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Analysis of foot-originating malignant bone tumors: Epidemiology, characteristics, and survival outcomes

Masatake Matsuoka [a,*], Tomohiro Onodera [a], Koji Iwasaki [b], Masanari Hamasaki [a], Taku Ebata [a], Yoshiaki Hosokawa [a], Ryuichi Fukuda [a], Eiji Kondo [c], Norimasa Iwasaki [a]

[a] Department of Orthopaedic Surgery, Faculty of Medicine and Graduate School of Medicine, Hokkaido University, North 15 West 7, Kita-Ku, Sapporo, Hokkaido 060-8638, Japan
[b] Department of Functional Reconstruction for the Knee Joint, Hokkaido University, Kita-15, Nish-7, Kita-ku, Sapporo, Hokkaido 060-8638, Japan
[c] Centre for Sports Medicine, Hokkaido University Hospital, North 14 West 5, Kita-Ku, Sapporo, Hokkaido 060-8648, Japan

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ABSTRACT

Background: The study examines the characteristics and outcomes of foot-originating malignant bone tumors via Surveillance Epidemiology and End Results (SEER) database analysis.
Methods: A retrospective review of 14,695 malignant bone tumor cases from 2000 to 2019 was conducted.
Results: Of the eligible cases, 147 (2.3 %) were foot-origin tumors, typically smaller and more commonly treated with surgery than those in other locations. These tumors were more frequently treated with surgical resection, with a higher proportion undergoing amputation. In contrast, foot-origin tumors were less often managed with chemotherapy and radiation. Foot-origin tumors exhibited higher survival rates compared to non-foot-origin tumors as shown in univariate analysis, although multivariate analysis did not reflect significant differences.
Conclusion: Foot-originating malignant bone tumors tend to be smaller and are frequently surgically treated, correlating with favorable survival outcomes. These findings point to early detection as a potential factor in the improved survival rates, not necessarily the tumor's origin.

1. Introduction

Primary malignant bone tumors are recognized as exceedingly rare entities in the spectrum of cancers [4,8,14]. These tumors account for less than 0.2 % of all neoplasms, underscoring their rarity and the challenges associated with studying them [2,19]. The low incidence rate has historically limited comprehensive research and understanding of these tumors, often leading to a lack of standardized treatment protocols.

Among primary malignant bone tumors, those originating in the foot represent an even rarer subset. While the overall clinical characteristics of primary malignant bone tumors have been documented to some extent, the specific features pertaining to foot-originating tumors remain largely unexplored [15]. This gap in knowledge presents significant challenges in diagnosis and management, often resulting in delayed or suboptimal treatment strategies [6,18].

In the realm of rare cancers, such as primary malignant bone tumors, large-scale database studies have begun to shed light on their clinical features [7,9,10]. Descriptive epidemiology, utilizing extensive databases, has proven to be a valuable tool in elucidating the characteristics of these rare neoplasms [13]. Similarly, there exists a potential to apply these methodologies to foot-originating bone tumors, leveraging large datasets to gain insights into their unique clinical presentations and outcomes.

Despite the acknowledged rarity of foot-originating malignant bone tumors, their clinical characteristics remain insufficiently defined. The purpose of this study is to investigate the specific features of these tumors using the Surveillance, Epidemiology, and End Results (SEER) database, the largest cancer registry of its kind in the

* Corresponding author.
E-mail addresses: masatakem@pop.med.hokudai.ac.jp (M. Matsuoka), tomozou@med.hokudai.ac.jp (T. Onodera), rockcape324@gmail.com (K. Iwasaki), hamasa.masa@gmail.com (M. Hamasaki), taku.e.19861210@gmail.com (T. Ebata), y_hosokawa48@yahoo.co.jp (Y. Hosokawa), ryuichi.fukuda.dream@gmail.com (R. Fukuda), eijik@med.hokudai.ac.jp (E. Kondo), niwasaki@med.hokudai.ac.jp (N. Iwasaki).

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United States. By analyzing this comprehensive dataset, we aim to provide a clearer understanding of the epidemiology, presentation, and outcomes of foot-originating malignant bone tumors, thereby contributing to improved diagnostic and therapeutic approaches.

