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ORIGINAL ARTICLE

Landscape of ultra-rare sarcomas: a nationwide study for epidemiology and prognosis

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Background: The concept of 'ultra-rare sarcoma' was established to raise awareness of the clinical challenges resulting from its rarity. Given the novelty of this classification and the consequent paucity of data, this study aimed to investigate the epidemiology and prognosis of ultra-rare sarcomas.

Design: We analyzed data from the Bone and Soft Tissue Tumor Registry in Japan from 2001 to 2019, comparing ultra-rare and non-ultra-rare sarcomas. To assess the prognostic impact of ultra-rare sarcomas, we used Kaplan—Meier survival analysis with propensity score matching, multivariate analysis, and a machine learning technique known as random survival forest.

Results: Among the 22 821 patients analyzed, ultra-rare sarcomas accounted for 18.9% of the cases. Ultra-rare bone sarcomas were older than non-ultra-rare bone sarcomas (mean age: 57.6 versus 39.2 years, $P < 0.001$), while ultra-rare soft tissue sarcomas appeared in younger patients (mean age: 49.4 versus 62.2 years, $P < 0.001$). For patients >80 years old with bone sarcomas and those <20 years old with soft tissue sarcomas, ultra-rare sarcomas constituted approximately half of the cases. Survival analysis indicated that ultra-rare bone sarcomas were associated with longer survival ($P = 0.022$), whereas ultra-rare soft tissue sarcomas showed no significant difference in overall survival ($P = 0.052$). When stratified by age, however, patients <40 years old with ultra-rare soft tissue sarcomas had shorter survival ($P < 0.001$). Multivariate analysis indicated hazard ratios of 0.73 for ultra-rare bone and 1.25 for ultra-rare soft tissue sarcomas. Random survival forest showed that the importance of ultra-rare sarcomas was relatively low compared with other parameters.

Conclusion: Ultra-rare sarcomas are more common among older bone sarcoma patients and younger soft tissue sarcoma patients. Young patients with ultra-rare soft tissue sarcomas have a significantly worse prognosis. Overall, while ultra-rare sarcomas have a generally minor impact on prognosis, their effects are more pronounced in specific age groups.

Key words: ultra-rare sarcoma, epidemiology, nationwide study, prognosis, propensity score matching

INTRODUCTION

Rare cancers are characterized by low incidence rates, although specific definitions may vary by country. In the USA, cancers with <15 cases per 100 000 individuals per year are classified as rare,[1] while in Europe, the threshold is <6 cases 100 000 individuals.[2] Research has classified 12 families of rare cancers, with broad consensus across Europe, categorizing sarcomas, including both bone and soft tissue types, within one of these families.[3] Among these rare sarcomas, the concept of 'ultra-rare sarcoma (URS)' has been established recently, defined as bone and soft tissue sarcomas with an annual incidence rate of fewer than one case per one million individuals.[4] Its 'ultra-rarity' poses significant challenges for diagnosis, understanding disease biology, generating clinical evidence for new drug development, and achieving formal authorization for novel therapies.[4] There are 22 types of bone sarcomas and 56 types of soft tissue sarcomas classified as ultra-rare, comprising ~20% of all bone and soft tissue sarcomas.[4] While it is known that the prognosis of rare cancers is generally worse than that of common cancers,[5] the prognosis for URS remains uncertain. This uncertainty is due to the relatively recent classification of URS and the consequent lack of comprehensive epidemiological data.

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In this study, we present (i) the epidemiology of URS and (ii) its impact on patient prognosis, based on data from a comprehensive nationwide database.

MATERIAL AND METHODS

Data collection

The Bone and Soft Tissue Tumor Registry in Japan is a nationwide, organ-specific cancer registry for bone and soft tissue tumors in Japan. Established in the 1950s, the registry is organized and funded by the Japanese Orthopaedic Association and promoted by the National Cancer Center in Japan.[6,7] Data from January 2001 to December 2019 were collected, excluding cases where the patient received treatment elsewhere, the pathological diagnosis was missing, the diagnosis was metastasis of carcinoma, or the diagnosis was inconclusive. The collected data included the following: date of first visit to the medical institution, age, sex, histologic diagnosis, histological malignancy, treatment details, TNM (tumor—node—metastasis) stage,[8] date of last follow-up, and outcome at the latest follow-up. Treatments were administered in accordance with Japanese guidelines.[9] This study was approved by the Musculoskeletal Tumor Committee of the Japanese Orthopaedic Association and the Institutional Review Board (IRB) of Kyushu University, Japan (IRB number 21161—00). This study was conducted in accordance with the Declaration of Helsinki.

Diagnosis and ultra-rare sarcoma definition

Pathologists at each facility determined histological diagnosis and malignancy according to the World Health Organization (WHO) classification.[10] As mentioned earlier, patients with diagnoses not listed in the WHO classification were excluded from the study due to inconclusive diagnosis. For histological types for which the WHO diagnostic criteria changed during the data collection period, we revised them to the corresponding updated histological types. The definition of URS was based on the list of histological types published in the consensus paper.[4]

Propensity score matching

Propensity scores were calculated as described previously.[11] All potential variables, including age, sex, TNM stage, histological malignancy, resection of the primary tumor, chemotherapy, and radiotherapy, were selected for analysis. Patients with missing data for any of these factors were excluded from the analysis. The R package *MatchIt* (version 4.5.5) was used to match patients from the non-URS and URS groups with equivalent propensity scores using the nearest-neighbor method.

