
Female vs Male	0.54 (0.19-1.55)	0.25
Primary tumor size		
< 8 cm vs > 8 cm	0.26 (0.09-0.73)	**0.01**
Bone location		
Extra-pelvic vs pelvic	1.44 (0.19-10.9)	0.72
Number of adjuvant cycle		
≤ 4 vs 5-6	2.86 (1.04-7.87)	**0.04**
Surgical margin		
R0 vs R1/2	1.02 (0.33-3.15)	0.96
	Multivariate	
Primary tumor size		
< 8 cm vs > 8 cm	0.33 (0.11-0.98)	**0.04**
Number of adjuvant cycle		
≤ 4 vs 5-6	1.76 (0.59-5.23)	0.30

Logistic regression analysis was performed on patients to evaluate clinicopathological variables (Table 3). Evaluated risk factors included age at diagnosis, gender, primary tumor size, localization, number of adjuvant cycles, and positive surgical margins. In the univariate model, age, gender, localization, surgical margin positivity did not have a significant differential effect (p> 0.05). In the univariate model, the primary tumor size and the number of adjuvant cycles had significant differentiating effect (p< 0.05). A significant independent (p< 0.05) differentiating effect was observed on primary tumor size (OR, 0.33; 95% CI: 0.11-0.98; p= 0.04) in the multivariate reduced model (Figure 1).

DISCUSSION

Over the past 50 years, survival rates of malignant bone sarcoma patient have significantly increased, largely due to advancements in chemotherapy. As the osteosarcoma is potentially curable, adults must undergo intensive chemotherapy and resection.[15,16]

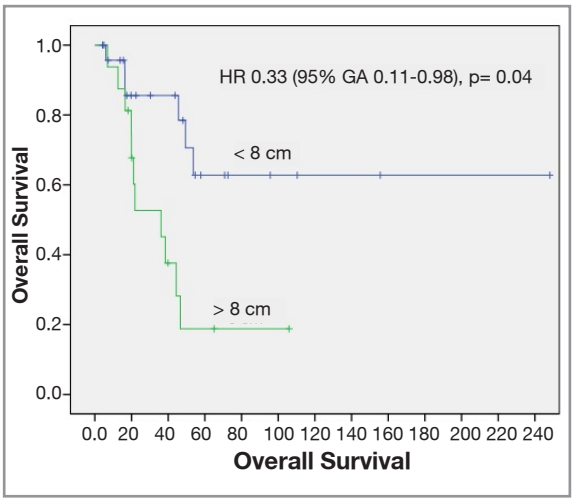

Figure 1. Multivariate Cox regression analysis overall survival and tumor size

In our study, while patients with osteosarcoma who underwent adjuvant therapy had a 4-year OS rate of 53.6%, the 4-year DFS rate was 50.2%. According to number of adjuvant cycles received; patients who received 4 or fewer adjuvant courses had a 4-year DFS rate of 27.1% and patients who received 5 or 6 courses had a rate of 69.2%. In the group with a primary tumor size less than 8 cm, he 4-year DFS was 66.1% and it was statistically significant in terms of survival in multivariate analysis. In conclusion, these data suggest that primary tumor size and the number of adjuvant chemotherapy cycles should be taken into account when determining treatment and survival strategies in osteosarcoma patients.

Osteosarcoma patients (n= 3482) were surveyed between 1973 and 2004 by the population-based Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute and survival rates were assessed for age groups of 0-24 years, 25-59 years, and 60-85 years. The relative 5-year OS rate was 61.6% in the 0 to 24 age group, 58.7% in the 25 to 59 age group, and 24.2% in the 60 to 85 age group.[4] In our study, rates of DFS and OS were found to be similar in the population under 30 years of age at diagnosis. The average male-to-female ratio in the same study was 1.22/1.[4] The male to female ratio in our study was 1.6/1, with 26 (61.9%) male patients and 16 (38.1%) female patients. This ratio demonstrated that men had a higher incidence of osteosarcoma. Exact reason of increased incidence of osteosarcoma among men is unknown. As the pathogenesis of osteosarcoma is thought to be influenced by the rate of bone growth, the rapid growth that occurs in the adolescence of males may explain the increased cases of osteosarcoma among men. Additionally, the ECOG performance score is also important in determining the treatment choice.The fact that 71.4% of our patients with an ECOG score of 0 and 28.6% of our patients with an ECOG score of 1 or 2 is important in the effective treatment tolerability.