2. Material and methods

2.1. Study design and data source

This retrospective study investigated all cases of malignant bone tumors registered in the SEER database. The SEER database, maintained by the National Cancer Institute, provides comprehensive information on cancer incidence, survival, and treatment across various geographical regions in the United States, making it an invaluable resource for oncological research. The SEER database encompasses 18 cancer registries, covering approximately 28 % of the entire United States population.

2.2. Case selection

Our study focused on representative cases of bone sarcoma recorded between 2000 and 2019, as per the Rare Cancer classification established by the Surveillance of Rare Cancer in Europe (51: Bone sarcoma) [3]. A total of 14,695 cases of malignant bone tumors with pathological confirmation were identified and included in this study. The cases were then categorized based on the location of tumor origin. Tumors originating in the foot were identified using the ICD-O code (C40.3). Cases with unknown primary tumor site, cause of death, tumor size, and status of lymph node or distant metastases at the time of diagnosis were excluded from the study. This exclusion was necessary to ensure the accuracy and reliability of the subsequent analyses. The study population was divided into two groups for analysis: tumors originating in the foot and tumors originating in other locations (Fig. 1).

2.3. Variables and data collection

The following background factors were investigated for each case: age, gender, ethnicity, tumor size (categorized as either ≥ 8 cm or < 8 cm), histopathological grade, histological subtype (classified as Osteosarcoma, Chondrosarcoma, Ewing sarcoma, or Other bone sarcoma), presence of lymph node or distant metastasis, surgical resection (Tissue-sparing/Amputaiton), radiation therapy, and chemotherapy. The SEER database utilizes an original histological grading system, which we converted to Federation Nationale des Centres de Lutte le Cancer (FNCLCC) grades [10,16], following previous reports: FNCLCC Grade 1 corresponds to SEER Grade 1, FNCLCC Grade 2 to SEER Grade 2, and

