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Data Availability Statement

All data were obtained from National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program database.

Ethical compliance

This study is approved by the Institutional Ethical Board of the First Affiliated Hospital of Sun Yat-sen University.

Authors' contributions section

Jingnan Shen and Hao yao conceived and designed the study. Xianbiao Xie, Yutong Zou and Lili Wen collected data and performed the analysis. Dongming Lv, Ziliang Zeng, Qinglin Jin and Yiying Bian provided statistics and software support. Xianbiao Xie, Yutong Zou and Lili Wen wrote the paper. Jingnan Shen and Hao yao reviewed and edited the manuscript. All authors read and approved the manuscript.

Consent for publication

For manuscripts containing any individual person's data in any form (including individual details, images or videos), consent to publish must be obtained from that person, or in the case

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Reginal Lymph Node Involvement is Associated With Poorer Survivorship in Patients With Malignant Bone Tumor

Background: Regional lymph node involvement is rare in patients with malignant bone tumors. We aimed to analyze the prevalence and prognostic implications in the lymph-involved patients with malignant bone tumors.

Materials and Methods: From 1988 to 2016, 9582 patients with primary malignant bone tumors in the SEER database were enrolled. Overall survival (OS) was computed using the Kaplan-Meier method. A multivariate analysis was performed using the Cox regression.

Results: 346 (3.63%) patients exhibited regional lymph node involvement. Lymph-involved patients had larger tumor size and more metastasis than patients without. Ewing sarcoma most frequently developed lymph node involvement. Lymph-involved patients (0.31 95% CI (0.26–0.37)) had lower 5-year OS rates than patients without lymph node involvement (0.66 95% CI (0.65–0.68)) ($p<0.001$).

Conclusions: Lymph node involvement is rare in patients with malignant bone tumors. They had a large tumor size, more distant metastasis and poor survival.

1 INTRODUCTION

Primary malignant bone tumors constitute a heterogeneous group of rare solid tumors, and the most prevalent types are osteosarcoma, chondrosarcoma and Ewing sarcoma. The metastatic pattern in primary malignant bone tumor is typically hematogenous, with the lung and bone as the most prevalent metastatic sites (1, 2). Although regional lymph node involvement is thought to be a relatively uncommon

event in patients with primary bone malignancies, it was reported to be associated with a poor survival in several studies of patients with various histological subtypes of tumors, such as osteosarcoma and chondrosarcoma (3-6). However, the overall proportion of regional lymph node involvement and its effect on the survival of patients with primary malignant bone tumors remain unclear.

Efforts to understand the percentage of patients with primary bone malignancies who develop regional nodal involvement and the histological subtypes that are more or less likely to undergo lymphatic spread may influence the decision to require the patient to undergo further advanced imaging tests, such as PET-CT, or regional lymph node biopsy. The status of the regional lymph nodes may alter the prognosis by substantially guiding the overall treatment strategy and potentially altering the range of resection or surgical method. However, currently, the process has not been systematically evaluated. Challenges include the low disease incidence and heterogeneity of histological subtypes.

Given the paucity of data describing these patients, we completed the current population-based study of this rare group of patients with primary malignant bone tumors and regional lymph node involvement. We provide a description of the prevalence, risk factors and effects on survival for this unique group of patients.

2 MATERIALS AND METHODS

2.1 Source of Patients

We accessed the US National Cancer Institute Surveillance Epidemiology and End Results (SEER) database, which collects and publishes cancer incidence and survival data (7), using the SEER*Stat version 8.3.5 (National Cancer Institute, Bethesda, MD,

112 USA) to obtain the data from patients with primary malignant bone tumors, including
113 clinical characteristics and outcomes and to answer the questions posed above.

114 **2.2 Inclusion and Exclusion Criteria**

115 The inclusion criteria were a histologically confirmed diagnosis of primary
116 malignant bone tumors from 1988 to 2016. The diagnosis was made when the patient
117 was alive, as we excluded a diagnosis determined at autopsy or a death certificate only.
118 Patients who were not diagnosed with bone malignancies as the first primary
119 malignancy and patients without available information on the status of regional lymph
120 node involvement were also excluded **(Figure 1)**.

