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Long-Term Observation of the Epidemiology and Survival of Osteosarcoma in a Rural Area of Japan

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Abstract

Objectives: No definitive risk factors for osteosarcoma have been identified. To assess regional differences, it is essential to minimize racial and other biases. However, few studies have examined this issue with minimal bias. This study aimed to evaluate regional variations in the incidence and characteristics of osteosarcoma in a rural prefecture with limited population mobility within ethnically homogeneous Japan. **Subject and Methods:** We retrospectively identified 40 patients with primary osteosarcoma who received treatment at our hospital from 2000 to 2024. Clinical data were collected. Akita City, the prefectural capital and most populous city in Akita Prefecture, was compared with other cities, towns, villages, and regions regarding incidence and prognosis. We also examined poor prognostic factors across all cases. **Results:** The incidence rate in Area 2 was significantly higher than that in Area 1 (P = 0.0269). Across municipalities, Oga City in Area 2 and Yuzawa City in Area 5 exhibited significantly higher incidence rates than Akita City (P = 0.0243 and P = 0.0477). Kaplan-Meier analysis comparing the prognosis of Area 1 with Areas 2 and 5 showed that only Area 2 had a significantly worse prognosis than Area 1. Univariate analysis of prognostic factors demonstrated that surgical treatment was the sole factor associated with improved prognosis. **Conclusion:** These findings suggest the existence of regional differences in the incidence and characteristics of osteosarcoma.

Keywords

Epidemiology, Osteosarcoma, Rural Area, Survival

1. Introduction

Osteosarcoma is the most common malignant bone tumor, typically occurring in

teenagers. It is slightly more prevalent among males, and several studies have explored its association with bone development [1] [2]. However, its incidence remains significantly lower than that of other cancers, and its etiology is still unclear. Unlike many malignancies, no definitive causative gene has been identified, and no molecular targeted therapies have been developed. Thus, both genetic and environmental risk factors for osteosarcoma remain undefined.

One approach to exploring these factors is through evaluating regional differences in osteosarcoma incidence and characteristics. Although several studies have addressed this, they vary widely in racial composition and geographic scope [3]-[6]. To accurately assess regional variation, it is necessary to minimize racial and other population-based biases. Nevertheless, few studies have conducted such analyses under low-bias conditions, and even fewer have statistically assessed the presence of regional disparities.

This study aimed to evaluate long-term regional differences in the incidence and clinical characteristics of osteosarcoma within a rural Japanese prefecture characterized by limited population movement and ethnic homogeneity.

2. Materials and Methods

2.1. Subjects

We retrospectively identified patients with primary osteosarcoma of the extremities or trunk who were treated at our institution between 2000 and 2024. Patients with secondary osteosarcoma due to Paget's disease or prior irradiation, as well as those with low-grade subtypes such as parosteal osteosarcoma, were excluded. Data were extracted from medical records, including age, sex, residence, tumor type and size, anatomical site, primary tumor treatment, presence of lung or other metastases, local recurrence, follow-up duration, and outcomes. Osteosarcoma subtypes were classified based on the 5th edition of the 2020 WHO classification [7]. For those undergoing surgery, treatment-related data included type of local therapy, use and histological evaluation of chemotherapy (Rosen and Huvos criteria), and surgical margins (Enneking staging system) [8] [9]. For patients without events, data were de-identified at the last follow-up.

Osteosarcoma incidence was calculated based on the municipality (city or town) and aggregated area of residence. As Akita Prefecture is a region experiencing significant population aging, all of its municipalities have seen a population decline since 2000. Consequently, because it was impossible to calculate an exact average population, a rough average was calculated instead. Population data for each locality were obtained from quinquennial surveys conducted between 2005 and 2025. "Average population" was defined as the sum of the populations for the years 2005, 2010, 2015, 2020, and 2025, divided by 5. Due to extensive municipal mergers in Akita Prefecture between 2000 and 2005, data from 2000 were excluded. Incidence rates were calculated as the number of cases per year per region during the 25-year study period, standardized using average population figures. Given that Akita City is both the prefectural capital and the most populous city in

Akita Prefecture, its incidence and prognosis were compared with those of other municipalities and regions. Poor prognostic factors were also evaluated across all cases. Overall survival was defined as the duration from the time of the initial visit. For surviving patients, the follow-up period was defined as the time until the last follow-up.