Statistical analysis

Welch's *t*-test was used to compare the averages of numerical variables between the two groups, while Fisher's exact test was used to compare the proportions of categorical variables among the groups. Missing values were excluded from these tests. Overall survival (OS) was defined as the time from the date of the first hospital visit to the date of death. To account for potential human error during registration, the Smirnov—Grubbs test was conducted for survival time, and patients identified as outliers were excluded from the analysis. OS was censored at the last follow-up date if the patient was known to be alive. OS was estimated using the Kaplan—Meier method and compared with the log-rank test. The Cox proportional hazards model was used to assess the association between potential risk factors and OS, using the same factors as in the propensity score calculations. Patients with any missing values in the variables were excluded from this analysis. Random survival forest analysis was carried out using the R package *randomForestSRC* (version 3.2.3) following the user manual.[12] The number of trees was set to 500. A P value < 0.05 was considered statistically significant in all tests. All statistical analyses were carried out using R (version 4.2.1, The R Foundation for Statistical Computing, Vienna, Austria) and RStudio (version 2023.12.1+402).

RESULTS

Sampled patients and ratio of ultra-rare sarcomas

In total, 50 550 patients with malignant tumors were initially registered. After applying exclusion criteria, 22 821 patients were included for analysis, comprising 5820 bone sarcoma patients and 17 001 soft tissue sarcoma patients (Figure 1). URS accounted for 18.9% of all patients, with 25.8% among bone sarcomas and 16.5% among soft tissue sarcomas (Figure 2A). Regarding histology, chordoma and undifferentiated pleomorphic sarcoma were the most prevalent types among ultra-rare bone sarcomas (29.8% and 25.1%, respectively) (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2025.105097), while pleomorphic liposarcoma and extraskeletal myxoid chondrosarcoma were the most prevalent among ultra-rare soft tissue sarcomas (11.2% and 9.6%, respectively) (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2025.105097).

Characteristics and outcomes

All characteristics and outcomes are shown in Table 1.

Bone sarcoma

Patients with URS were significantly older on average (57.6 years) compared with non-URS patients (39.2 years, $P < 0.001$). Non-URS patients exhibited a bimodal age distribution, peaking at 15 and 70 years, whereas the URS group showed a unimodal distribution centered around 70 years (Figure 2B). Sex distribution did not differ significantly between the groups ($P = 0.25$). In terms of tumor stage, a higher percentage of URS patients were diagnosed at stage I (29.7% versus 23.8% non-URS, $P < 0.001$). Conversely, non-URS patients were more prevalent at stage II (59.9% versus 53.7% for URS). High-grade sarcomas were more frequent in non-URS cases (75.5% versus 68.2%, $P < 0.001$). Treatment