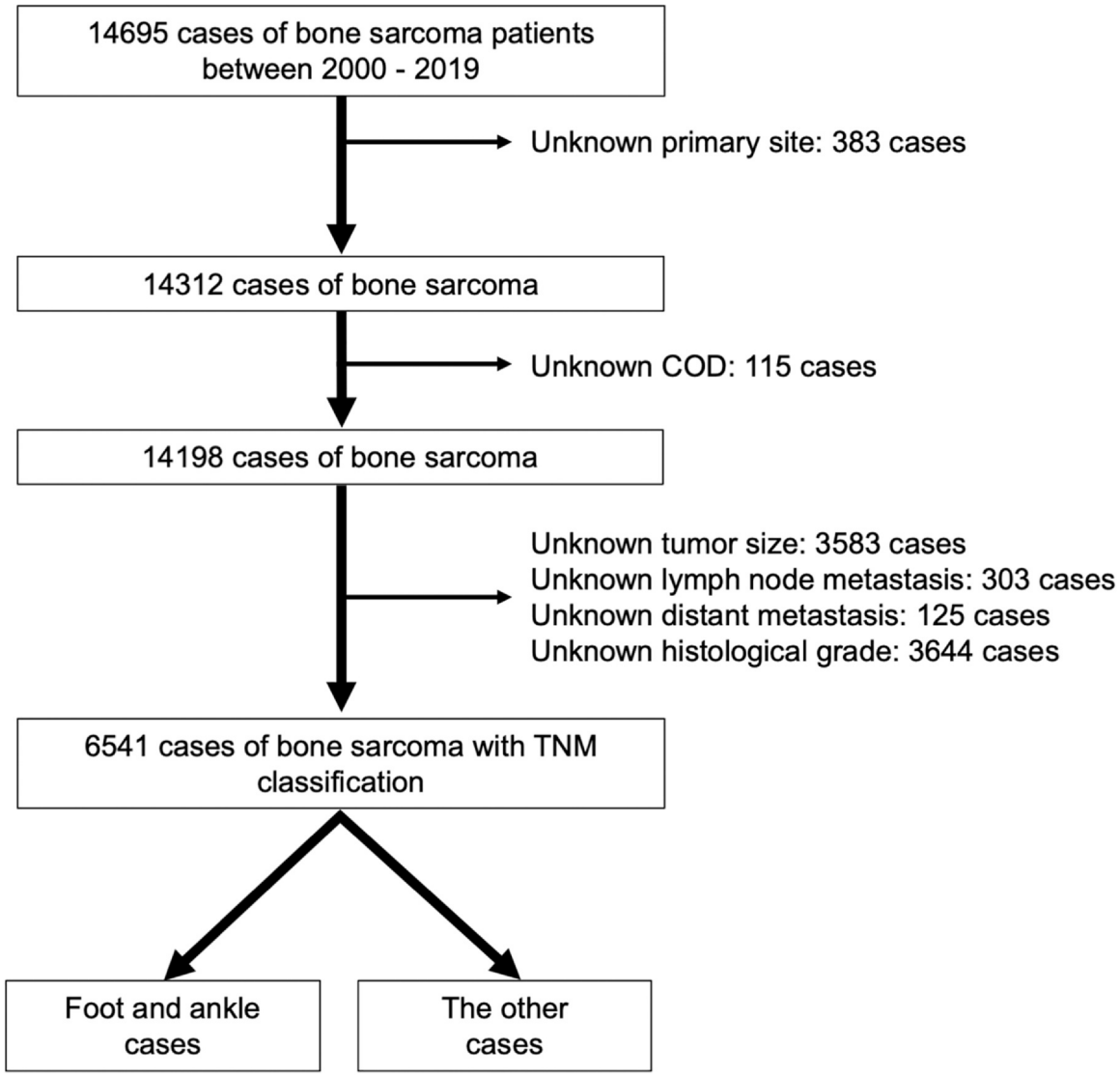

Fig. 1. A flowchart visually illustrates the step-by-step process used to include patients in this specific cohort.

Table 1
Baseline characteristics of all patients with foot-origin primary bone sarcoma. Statistical analysis was conducted using the Wilcoxon test.

	Foot and ankle	The other	P Value
Number	147	6394	
Age			0.10
0–14	11 (7 %)	920 (14 %)	
15–39	51 (35 %)	2096 (33 %)	
40–64	51 (35 %)	2141 (33 %)	
65 +	34 (23 %)	1237 (19 %)	
Sex			
Male	93 (63 %)	3540 (55 %)	0.06
Female	54 (37 %)	2854 (45 %)	
Race			0.80
White	118 (80 %)	5265 (82 %)	
Black	13 (9 %)	605 (9 %)	
Asian or Pacific Islander	14 (10 %)	435 (7 %)	
American Indian/Alaska Native	1 (1 %)	49 (1 %)	
Unknown	1 (1 %)	40 (1 %)	
Tumor size			< 0.0001
8 cm ≧	108 (73 %)	3510 (55 %)	
8 cm <	39 (27 %)	2884 (45 %)	
Lymph node metastasis			0.09
Yes	3 (2 %)	49 (1 %)	
No	144 (98 %)	6345 (99 %)	
Distant metastasis			0.31
Yes	20 (14 %)	976 (15 %)	
No	127 (86 %)	5418 (85 %)	
Histological grade			0.25
Low	26 (18 %)	1236 (19 %)	
High	121 (82 %)	5158 (81 %)	
Histological subtype			0.20
Osteogenic sarcoma	47 (32 %)	2543 (40 %)	
Chondrogenic sarcoma	77 (52 %)	2816 (44 %)	
Notochordal sarcoma	0	89 (1 %)	
Vascular sarcoma	2 (1 %)	49 (1 %)	
Ewings sarcoma	9 (6 %)	348 (5 %)	
Other high-grade sarcoma	1 (1 %)	119 (2 %)	
Other bone sarcoma	11 (7 %)	430 (7 %)	
Surgery			0.04
Yes	140 (95 %)	5766 (90 %)	
No/Unknown	7 (5 %)	628 (10 %)	
Chemotherapy			0.03
Yes	53 (36 %)	2876 (45 %)	
No/Unknown	94 (64 %)	3518 (55 %)	
Radiation			< 0.0001
Yes	4 (3 %)	1049 (16 %)	
No/Unknown	143 (97 %)	5345 (84 %)	

FNCLCC Grade 3 to SEER Grade 3. SEER Grade 1 was classified as low grade, while SEER Grades 2–4 were considered high grade. These variables were chosen for their potential impact on patient outcomes and their relevance in cancer research.