This study was approved by the Institutional Review Board for Clinical Research at Akita University (Approval Number: 3313) and was conducted in accordance with the Declaration of Helsinki (1975, revised 1983).

2.2. Statistical Analyses

Continuous variables are presented as mean ± standard deviation. Group comparisons were performed using Student's t-test, Welch t-test, and Chi-squared (χ^2) test. Overall survival was analyzed using the Kaplan-Meier method, with comparisons made using the Generalized Wilcoxon test. Factors associated with overall survival were evaluated using a Cox proportional hazards model. Statistical significance was set at $P < 0.05$.

3. Results

The clinicodemographic characteristics of patients are presented in Table 1.

Table 1. Patient characteristics.

Characteristics	Patients
Number	40
Age	37.6 ± 25.8 (10 - 84)
Sex—Male/Female	23/17
Size	88.5 ± 33.7 (44 - 165)
Location—Extremity/Axial	38/2
Histological subtype	
Conventional	39
Osteoblastic	18
Chondroblastic	5
Fibroblastic	8
Unknown	8
High-grade surface	1
Surgical treatment for primary tumor	32
Surgical margin—adequate/inadequate	29/3
Amputation surgery	14
All chemotherapy	32
Perioperative chemotherapy	27

Continued

Histological evaluation after chemotherapy	
Grades—I/II/III/IV/Unknown	16/9/0/0/2
All radiotherapy	11
Perioperative radiotherapy for the primary tumor	3
Radiotherapy for primary tumor without surgical treatment	3
Local recurrence	5
All distant metastases	24
Distant metastasis at the time of presentation to our institutions.	6
Follow-up period	80.1 ± 87.1 (1 - 372)
Outcome at the last follow-up—NED/AWD/DOD	16/2/22

Forty patients (23 males and 17 females) with primary osteosarcoma were included. Thirty-nine cases were conventional osteosarcoma, and one case was high-grade surface osteosarcoma. The mean age was 37.6 years (range: 10 - 84 years), and the mean follow-up duration was 80.1 months (range: 3 - 316 months). The mean tumor size was 88.5 mm (range: 44 - 165 mm). Primary lesions were located in the extremities in 38 patients (95%) and in axial sites in 2 (5%). Specifically, tumors involved the distal femur in 14 patients, the proximal tibia in 9, the proximal fibula in 4, the proximal humerus in 3, the proximal femur in 3, the distal radius in 2, the distal tibia in one, the femoral shaft in one, the rib in one, the pelvis in one, and the patella in one. Surgical treatment of the primary tumor was performed in 32 patients (80%), achieving adequate tumor-free margins in 90.6% (n = 29). Amputation was required in 43.8% (n = 14) of surgical cases. Chemotherapy, including neoadjuvant therapy and treatment after relapse, was administered to 32 patients, with perioperative chemotherapy performed in 27. Regimens included NECO95J, ifosfamide–doxorubicin, doxorubicin, ifosfamide, methotrexate–ifosfamide, and etoposide [10] [11]. According to the Rosen and Huvos criteria, 16 patients were classified as Grade I, 9 as Grade II, and none as Grades III or IV. Radiotherapy was administered to 11 patients; treatment of the primary tumor was performed in 6, including heavy particle irradiation in one and proton-beam radiotherapy in one. Local recurrence occurred in 15.6% (n = 5) of surgical patients. Distant metastases developed in 60% (n = 24), and metastases at diagnosis were observed in 15% (n = 6). Patient outcomes were as follows: 16 patients had no evidence of disease (NED), 2 were alive with disease (AWD), and 22 had died of disease (DOD). The 5-year survival rate was 55.9%.