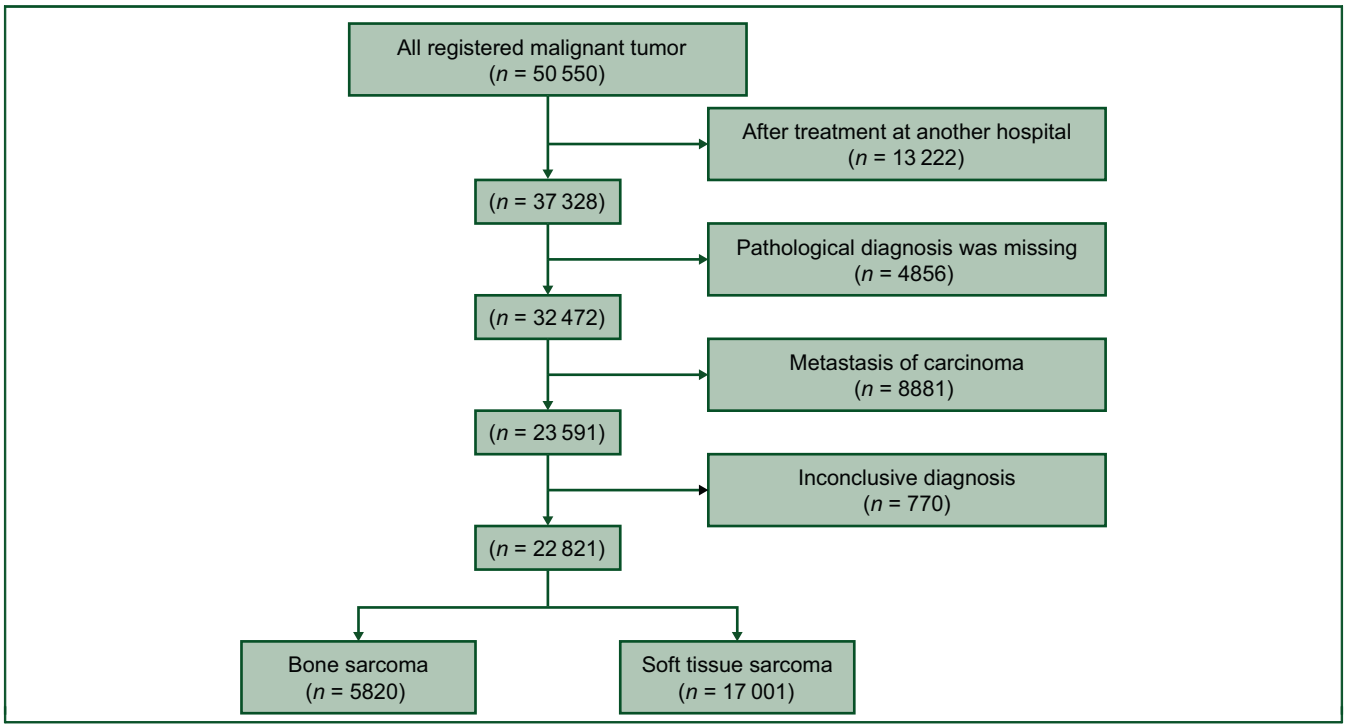

Figure 1. **Study sample flowchart.**

patterns differed significantly between the groups: primary surgical resection and chemotherapy were more frequently utilized in non-URS patients (77.3% and 54.9%, respectively) compared with those with URS (57.7% and 30.8%, $P < 0.001$ for both). Conversely, URS patients were more likely to receive radiotherapy (36.3% versus 17.0% for non-URS, $P < 0.001$). Regarding disease status, non-URS patients had a higher percentage of individuals with no evidence of disease (NED) compared with the URS group (62.2% versus 47.4%, $P < 0.001$). In contrast, the URS group had a higher percentage of patients classified as alive with disease (AWD) (30.6% versus 15.7%, $P < 0.001$). Additionally, a higher percentage of non-URS patients underwent limb-salvaging procedures compared with URS patients (84.3% versus 82.5%, $P < 0.001$).

Soft tissue sarcoma

On average, patients with URS were younger (49.4 years) compared with non-URS patients (62.2 years, $P < 0.001$). The age distribution of the non-URS group exhibited a single peak around 70 years, whereas the URS group exhibited a more evenly distributed pattern (Figure 2C). There was a slight female predominance in the URS group compared with the non-URS group (46.6% versus 43.6%, $P = 0.004$). Regarding the tumor stage, a higher proportion of non-URS patients were diagnosed at stage I (39.1% versus 19.2% for URS). In contrast, URS patients were more frequently diagnosed at stage IV (26.3% versus 7.8% for non-URS, $P < 0.001$). High-grade sarcomas were more prevalent in URS cases than non-URS cases (80.0% versus 60.6%, $P < 0.001$). Treatment patterns also differed significantly: non-URS

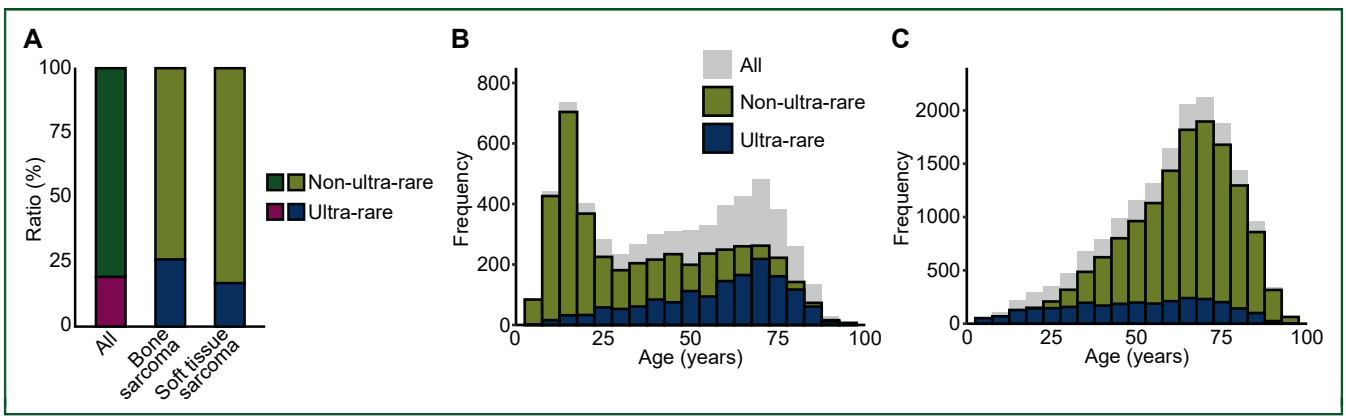

Figure 2. **Ratio of ultra-rare sarcoma (A), age distribution for bone sarcoma (B), and soft tissue sarcoma (C).**