121 **2.3 Selection of Patients**

122 The codes of bone malignancies in the International Classification of Diseases for
123 Oncology are 8830/3, malignant fibrous histiocytoma; 9180/3, osteosarcoma not
124 otherwise specified; 9181/3, chondroblastic osteosarcoma; 9182/3, fibroblastic
125 osteosarcoma; 9183/3, telangiectatic osteosarcoma; 9184/3, osteosarcoma in Paget
126 disease of bone; 9185/3, small cell osteosarcoma; 9186/3, central osteosarcoma; 9187/3,
127 intraosseous well-differentiated osteosarcoma; 9192/3, parosteal osteosarcoma; 9193/3,
128 periosteal osteosarcoma; 9194/3, high grade surface osteosarcoma; 9200/3,
129 osteosarcoma, malignant; 9220/3, chondrosarcoma not otherwise specified; 9221/3,
130 juxtacortical chondrosarcoma; 9230/3, chondroblastoma, malignant; 9231/3, myxoid
131 chondrosarcoma; 9240/3, mesenchymal chondrosarcoma; 9242/3, clear cell
132 chondrosarcoma; 9243/3, dedifferentiated chondrosarcoma; 9250/3, giant cell tumor of
133 the bone, malignant; 9251/3, malignant giant cell tumor of soft tissue; 9252/3,

malignant tenosynovial giant cell tumor; 9260/3, Ewing sarcoma; 9261/3, adamantinoma of long bones; 9370/3, chordoma, NOS; 9371/3, chondroid chordoma; and 9372/3, dedifferentiated chordoma. In the SEER database, 20541 patients diagnosed with bone malignancies from 1988 to 2015 were identified, and 9582 patients who met the inclusion criteria were included in this study. Then, we separated all patients into two groups according to the status of regional lymph node involvement.

The requirements of institutional review board (IRB) approval and written informed consent were waived due to the retrospective nature of the study of cases in the publicly available SEER database.

2.4 Statistical Analysis

All statistical analyses were performed using R software (R Foundation for Statistical Computing, Vienna, Austria). Proportions of patients with different clinical characteristics were calculated using descriptive statistics. Patients were separated into two groups depending on the status of regional lymph node involvement. The chi-square test and Fisher's exact test were used to identify the differences in categorical variables between the two groups. A Kaplan-Meier curve was constructed to estimate the overall survival, and a log-rank test was applied to identify the significance of differences in survival between groups. A Cox proportional hazard regression analysis was performed to calculate the hazard ratios with 95% confidence intervals and to determine the effect of regional lymph node involvement on the prognosis, while controlling for the effects of age, sex, race, tumor size, tumor location, tumor grade, distant metastasis. Statistical significance was determined using an α error of 0.05.

3 RESULTS

3.1 Characteristics of Patients

A total of 9582 patients with primary malignant bone tumors were included in our analysis, including 5579 males (58.22%) and 4003 females (41.78%). The most frequent histological subtypes were chondrosarcoma (25.11% [2406/9582]) and osteosarcoma (24.64% [2361/9582]). Regarding the primary tumor location, most tumors were located in a lower extremity, which was observed in 3611 patients (37.69%). One thousand one hundred thirty-one patients (11.8%) were noted to have distant metastasis at the time of the initial diagnosis. Three hundred forty-six (3.61%) patients were reported to have regional lymph node involvement, while 9236 (96.39%) did not **(Table 1)**.