2.4. Statistical analysis

The characteristics of tumors originating in the foot were investigated using the Chi-square test. This test was employed to examine the association between the location of tumor origin and various background factors. Additionally, to investigate the survival of foot-originating tumors, a univariate analysis using the Wilcoxon test and a multivariate analysis using the Cox proportional hazards model were conducted. All data were analyzed using JMP Pro version 16.0.0 statistical software (SAS Institute, Cary, NC).

3. Results

3.1. Study population and tumor characteristics

Out of the total cases reviewed, 6541 met the inclusion criteria. Among these, 147 cases (2.3 %) were identified as originating in the foot. When comparing demographic and clinical characteristics between foot-origin tumors and tumors from other locations, several notable differences and similarities were observed.

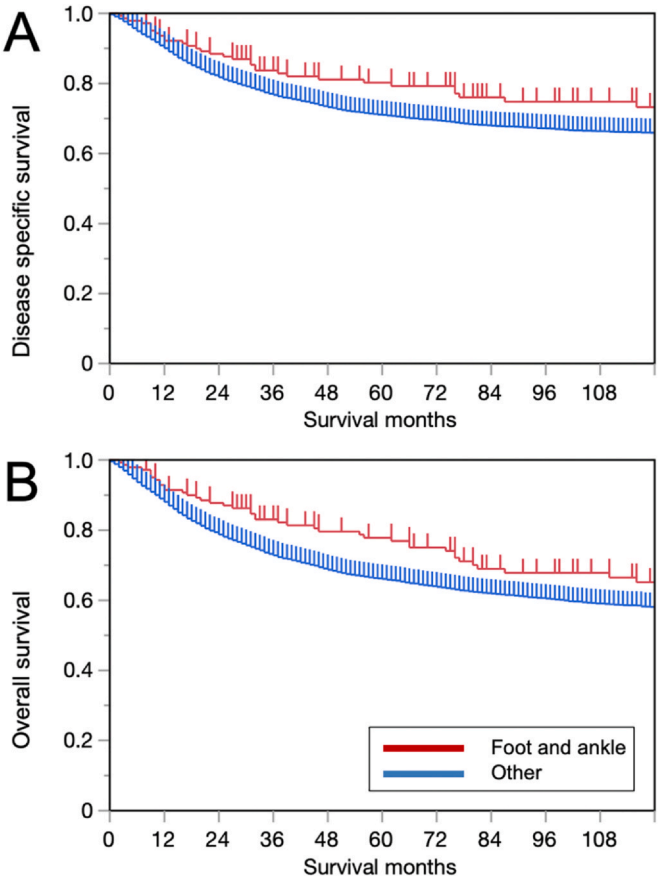

Fig. 2. Kaplan-Meier curves were generated to illustrate disease-specific survival (A) and overall survival (B) in patients with foot originating primary bone sarcoma.

3.2. Demographic and clinical characteristics

In our study, we observed that the distribution of age, gender, race, pathological malignancy grade, lymph node metastasis, distant metastasis and histological subtype did not vary significantly between tumors originating in the foot and those from other locations, as detailed in Table 1. It is noteworthy, however, that substantial differences were discovered in other variables. Specifically, foot-origin tumors were predominantly smaller in size, with a significant majority being 8 cm or less in diameter ($P < 0.0001$). Furthermore, these tumors were more frequently treated with surgical resection, with a higher proportion of cases undergoing amputation as the surgical approach, hinting at either a greater preference for, or a higher feasibility of, surgical approaches in these cases ($P < 0.0001$). In contrast, foot-origin tumors were less often managed with chemotherapy ($P = 0.03$) and radiation therapy ($P < 0.0001$).

In the subclass analysis according to histological subtypes, osteosarcoma and chondrosarcoma showed trends almost identical to the overall trends (Supplemental Table 1 and 2). In Ewing sarcoma, foot-origin tumors had a higher incidence of lymph node metastasis ($P < 0.0001$) and were less likely to receive chemotherapy ($P = 0.0004$). On the other hand, radiation therapy was administered at similar rates for foot-origin tumors and tumors originating in other locations ($P = 0.26$, Supplemental Table 3). In other bone sarcoma, foot-origin tumors had a lower proportion of white patients but a higher proportion of Asian or Pacific Islander patients ($P = 0.01$), and all cases were of high histological malignancy