Akita Prefecture, located in northeastern Japan away from Tokyo (**Figure 1(a)**), comprises 25 cities, towns, and villages. Over the past 25 years, osteosarcoma cases were identified in 12 cities and 2 towns. The prefectural capital, Akita City, was designated Area 1. Taking into account the presence of mountains and transportation accessibility, six zones were delineated in a clockwise direction starting

from Akita City. The cities of Oga and Katagami and Hachirogata Town in the northwest were designated Area 2; the cities of Noshiro, Kitaakita, and Odate in the north as Area 3; the cities of Semboku and Daisen in the east as Area 4; the cities of Yokote and Yuzawa and Ugo Town in the southeast as Area 5; and the cities of Yurihonjo and Nikaho in the southwest as Area 6 (Figure 1(b)).

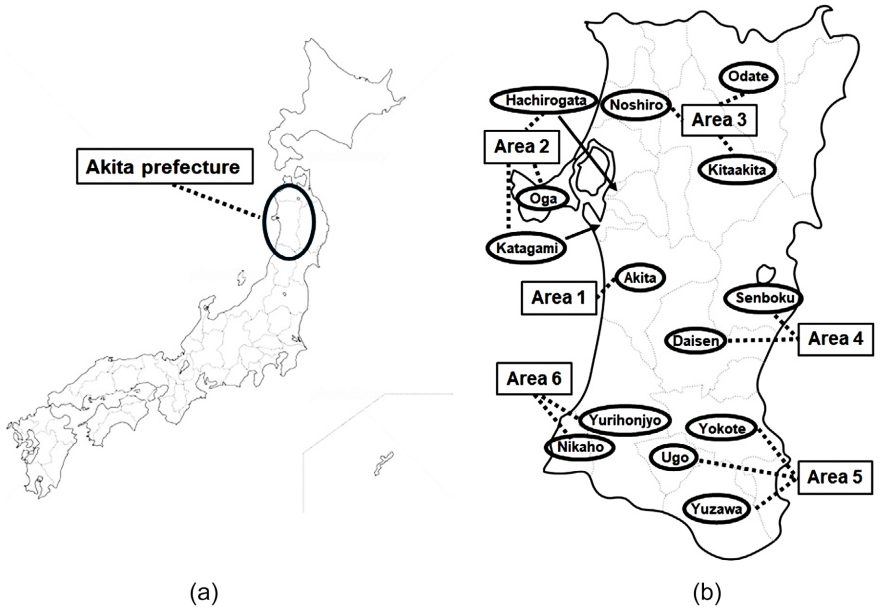

Figure 1. Akita Prefecture's location in Japan (a) and a map of municipalities within Akita Prefecture where osteosarcoma cases occurred (b). The prefectural capital, Akita City, was designated as Area 1, and the surrounding cities and towns were classified into six areas arranged clockwise from Akita City.

The annual incidence rate of osteosarcoma in Akita City (Area 1) was 1 in 787,898. The incidence rate in Area 2 was significantly higher at 1 in 242,738 (P = 0.0269). Among municipalities, Oga City in Area 2 and Yuzawa City in Area 5 had incidence rates of 1 in 179,500 and 1 in 232,875, respectively, both significantly higher than that in Akita City (P = 0.0243 and P = 0.0477) (Table 2).

Table 2. Comparison of osteosarcoma incidence rates in each region.

Variables	Number (<20 years old)	Average population	Rate of occurrence (number/year)	P value Vs. Area 1 or Akita
Area 1—Akita	10 (4)	315,159	1/787,898	-
Area 2	7 (1)	67,967	1/242,738	0.0269
Oga	4 (1)	28,720	1/179,500	0.0243
Hachirogata	1 (0)	6099	1/152,475	0.5201
Katagami	2 (0)	33,147	1/414,338	0.7247
Area 3	3 (2)	161,612	1/1,346,763	0.5953
Noshiro	1 (0)	54,459	1/1,361,475	0.9182