Table 1. Patient characteristics and outcome

Characteristic	Non-ultra-rare (n = 4318)	Bone sarcoma	P value	Non-ultra-rare (n = 14 198)	Soft tissue sarcoma	P value
		Ultra-rare (n = 1502)			Ultra-rare (n = 2 805)	
Age (years), mean (SD)	39.2 (23.8)	57.6 (19.0)	<0.001[a]	62.2 (16.7)	49.4 (22.0)	<0.001[a]
Sex, n (%)			0.25[b]			0.004[b]
Female	1892 (43.8)	632 (42.1)		6190 (43.6)	1307 (46.6)	
Male	2426 (56.2)	870 (57.9)		8008 (56.4)	1498 (53.4)	
TNM stage, n (%)			<0.001[b]			<0.001[b]
I	947 (23.8)	389 (29.7)		5152 (39.1)	484 (19.2)	
II	2383 (59.9)	704 (53.7)		2431 (18.5)	573 (22.7)	
III	66 (1.7)	29 (2.2)		4560 (34.6)	803 (31.8)	
IV	580 (14.6)	189 (14.4)		1032 (7.8)	664 (26.3)	
Unknown	342	191		1023	281	
Histological malignancy, n (%)			<0.001[b]			<0.001[b]
High grade	3128 (75.5)	936 (68.2)		8257 (60.6)	2116 (80.0)	
Low grade	1013 (24.5)	436 (31.8)		5363 (39.4)	528 (20.0)	
Unknown	177	130		578	161	
Primary resection, n (%)			<0.001[b]			<0.001[b]
Yes	3318 (77.3)	866 (57.7)		11 606 (82.0)	2062 (74.0)	
No	976 (22.7)	635 (42.3)		2556 (18.0)	724 (26.0)	
Unknown	24	1		36	19	
Chemotherapy, n (%)			<0.001[b]			<0.001[b]
Yes	2359 (54.9)	462 (30.8)		3306 (23.3)	1212 (43.6)	
No	1938 (45.1)	1040 (69.2)		10 853 (76.7)	1568 (56.4)	
Unknown	21	0		39	25	
Radiotherapy, n (%)			<0.001[b]			<0.001[b]
Yes	730 (17.0)	542 (36.3)		2729 (19.3)	783 (28.2)	
No	3565 (83.0)	953 (63.7)		11 437 (80.7)	1992 (71.8)	
Unknown	23	7		32	30	
Final outcome, n (%)			<0.001[b]			<0.001[b]
NED	2570 (62.2)	688 (47.4)		9574 (70.0)	1426 (53.5)	
AWD	649 (15.7)	443 (30.6)		2131 (15.6)	569 (21.3)	
DOD	859 (20.8)	293 (20.2)		1702 (12.4)	640 (24.0)	
DOOD	55 (1.3)	26 (1.8)		279 (2.0)	31 (1.2)	
Unknown	185	52		512	139	
Limb salvage, n (%)			<0.001[b]			<0.001[b]
Salvage	3486 (84.3)	1196 (82.5)		12 573 (91.9)	2243 (84.1)	
Amputation	409 (9.9)	98 (6.8)		463 (3.4)	178 (6.7)	
Others	238 (5.8)	156 (10.8)		650 (4.7)	245 (9.2)	
Unknown	185	52		512	139	

'Unknown' cases were excluded in the calculation of percentage distribution and statistical test.
AWD, alive with disease; DOD, died of disease; DOOD, died of other disease; NED, no evidence of disease; SD, standard deviation; TNM, tumor—node—metastasis.
[a]Welch's t-test.
[b]Fisher's exact test.

patients had a higher likelihood of undergoing primary surgical resection compared with URS patients (82.0% versus 74.0%, $P < 0.001$). In contrast, URS patients were more likely to receive chemotherapy (43.6% versus 23.3%, $P < 0.001$) and radiotherapy (28.2% versus 19.3%, $P < 0.001$). In terms of disease status, non-URS patients were more commonly classified as NED compared with URS patients (70.0% versus 53.5% URS, $P < 0.001$). Conversely, URS patients were more frequently classified as AWD (21.3% versus 15.6%, $P < 0.001$) or having died of disease (24.0% versus 12.4%, $P < 0.001$) compared with non-URS patients. Furthermore, a higher percentage of non-URS patients underwent limb-salvaging procedures compared with URS patients (91.9% versus 84.1% URS, $P < 0.001$).

Survival time analysis

The five-year survival rate was 69.7% [95% confidence interval (CI) 68.1% to 71.3%] for all bone sarcomas (Figure 3A) and 76.0% (95% CI 75.0% to 76.9%) for all soft tissue sarcomas (Figure 3B). When stratifying the groups into non-URS and URS, there was no significant difference in OS for bone sarcoma ($P = 0.076$) (Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2025.105097). Specifically, the 5-year survival rate was 70.2% (95% CI 68.4% to 72.1%) for non-ultra-rare bone sarcomas and 68.2% (95% CI 64.9% to 71.6%) for ultra-rare bone sarcomas. In contrast, OS was significantly worse in the URS group for soft tissue sarcomas ($P < 0.0001$) (Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2025.105097). The 5-year survival rate was 78.2% (95% CI 77.2% to 79.2%) for non-ultra-rare soft tissue sarcomas and 64.9% (95% CI 62.5% to 67.5%) for ultra-rare soft tissue sarcomas. Propensity score matching was carried out to address biases in patient characteristics. After matching, 1258 pairs of bone sarcoma and 2372 pairs of soft tissue sarcoma were selected for analysis. Patient characteristics following propensity matching are detailed in Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2025.105097. In the adjusted survival time