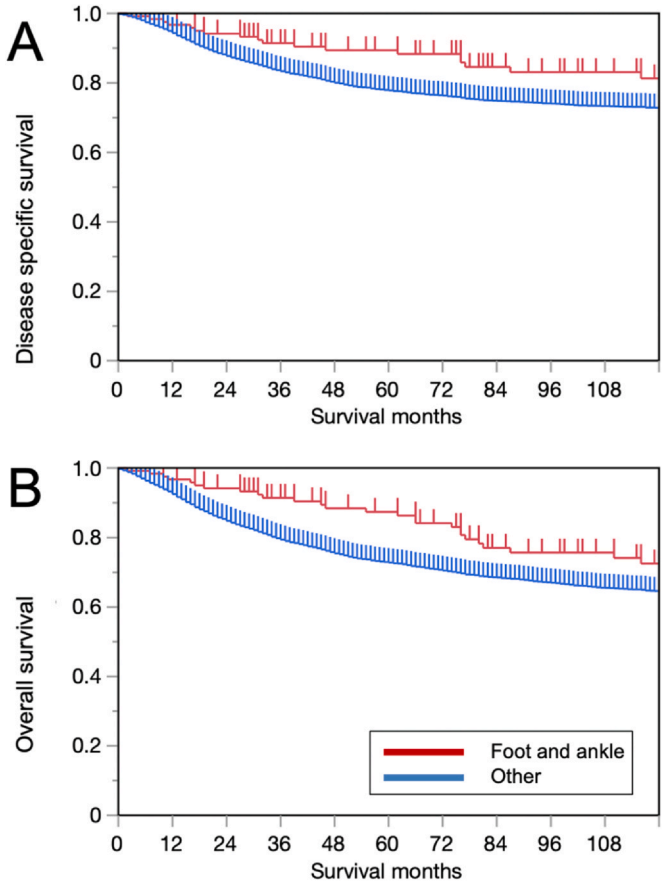

Fig. 3. Kaplan-Meier curves were constructed to depict disease-specific survival (A) and overall survival (B) in patients with localized tumor.

(P = 0.09). Regarding surgery, while a higher proportion of foot-origin tumors were eligible for surgical resection (P = 0.01), the rate of amputation was similar to that of tumors originating in other locations (Supplemental Table 4).

3.3. Survival analysis

The 5-year disease-specific survival (DSS) rate was significantly higher in the group with foot-origin tumors at 80 %, compared to 71 % in the group with non-foot-origin tumors (P = 0.02, Fig. 2A). Similarly, the 5-year overall survival (OS) rate was also significantly higher in the foot-origin group at 80 %, compared to 71 % in the non-foot group (P = 0.04, Fig. 2B). In the subclass analysis according to histological subtypes, the 5-year DSS rate tended to be higher in the group with foot-origin tumors at 77 %, compared to 63 % in the group with non-foot-origin tumors in osteosarcoma (P = 0.06, Supplemental Fig. 1A). Similarly, the 5-year OS rate also showed a tendency to be higher in the foot-origin group at 75 %, compared to 60 % in the non-foot-origin group (P = 0.08, Supplemental Fig. 1B). In chondrosarcoma, the survival of foot-origin tumors was also better compared to non-foot-origin tumors (DSS 93 % in foot vs 81 % in non-foot, P = 0.03; OS 91 % in foot vs 75 % in non-foot, P = 0.01, Supplemental Fig. 2). In Ewing sarcoma, the survival of foot-origin tumors was unfavorable compared to non-foot-origin tumors (DSS 72 % in foot vs 71 % in non-foot, P = 0.02; OS 42 % in foot vs 69 % in non-foot, P = 0.04, Supplemental Fig. 3). In other bone sarcoma, the survival of foot-origin tumors was comparable to non-foot-origin tumors (DSS 41 % in foot vs 66 % in non-foot, P = 0.13; OS 27 % in foot vs 56 % in non-foot, P = 0.31, Supplemental Fig. 4).