Continued

Kitaakita	1 (1)	33,374	1/834,350	0.6472
Odate	1 (1)	73,779	1/1,844,475	0.6519
Area 4	4 (1)	109,922	1/687,012	0.9415
Senboku	2 (0)	27,119	1/338,988	0.5572
Daisen	2 (1)	82,803	1/1,035,038	0.9982
Area 5	12 (7)	153,563	1/319,922	0.0512
Yokote	5 (3)	91,663	1/458,315	0.4887
Yuzawa	5 (3)	46,575	1/232,875	0.0477
Ugo	2 (1)	15,325	1/191,563	0.1952
Area 6	4 (1)	105,222	1/657,638	0.9979
Yurihonjyo	3 (1)	79,860	1/665,500	0.9295
Nikaho	1 (0)	25,362	1/534,050	0.7139

Univariate analysis of prognostic factors demonstrated that only surgical treatment was significantly associated with improved survival; no other clear adverse prognostic factors were identified (Table 3).

Table 3. Univariate analysis of factors affecting prognosis.

Variables	Hazard Ratio	95% CI	P
Age	1.007	0.990 - 1.024	0.4298
Sex—female	1.187	0.512 - 2.752	0.6900
Past inappropriate surgery	2.242	0.658 - 7.646	0.1970
Size	1.003	0.991 - 1.015	0.6199
Location—axial	5.997	0.624 - 57.660	0.1209
Surgical treatment for the primary tumor	0.118	0.039 - 0.351	0.0001
Radiotherapy for the primary tumor	1.801	0.663 - 4.892	0.2486
Perioperative chemotherapy	0.668	0.260 - 1.715	0.4019
Histological evaluation after chemotherapy	0.928	0.310 - 2.783	0.8946
Surgical margin—inadequate	0.622	0.082 - 4.748	0.6474
Local recurrence	1.716	0.551 - 5.340	0.3514
Amputation for primary tumor	1.738	0.646 - 4.674	0.2733
Area 2	2.234	0.818 - 6.102	0.1169
Area 5	0.766	0.282 - 2.079	0.6011

When Kaplan-Meier curves were used to compare prognoses, patients in Area 2 had significantly worse outcomes than those in Area 1 (Figure 2).

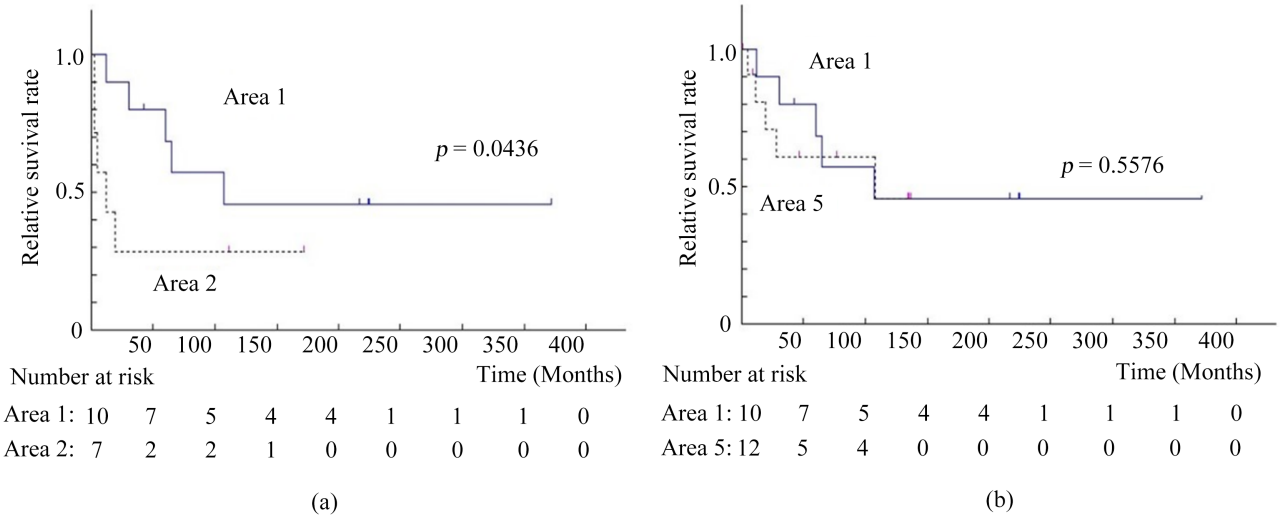

Figure 2. Kaplan-Meier curves illustrating overall survival comparing Area 1 with Area 2 (a) and Area 5 (b). Only Area 2 demonstrated a significantly poorer prognosis than Area 1 (P = 0.0436).