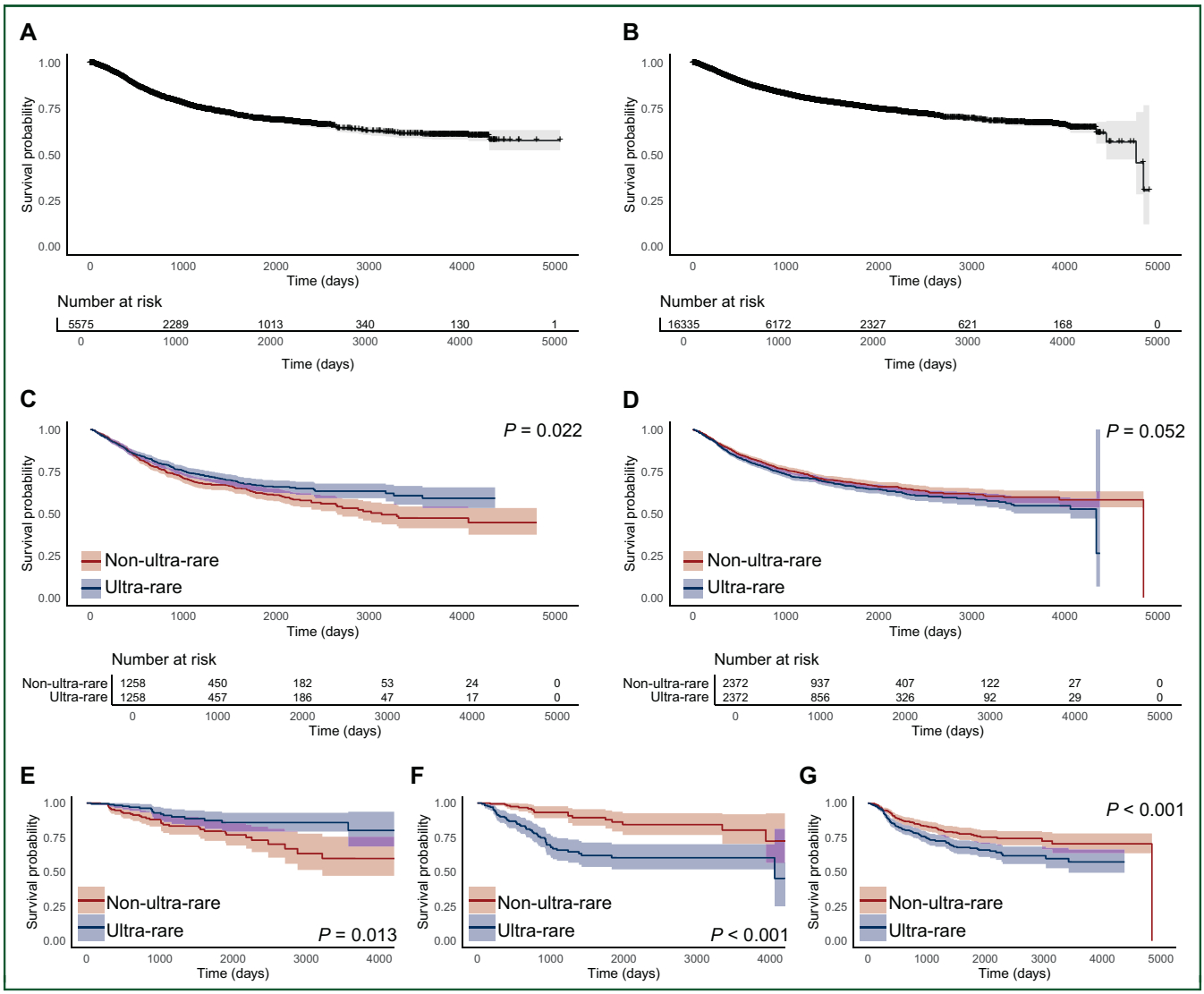

Figure 3. Overall survival for all bone sarcoma patients (A) and all soft tissue sarcoma patients (B). Overall survival for propensity score-matched patients of bone sarcoma (C) and soft tissue sarcoma (D). (E)-(G) represent the overall survival of propensity score-matched patients stratified by age: bone sarcoma patients aged 20-39 years (E), soft tissue sarcoma patients under 20 years of age (F), and soft tissue sarcoma patients aged 20-39 years (G). *P* value was calculated using log-rank test. The light color bands indicate the 95% confidence intervals.

analysis, URS showed significantly longer survival durations in bone sarcomas ($P = 0.022$) (Figure 3C). No statistically significant difference, however, was observed in soft tissue sarcomas ($P = 0.052$) (Figure 3D). Given that previous studies indicate worse prognoses for rare cancers as patients age,[2] we conducted a survival analysis stratified by age, applying propensity score matching to account for biases in patient characteristics. Ultra-rare bone sarcomas exhibited significantly longer survival durations in the 20-39-year-old subgroup ($P = 0.013$) (Figure 3E). Conversely, ultra-rare soft tissue sarcomas showed significantly shorter survival durations in the under-40-year-old subgroup ($P < 0.0001$ for under 20 years, $P = 0.0007$ for 20-39 years) (Figure 3F and G). In the over-40-year-old subset, no significant differences were observed between the URS and non-URS groups (Supplementary Figure S2, available at https://doi.org/10.1016/j.esmoop.2025.105097).