Subsequent analyses on patients with localized tumors showed that the 5-year DSS rate was significantly higher in the foot-origin group at 89 %, in comparison to 78 % in the non-foot group (P = 0.02, Fig. 3A). The 5-year OS rate was also significantly higher in the foot-origin group at 87 %, vs 73 % in the non-foot group (P = 0.01, Fig. 3B). Analysis of patients with histologically high-grade tumors yielded interesting results. The 5-year DSS rate was higher in the foot-origin group at 77 %, compared to 66 % in the non-foot group, and this difference was statistically significant (P = 0.03, Fig. 4A). Similarly, the 5-year OS rate was significantly higher in the foot-origin group at 75 %, as opposed to 61 % in the non-foot group (P = 0.01, Fig. 4B).

In the multivariate analysis, after adjusting for various confounding factors, the location of tumor origin (foot vs other locations) did not significantly impact survival outcomes. For overall patients, the hazard ratios (HR) were as follows: DSS: HR 0.8, 95 % Confidence interval (CI): 0.6–1.2; OS: HR 0.8, 95 % CI: 0.6–1.1. In patients with localized tumors, the HRs were: DSS: HR 0.7, 95 % CI: 0.4–1.03; OS: HR 0.7, 95 % CI: 0.5–1.01. Patients with high-grade tumors had HRs of: DSS: HR 0.8, 95 % CI: 0.6–1.2; OS: HR 0.8, 95 % CI: 0.6–1.1. In the subclass analysis according to histological subtypes, though Ewing sarcoma and other bone sarcomas had too few cases to be included in the multivariate analysis, in osteosarcoma, the DSS rate was significantly higher in foot-origin tumors, whereas the OS rate was similar between groups (Osteosarcoma: DSS: HR 0.6, 95 % CI: 0.3–0.97; OS: HR 0.6, 95 % CI: 0.4–1.1). In chondrosarcoma, survival rates were similar between foot-origin tumors and those originating in other locations (Chondrosarcoma: DSS: HR 0.6, 95 % CI: 0.3–1.1; OS: HR 0.6, 95 % CI: 0.4–1.001).

4. Discussion

This study, leveraging the extensive data from the SEER database, reveals several critical insights into the characteristics and outcomes of foot-originating malignant bone tumors. Notably, these tumors are predominantly smaller in size and are more frequently treated with surgical resection. On the other hand, the incidence rate of distant metastasis was similar between tumors originating in the foot and those originating elsewhere. Regarding survival, survivals in entire cohort for tumors originating in the foot was favorable compared to other locations. However, in multivariate analysis, survival rates were equivalent between both groups. These results suggest that the nature of tumors originating in the foot is comparable to those in other locations. However, the smaller tumor diameter and the higher feasibility of surgical resection in tumors originating in the foot suggest that early detection is more achievable in these cases. This leads to better survival outcomes for patients with foot-originating malignant bone sarcoma in the entire cohort.

In the context of primary malignant bone tumors originating from small bones, Ogose et al. reported in their analysis of 111 cases that malignant bone tumors originating from the Hand/Foot were prone to distant metastasis and were associated with decreased survival [12]. On the other hand, survival analysis of primary malignant bone tumors originating from the Hand, using the SEER database, which is one of the largest publicly available cancer databases, reported better survival compared to other sites [5]. In this study, we utilized the SEER database to investigate tumors originating from the foot and demonstrated that survival rates were favorable, comparable to those of tumors originating from the hand. It is possible that previous study suggesting decreased survival in malignant bone tumors originating from small bones lacked sufficient statistical power.

It has been reported that bone and soft tissue tumors originating in the hand are more likely to be detected at a smaller size due to the sparse soft tissue in this area [1,11]. This anatomical characteristic makes it easier for patients to become aware of symptoms, leading to earlier detection. It has become clear through this study that the