3.2 Differences in characteristics between patients with and without regional lymph node involvement

Briefly, patients with regional lymph node involvement were more likely to have a larger tumor size (81.69% [241 of 295] versus 67.84% [5152 of 7594], OR (odds ratio) = 2.1, 95% CI, 1.6-2.9; $p < 0.001$), than patients without this presentation. A higher percentage of distant metastasis (52.36% [155 of 296] versus 11.86% [976 of 8230], OR (odds ratio) = 8.1, 95% CI, 6.4-10.4; $p < 0.001$) was also observed in patients with regional nodal involvement. Moreover, compared with other histological types, a higher proportion of patients with Ewing sarcoma exhibited regional lymph node involvement (8.8% [115 of 1305] versus 2.8% [231 of 8277], OR (odds ratio) = 3.4, 95% CI, 2.7-4.2; $p < 0.001$) (**Table 2)**.

3.3 Association between histological subtypes and the prevalence of regional lymph node involvement

The incidence of regional lymph node involvement varies among histological subtypes. The prevalence of regional lymph node involvement was 8.81% [115 of 1305; 95% CI, 7.27-10.35] in patients with Ewing sarcoma, followed by 3.64% [96 of 1305; 95% CI, 2.92-4.36] in patients with malignant fibrous histiocytoma, 3.09% [73 of 2361; 95% CI, 2.39-3.76] in patients with osteosarcoma, 2.22% [4 of 180; 95% CI, 0.04-4.39] in patients with giant cell tumor of the bone, 1.99% [48 of 2406; 95% CI, 1.43-2.55] in patients with chondrosarcoma and 1.52% [10 of 657; 95% CI, 0.58-2.46] in patients with chordoma. Regional lymph node involvement was not noted in 13 subtypes of primary malignant bone tumors: osteosarcoma in Paget disease of bone, small cell osteosarcoma, intraosseous well-differentiated osteosarcoma, parosteal osteosarcoma, periosteal osteosarcoma, high grade surface osteosarcoma, juxtacortical chondrosarcoma, malignant chondroblastoma, malignant giant cell tumor of soft tissues, malignant tenosynovial giant cell tumor, adamantinoma of long bones, chondroid chordoma and dedifferentiated chordoma **(Table 3)**.

We observed a clear association between the histological subtype and the prevalence of regional lymph node involvement. Compared with the overall proportion of patients presenting with regional lymph node involvement (3.63% [346 of 9582]; 95% CI, 3.25-4.00), a higher proportion of patients with Ewing sarcoma presented with regional lymph node metastasis (8.81% [115 of 1305; 95% CI, 7.27-10.35; $p<0.001$]). The proportion of patients with nodal metastasis with myxoid chondrosarcoma (4.49%

[16 of 356; 95% CI, 2.33-6.66; p=0.476) and dedifferentiated chondrosarcoma (3.98% [7 of 176; 95% CI, 1.06-6.89; p=0.491]) appeared to be numerically higher than the overall proportion, but the differences were not statistically significant.

3.4 Relationship between regional lymph node involvement and the prognosis

Overall survival was worse for patients with primary malignant bone tumors presenting with regional lymph node involvement than patients without regional nodal disease (p<0.001). The estimated 5-year overall survival rates of patients with and without regional lymph node involvement were 31% (95% CI, 26–37%) and 66% (95% CI, 65–68%), respectively **(Figure 2A)**.

A subgroup analysis also confirmed these results. For patients without distant metastasis, regional lymph node involvement was also associated with a worse 5-year survival: 42% for patients with regional node involvement (95% CI, 34%-52%) and 72% for patients without lymph node involvement (95% CI, 71-73%; $p < 0.001$) **(Figure 2B)**. For patients presenting with metastatic disease, regional lymph node involvement was associated with a worse 5-year overall survival; the estimated rate was 20% for patients with regional lymph node involvement (95% CI, 12-28%) and 29% for patients without this presentation (95% CI, 25-32%; p=0.0061) **(Figure 2C)**. In patients with osteosarcoma, the 5-year overall survival was 16% (95% CI, 9-32%) for patients with regional lymph node involvement and 63% (95% CI, 58-63%; $p < 0.001$) for patients without this presentation **(Figure 2D)**. The 5-year overall survival rate was 43% (95% CI, 33%-55%) for patients with Ewing sarcoma presenting with regional lymph node involvement and 65% (95% CI, 61%-68%; $p < 0.001$) for patients without this

presentation **(Figure 2E)**. In patients with malignant fibrous histiocytoma, the 5-year overall survival rate was 22% (95% CI, 21-31%) for patients with regional lymph node involvement and 60% (95% CI, 57%-61%; $p < 0.001$) for patients without regional lymph node involvement **(Figure 2F)**.