Multivariate analysis to estimate risks

To assess the relative risk factors, hazard ratios (HR) were calculated using a Cox proportional hazards regression model (Figure 4). TNM stage IV at the initial visit demonstrated the highest HR in both groups (8.29, 95% CI 4.65-14.79 for bone sarcoma, 10.26, 95% CI 6.47-16.26 for soft tissue sarcoma), whereas surgical resection of the primary lesion showed the lowest HR in both groups (0.58, 95% CI 0.50-0.67 for bone sarcoma, 0.47, 95% CI 0.43-0.52) for soft tissue sarcoma). In bone sarcoma, URS demonstrated a lower HR compared with non-URS (0.73, 95% CI 0.63-0.85). In contrast, in soft tissue sarcoma, URS demonstrated a higher HR (1.25, 95% CI 1.13-1.38). To further explore differences in prognostic factors between URS and non-URS, subgroup analyses were conducted separately for each group (Supplementary Figure S3,

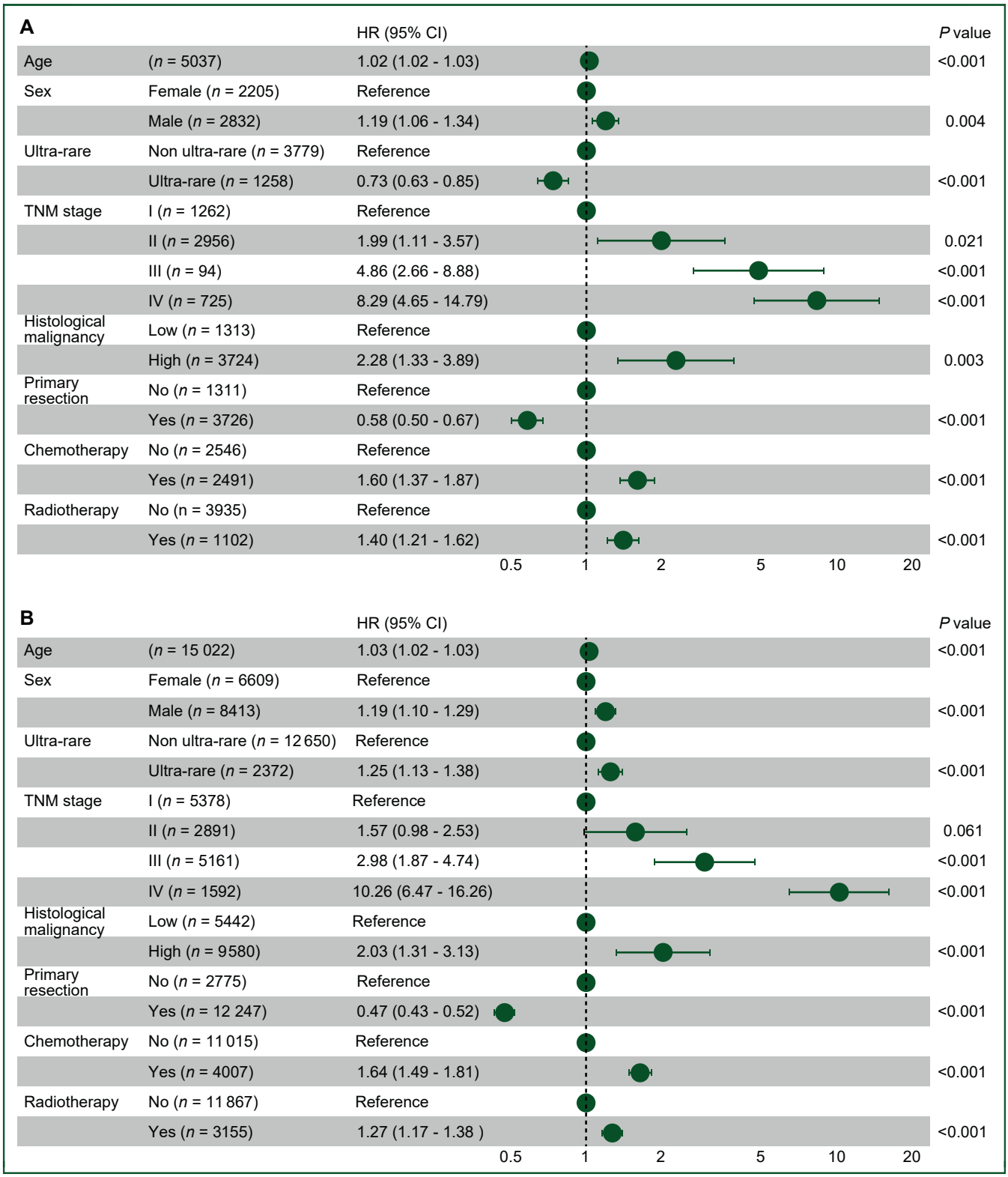

Figure 4. Multivariate analysis of bone sarcoma (A) and soft tissue sarcoma (B) for potential prognostic factors using Cox proportional hazards model.
CI, confidence interval; HR, hazard ratio; TNM, tumor—node—metastasis.