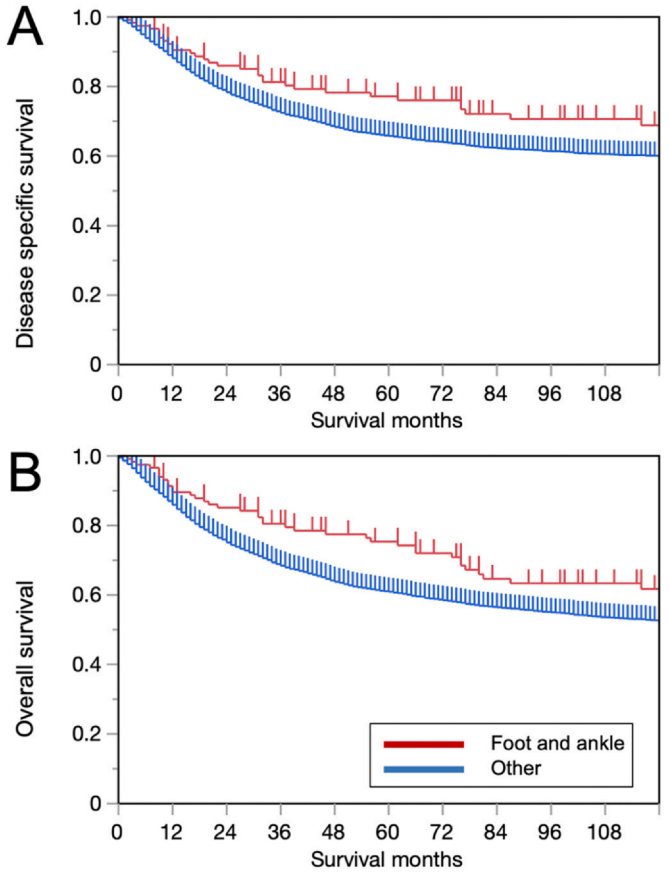

Fig. 4. Kaplan-Meier curves were constructed to depict disease-specific survival (A) and overall survival (B) in patients with histological high-grade tumor.

same applies to tumors originating in the foot. These tumors are often first diagnosed by orthopedic foot surgeons [17], and it is considered necessary to bear this in mind during routine clinical practice.

This study, despite its comprehensive analysis of foot-originating malignant bone tumors using the SEER database, encounters several limitations. Firstly, the inherent rarity of these tumors poses a significant challenge to drawing broad generalizations, as the low incidence rate restricts the size of the sample and thus the statistical power of the findings. Secondly, the retrospective nature of the study, relying on historical data from a registry, may lead to inherent biases, such as selection bias and information bias, particularly in the accuracy and completeness of recorded data. Thirdly, this study identified tumors originating in the foot according to the ICD-O code, and no further information on the location was obtained. Future investigations will need to include such information. Lastly, the study's focus on foot-originating tumors within the United States limits its geographic and demographic representativeness, raising concerns about the applicability of the findings to other populations or healthcare settings with different diagnostic and treatment approaches. This geographic limitation may also influence the observed survival rates and treatment choices, as they are subject to the specific medical practices and healthcare accessibility within the United States. These limitations underscore the need for cautious interpretation of the results and suggest a potential avenue for future research in more diverse settings and with prospective study designs.

In conclusion, this study contributes valuable insights into the characteristics and management of foot-originating malignant bone tumors. Key findings include the smaller size of these tumors and their frequent treatment via surgical resection, with favorable survival rates compared to tumors in other locations. However, these results should be interpreted with caution due to the study's limitations, such as its retrospective design, the rarity of the tumor type, and its geographic focus on the United States. These factors may affect the generalizability of the findings. Further research in more diverse settings is necessary to validate and expand upon these observations.

Ethical Considerations

Ethical approval for this study was waived by Hokkaido university hospital review board because the study was conducted in accordance with the principles of secondary data use, ensuring that patient confidentiality and privacy were maintained throughout the research process.

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Author contributions

MM was involved in the design of the study; performed the clinical assessment, analysis, and interpretation of data; and drafted and revised the manuscript. TO and RF assisted with data interpretation and revised the manuscript for important intellectual content. KI, MH, TE, YH, EK, and NI were involved in data acquisition and revised the manuscript critically for important intellectual content. All authors have read and approved the final manuscript.

Declaration of Competing Interest

None.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.fas.2024.05.016.