Histological subtypes provide further insight into the morphological and molecular aspects of the tumor and help to direct treatment approaches. For instance, while high-grade tumors tend to be more aggressive, low-grade cancers may have a better prognosis. As a result, accurate identification of histological subtypes is critical for increasing the efficacy of adjuvant therapy and assisting patients in achieving better outcomes. The most prevalent histological subtype, conventional osteosarcoma, accounts for approximately 90% of osteosarcoma cases.[8,9] All of the patients in our study had high-grade histology.

Adjuvant treatment regimens for osteosarcoma in adults are customized based on the characteristics of the tumor, the patient's age, general health status, and staging. Cisplatin and doxorubicin are the two cytotoxic chemotherapy drugs that make up the main of a treatment plan. In the right patients, this regimen can also be combined with high-dose methotrexate and/or ifosfamide. The majority of research on combination regimens comes from neoadjuvant investigations. The influence of postoperative chemotherapy on survival was revealed in a study carried out in the 1970s, in which 4-year OS rates were increased from less than 20% to 40%-60%.[29] Unfortunately, there are no only adjuvant treatment studies of these regimens. Therefore, the outcomes of post-surgical adjuvant treatment are important. The most frequently advised combination for adults is doxorubicin plus cisplatin.[26–28] In our study, the majority of patients (69%) received cisplatin plus doxorubicin. The dose of cisplatin in the doxorubicin and cisplatin combination is determined at 100 mg/m^2. There is no clear data on how many courses should be utilized as adju-

vant therapy. Five or six treatment cycles are the preferred number of adjuvant courses at our clinic. Four cycles may be administered, depending on the patient's tolerance. In patients with 4 or fewer adjuvant cycles, the 4-year OS rate was 24.3%, and in patients with more than 4 cycles the rate was 79.5%. The 4-year DFS rate was 27.1% in patients who received 4 or fewer adjuvant courses, but it was 69.2% in patients who received more than 4 courses, the difference was statistically significant. One of an important result of our study is that DFS and OS outcomes improve when the number of adjuvant courses is above.[4]

The long bones are the most frequent main sites for osteosarcoma especially the large extremity bones the knee, arm, and leg bones. In addition, osteosarcoma can rarely form in other bones, including the hip bone, spine, ribs, and jaw. Osteosarcoma located in the pelvis represents a rarer variant of this rare and aggressive type of bone cancer. Due to their location near the center of the body, osteosarcomas in the pelvis might become more difficult and complicated to surgically remove. The prognosis for these individuals can be improved with a multidisciplinary approach. However, treatment of these tumors is usually difficult and involves multiple factors that affects long-term survival. Twenty-six (2.5%) had primary osteosarcoma of the pelvis in four studies that retrospectively examined 1054 patients with osteosarcoma between 1993 and 2005. Two of the nine patients with metastases at the time of diagnosis are still alive. Of the remaining 17 patients, five had localized disease and were still alive. 5-year DFS rates for pelvic localized and metastatic disease were 22% versus 23%, and 5-year OS rates were 47%versus 22%. Five years DFS and OS for patients with non-pelvic osteosarcoma were 57% and 69%, respectively.[14] Also in our study, the pelvis-localized group had similar rates of OS and DFS.

This cohort was made up of patients who did not receive neoadjuvant therapy. We have demonstrated that OS and DFS rates are influenced by the number of systemic adjuvant therapy courses above 4 and a primary tumor size of 8 cm or less. For patients who haven't had neoadjuvant therapy, postoperative treatment as early as possible should be targeted.

If we acknowledge the limitations and disadvantages of our study; it was not a randomized controlled trial. Due to its retrospective nature, a homogeneous distribution of the patients could not be achieved. Though, real-world data were presented as we had patients in our clinic. There were very few patients with vertebral and pelvic osteosarcoma. Since it was impossible to determine how many segments of the vertebra and pelvis of these patients had been affected, they were accepted as T1 according to their general and clinical status and those that affected the pelvis being divided into T1a and T1b.

Even though osteosarcoma is a rare tumor, another drawback was the low number of patients who only received adjuvant treatment. Because the clinical records did not contain information on every patient's cause of death, it was not possible to analyze cancer-specific survival.

Conclusion

In conclusion, patients with a primary tumor size of less than 8 cm had a better prognosis. However, the number of adjuvant treatments administered did not reach statistical significance and tended to predict the outcomes. These findings underscore the importance of tumor size as a significant predictor of outcomes and provide valuable insights for prognostic considerations in patients with this medical condition. Further research with a larger cohort is needed to validate the impact of the number of adjuvant treatments on outcomes.

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