available at https://doi.org/10.1016/j.esmoop.2025.105097). While most categories showed no differences between the URS and non-URS groups, in bone sarcomas, surgical resection of the primary lesion was associated with a significantly lower HR in the non-URS subgroup (0.49, 95% CI 0.41-0.58), whereas no significant association was observed in the URS subgroup (0.97, 95% CI 0.73-1.29).

Random survival forest analysis

Finally, we utilized random survival forest analysis to determine the relative importance of each variable in predicting prognosis across all factors. Random survival forest is a machine learning technique adapted from random forest for survival analysis of right-censored data, providing a fully nonparametric measure of variable importance.[12] The analysis indicated that the TNM stage exhibited the highest importance among all variables (0.27 for both bone sarcoma and soft tissue sarcoma). In contrast, URS showed relatively low importance in both bone sarcoma and soft tissue sarcoma (0.012 and 0.005, respectively) (Supplementary Figure S4, available at https://doi.org/10.1016/j.esmoop.2025.105097).

DISCUSSION

In this study, we explored the epidemiology and prognosis of URS. Our findings revealed the characteristic differences between URS and non-URS groups, revealing that ultra-rare bone sarcomas generally exhibit a favorable prognosis compared with non-ultra-rare bone sarcomas. In contrast, ultra-rare soft tissue sarcomas show a slightly elevated HR. Additionally, the impact of ultra-rare status on prognosis appears to be less significant compared with other prognostic factors. To the best of our knowledge, this study represents the first comprehensive investigation into the epidemiology and prognosis of URS, offering novel insights into their influence on patient outcomes. The robustness of our research is supported by substantial sample sizes and the application of advanced statistical methodologies. The multifaceted approach, including propensity score matching for survival analysis, Cox regression for multivariate analysis, and random survival forest for assessing variable importance, enhances the reliability and depth of our findings.

Discordant diagnoses are reported in 8%-14% of sarcoma cases, attributed in part to the rarity of sarcomas.[13,14] The infrequency of encounters with URS in clinical practice can contribute to misdiagnoses. Our study revealed that URS constitute a notable proportion, ∼20% of the entire sarcoma population, consistent with previous findings.[4] Specifically, among patients >80 years old with bone sarcomas and those <20 years old with soft tissue sarcomas, URS and non-URS cases are nearly equally represented, as illustrated in Figure 2. These findings underscore the importance of considering URS as a diagnostic possibility, particularly in elderly patients presenting with bone sarcomas and young patients with soft tissue sarcomas.

Focusing on treatment, the gold standard for sarcoma management in Japan is surgical resection whenever resectable.[9] For unresectable tumors, chemotherapy and/or radiotherapy are typically administered. While certain sarcomas routinely undergo chemotherapy as part of their treatment, in many cases, surgical resection alone is considered sufficient. In other words, inoperable patients are more likely to receive chemotherapy or radiotherapy, which leads to a poorer prognosis as shown in Figure 4. This trend can also be inferred from the proportion of treatments. URS patients underwent surgical resection less frequently than non-URS patients in both bone and soft tissue sarcomas. Regarding soft tissue sarcoma, this tendency is probably due to the higher proportion of URS patients with advanced TNM stage sarcoma compared with non-URS patients, as shown in Table 1. In contrast, the proportion of TNM stages in bone sarcoma was not as skewed as that in soft tissue sarcoma; nevertheless, the frequency of surgical resection was low. One possible explanation is that URS patients tend to be older than non-URS patients, as shown in Figure 2, which may have led to an increased proportion of inoperable patients. These biases in treatments and patient characteristics can impact prognosis, emphasizing the importance of adjustment by propensity score in ensuring more robust and reliable results.

In terms of the prognosis, it is generally reported that rare cancers tend to have poorer outcomes compared with more common cancers.[5] Therefore, we initially expected that URS would demonstrate worse prognoses than non-URS, akin to other rare cancers. Our study, however, revealed a contrary finding: while URS showed a worse prognosis in soft tissue sarcomas, they exhibited a better prognosis in bone sarcomas. The unexpected result may be attributed to the significant variability in prognosis among different histological types within URS. For instance, our analysis indicated that the overall 5-year survival rate for all ultra-rare bone sarcomas was 68.2%. Notably, chordoma, which comprises 29.8% of ultra-rare bone sarcomas, demonstrated a 5-year survival rate of 67.5%.[15] In contrast, another type, dedifferentiated chondrosarcoma, accounting for 7.9% of ultra-rare bone sarcomas, exhibited a notably lower survival rate of 18%.[16]