References

[1] Brien EW, Terek RM, Geer RJ, Caldwell G, Brennan MF, Healey JH. Treatment of soft-tissue sarcomas of the hand. J Bone Jt Surg Am 1995;77(4):564–71. https://doi.org/10.2106/00004623-199504000-00009
[2] Folkert IW, Devalaraja S, Linette GP, Weber K, Haldar M. Primary bone tumors: challenges and opportunities for CAR-T therapies. J Bone Min Res 2019;34(10):1780–8. https://doi.org/10.1002/jbmr.3852
[3] Gatta G, Capocaccia R, Botta L, et al. Burden and centralised treatment in Europe of rare tumours: results of RARECAREnet-a population-based study. Lancet Oncol 2017;18(8):1022–39. https://doi.org/10.1016/S1470-2045(17)30445-X
[4] Horvai A, Unni KK. Premalignant conditions of bone. J Orthop Sci 2006;11(4):412–23. https://doi.org/10.1007/s00776-006-1037-6
[5] Ike S, Matsuoka M, Onodera T, et al. Primary malignant osseous neoplasms in the hand. Anticancer Res 2022;42(3):1635–40. https://doi.org/10.21873/anticanres.15639
[6] Jawad MU, Farhan SB, Haffner MR, et al. Malignant neoplasms originating from the bones of the foot: predilection of hematological malignancies and sex-related and ethnic disparities in amputation. J Surg Oncol 2021;124(8):1468–76. https://doi.org/10.1002/jso.26633
[7] Kobayashi H, Zhang L, Hirai T, Tsuda Y, Ikegami M, Tanaka S. Comparison of clinical features and outcomes of patients with leiomyosarcoma of bone and soft tissue: a population-based cohort study. Jpn J Clin Oncol 2022;52(2):143–50. https://doi.org/10.1093/jjco/hyab176
[8] Lewin J, Puri A, Quek R, et al. Management of sarcoma in the Asia-Pacific region: resource-stratified guidelines. Lancet Oncol 2013;14(12):e562–70. https://doi.org/10.1016/S1470-2045(13)70475-3

[9] Matsuoka M, Onodera T, Yokota I, et al. Does primary tumor resection in patients with metastatic primary mobile vertebral column sarcoma improve survival? World Neurosurg 2022. https://doi.org/10.1016/j.wneu.2022.04.047
[10] Matsuoka M, Onodera T, Yokota I, et al. Comparison of clinical features between patients with bone and soft tissue fibrosarcomas. J Surg Oncol 2022;126(7):1299–305. https://doi.org/10.1002/jso.27049
[11] McPhee M, McGrath BE, Zhang P, Driscoll D, Gibbs J, Peimer C. Soft tissue sarcoma of the hand. J Hand Surg Am 1999;24(5):1001–7. https://doi.org/10.1053/jhsu.1999.1001
[12] Ogose A, Unni KK, Swee RG, May GK, Rowland CM, Sim FH. Chondrosarcoma of small bones of the hands and feet. Cancer 1997;80(1):50–9.
[13] Ogura K, Higashi T, Kawai A. Statistics of bone sarcoma in Japan: report from the bone and soft tissue tumor registry in Japan. J Orthop Sci 2017;22(1):133–43. https://doi.org/10.1016/j.jos.2016.10.006
[14] Strauss SJ, Frezza AM, Abecassis N, et al. Bone sarcomas: ESMO-EURACAN-GENTURIS-ERN PaedCan Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol 2021;32(12):1520–36. https://doi.org/10.1016/j.annonc.2021.08.1995
[15] Toepfer A, Harrasser N, Recker M, et al. Distribution patterns of foot and ankle tumors: a university tumor institute experience. BMC Cancer 2018;18(1):735. https://doi.org/10.1186/s12885-018-4648-3
[16] Trojani M, Contesso G, Coindre JM, et al. Soft-tissue sarcomas of adults; study of pathological prognostic variables and definition of a histopathological grading system. Int J Cancer 1984;33(1):37–42. https://doi.org/10.1002/ijc.2910330108
[17] Tsuda Y, Fujiwara T, Stevenson JD, Abudu A. Surgical outcomes of bone sarcoma of the foot. Jpn J Clin Oncol 2021;51(10):1541–6. https://doi.org/10.1093/jjco/hyab118
[18] Wang Z, Li S, Li Y, et al. Prognostic factors for survival among patients with primary bone sarcomas of small bones. Cancer Manag Res 2018;10:1191–9. https://doi.org/10.2147/CMAR.S163229
[19] Xu Y, Shi F, Zhang Y, et al. Twenty-year outcome of prevalence, incidence, mortality and survival rate in patients with malignant bone tumors. Int J Cancer 2024;154(2):226–40. https://doi.org/10.1002/ijc.34694