4. Discussion

The findings of this study demonstrated considerable regional variation in the incidence of osteosarcoma within a single prefecture in Japan. Additionally, areas with the highest incidence rates were associated with poorer prognoses. These results indicate that incidence and tumor characteristics may differ by region. Several epidemiological investigations have examined regional differences in osteosarcoma, assessing variations across countries, among ethnic groups within a country, and within individual states in the United States, with inconsistent findings [3]-[5]. Furthermore, there is limited statistical evidence supporting such differences. Many prior reports analyzed populations with diverse ethnic backgrounds, potentially introducing biases. The influence of race on osteosarcoma has been described in previous studies [12] [13], including reports identifying racial and economic disparities [14]. Conversely, Japan is essentially a mono-ethnic nation. Akita Prefecture is among the most rural regions of Japan. Akita Prefecture's population has steadily declined from 1.18 million in 2000 to an estimated 890,000 by 2024. Additionally, the proportion of older adults aged ≥ 65 years is projected to reach 39.7% in 2024, the highest aging rate in Japan. Because the facility conducting this study is the sole institution in Akita Prefecture capable of treating bone and soft tissue tumors, nearly all patients in the region are treated there, allowing comprehensive assessment of incidence. To date, no report has described such an extensive, 25-year observational study of an entire rural prefecture with minimal racial variation and little migration. This setting enables a more accurate evaluation of how a patient's place of residence may influence disease characteristics.

This study could not definitively determine whether the observed regional differences in incidence and tumor features arose from environmental or genetic factors. Among patients included, 47.5% (19 cases) were aged ≥ 30 years, 22.5% (nine

cases) were older adults aged ≥ 65 years, and 10% (four cases) were aged ≥ 80 years. The proportion of older adults was comparatively high, making it unlikely that genetic factors alone account for these patterns and suggesting that environmental influences may contribute.

The 5-year survival rate in this study was 55.9%, reflecting a poorer prognosis compared with typical outcomes. Because some cases dated to around 2000, one possible explanation is that surgical techniques were less advanced during that period. Furthermore, 40% of patients were younger than 20 years, while 22.5% were older adults aged ≥ 65 years, indicating an increased proportion of older adults. Osteosarcoma in older adults has been associated with worse outcomes compared with younger individuals [15], likely affecting survival rates in this cohort. Preoperative chemotherapy was ineffective in all cases, and distant metastases developed in 60% (24 cases), significantly influencing prognosis. Limited tolerance of preoperative chemotherapy among older adults may have contributed to these results. In the present analysis, Area 2 exhibited both a higher incidence rate and a poorer prognosis compared to Area 1. Due to the small number of cases, it was not possible to demonstrate statistical significance regarding detailed clinical information such as age or site of occurrence; however, there was a trend toward occurrence at an older age in Area 2. It is possible that something like this is influencing the situation. However, younger patients received established treatment protocols. Potential regional differences in chemotherapy efficacy warrant further large-scale research across broader geographic areas.

To our knowledge, this study is the first to examine long-term trends in osteosarcoma among patients residing in a region with minimal racial diversity and low migration. However, this study has several limitations. Although the 25-year observation period is lengthy, the absolute number of cases was inevitably small due to the rural setting, posing a major constraint. More detailed evaluations might be feasible in urban centers such as Tokyo, where larger populations reside, although areas with substantial influx from across Japan and abroad are less suitable for research of this nature. In the future, collaboration with other rural prefectures and the examination of common patterns among high-incidence areas may help clarify environmental and genetic factors.

In conclusion, this study suggests the possibility of regional differences in the incidence and characteristics of osteosarcoma. Whether these disparities are driven by genetic or environmental causes remains uncertain. Broader studies across multiple regions of Japan will be essential to elucidate the underlying factors.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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