Our analysis also examined the impact of being classified as URS on prognosis relative to other factors. Multivariate analysis revealed an HR of 0.73 for bone sarcoma and 1.25 for soft tissue sarcoma, indicating statistically significant differences, but with HRs close to 1, suggesting a relatively modest impact on prognosis. This finding was further supported by random survival forest analysis, which identified ultra-rare status as the second least important factor for bone sarcoma prognosis and the least important factor for soft tissue sarcoma prognosis. The high importance of TNM stage and age in predicting prognosis,[17–19] as indicated in our analysis, validates our analysis. We speculate that the moderate impact of URS on prognosis could be attributed to the inherent heterogeneity of sarcomas[20] and limitations in available data, such as the absence of Eastern Cooperative Oncology Group performance status (ECOG PS) and incomplete information on primary tumor depth. ECOG PS was not recorded in the registry, and depth data were missing in a significant portion of cases, necessitating their exclusion from this analysis. Including these factors could potentially alter the perceived importance of URS. Nevertheless, our survival analysis revealed that the impact of URS varies among different age groups. Specifically, we observed a detrimental effect of URS on the prognosis of patients <40 years old with soft tissue sarcoma. To further

investigate this finding, the histological subtypes of soft tissue sarcoma patients <40 years old are summarized in Supplementary Table S4, available at https://doi.org/10.1016/j.esmoop.2025.105097. Myxoid round cell liposarcoma and synovial sarcoma constituted the majority of non-URS cases (28.9% and 25.8%, respectively); in contrast, extraskeletal Ewing sarcoma, alveolar soft part sarcoma, and alveolar rhabdomyosarcoma were predominant in the URS group (15.0%, 14.8%, and 13.6%, respectively). According to the literature, the 5-year survival rates for each subtype are as follows: 79%-91% for myxoid round cell liposarcoma,[21] and 63% for synovial sarcoma,[22] which are non-URS, whereas 53%-67% for extraskeletal Ewing sarcoma,[23,24] 68% for alveolar soft part sarcoma,[25] and 47% for alveolar rhabdomyosarcoma,[26] which are URS. URS groups tend to exhibit poorer 5-year survival rates, which may contribute to the worse prognosis observed in patients under 40 years old in the URS group. These findings emphasize the importance of prioritizing research on ultra-rare soft tissue sarcomas occurring in younger patients and highlight the need for clinical trials targeting these specific URS.[27,28]

This study has some limitations that warrant consideration. The database used in this study spans from 2001 to 2019, a period during which treatment strategies evolved continuously and new therapeutic agents, such as pazopanib,[29] trabectedin,[30] and eribulin[31] were introduced. These advancements likely influenced treatment outcomes; thus, caution is necessary when interpreting the results. Additionally, although this database included information on the drugs administered, it did not provide details on the number of treatment lines or the order in which treatments were given, which could potentially impact the results. Furthermore, it was hypothesized that the URS could contribute to diagnostic delays, thereby delaying treatment initiation. An analysis was proposed to investigate the duration between the initial visit and the pathological diagnosis. This analysis, however, was impeded by insufficient records concerning the date of pathological diagnosis. Addressing this gap by collecting more comprehensive data on diagnostic timelines poses a crucial challenge for future research endeavors.

In summary, our study has provided valuable insights into the epidemiology and prognosis of URS. We found that diagnosing bone sarcomas in patients aged >80 years old and soft tissue sarcomas in patients <20 years old, where URS occurrence is more prevalent, requires careful consideration. Additionally, our analysis revealed that ultra-rare bone sarcomas generally exhibit a more favorable prognosis compared with ultra-rare soft tissue sarcomas, which tend to have a slightly worse outlook. Although the impact of being classified as ultra-rare on prognosis is relatively modest when compared with other prognostic factors, we observed a significantly poorer prognosis for ultra-rare soft tissue sarcomas in patients <40 years old. This emphasizes the need for focused research on specific histological types within this younger demographic. To enable more refined predictive analysis, it is essential to carry out analyses specific to histological types and enhance the database by gathering more detailed data, which are the key future challenges.

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DISCLOSURE

MN is a current employee of Eli Lilly Japan K.K. ME reports payment or honoraria for lectures, presentations, speaker's bureaus, manuscript writing or educational events from Bayer, Daiichi-Sankyo, Kyowa Kirin, Eisai, Boehringer Ingelheim, Taiho, and Teijin. ME reports participation on a data safety monitoring board or advisory board of Chugai and Boehringer Ingelheim. YN reports grants or contracts from AYUMI Pharmaceutical Corporation and Kyocera Corporation. YN is the president of the Japanese Orthopaedic Association. All of these are unrelated to this study. All other authors have declared no conflicts of interest.

DATA SHARING

The data from the Bone and Soft Tissue Tumor Registry in Japan are not publicly accessible due to the privacy of individuals and are stored on the servers of the Musculoskeletal Tumor Committee of the Japanese Orthopaedic Association. The study protocol, statistical analysis plan, and analysis codes are available upon request to the corresponding author.

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