Next, we built a multivariate Cox proportional hazard model to assess the independent effect of regional node involvement on the overall survival. Based on the results of the univariate analysis, covariates included in the Cox model were age, sex, race, tumor size, primary tumor site, distant metastasis, grade and histological type. All covariates, except race and primary tumor site, met the proportional hazard assumption. The estimated hazard ratio (HR) of death in patients with regional lymph node involvement was 1.74 (95% CI, 1.48-2.05; $p < 0.001$) compared with patients without regional lymph node involvement **(Figure 3)**.

4 DISCUSSION

Primary malignant bone tumors are a collection of rare malignancies that presents inherent challenges to risk stratification and our understanding of this heterogeneous group of diseases. Factors associated with poorer survival include histological subtypes, older age, distant metastasis, primary tumor site and sensitivity to chemotherapy, among others (8-12). Regional lymph node involvement is thought to be rare in patients with primary malignant bone tumors, although the overall prevalence of nodal involvement is poorly defined in the existing reports (13, 14). Likewise, our systematic understanding of the effect of regional lymph node involvement on primary bone malignancies is also limited, and we were only able to identify several limited studies

on the survival of patients with osteosarcoma, chondrosarcoma and Ewing sarcoma presenting with and without lymph node metastasis (15-17). As shown in the current study, 3.63% of all patients with primary malignant bone tumors presented with regional lymph node involvement. Nodal involvement was associated with the histological subtype. More importantly, regional lymph node involvement independently indicated poorer survival for patients with primary malignant bone tumors, which affects the evaluation of the prognosis and treatment plans.

Consistent with previous studies, our results reveal that regional lymph node involvement is rare in patients with primary malignant bone tumors, with a prevalence of 3.63%. Previous studies report a prevalence of nodal involvement in osteosarcoma ranging from <1% to 10% (16). An analysis of chondrosarcoma based on the SEER database reviewed a prevalence of 1.3% (15). The metastatic pattern of primary malignant bone tumors is typically hematogenous, and the reason for the rarity of regional lymph node involvement has not been clearly clarified to date. Some researchers postulated that the paucity of lymphatic channels in bone may explain the rare incidence of regional lymph node involvement (18).

Based on our findings, patients with regional lymph node involvement were more likely to have a larger tumor size, a higher percentage of distant metastasis and to be diagnosed with Ewing sarcoma than patients without regional lymph node involvement. The involvement of regional lymph nodes is a signal of the extent of tumor invasion. Therefore, as a marker of tumor invasion, the observation of a larger tumor size in patients with regional nodal involvement is reasonable. Primary malignant bone tumors

typically display hematogenous metastasis. As a significant adverse factor, the consistent appearance of distant metastasis with regional nodal involvement is rational. We reported substantial variation in the risk of regional lymph node involvement among patients with different histological subtypes of primary malignant bone tumors. Ewing sarcoma (8.81%) was associated with a higher risk of regional lymph node involvement than other subtypes of bone malignancies, followed by myxoid chondrosarcoma (4.49%) and dedifferentiated chondrosarcoma (3.98%). Jimi Huh et al. conducted a single institution study and found that the most frequent site of metastasis in patients with Ewing sarcoma was the lymph nodes (19). Based on the current study, the proportion of lymph node involvement was also higher when Ewing sarcoma originated from bone rather than the soft tissue. Researchers have not clearly determined why the proportions of patients with regional nodal involvement differ among histological subtypes. A few explanations have been provided in previous studies. According to Edwards et al. (18), lymphatic vessels are lacking in bone tumors, but they are present in tumors that have extended into the periosteum and surrounding soft tissue. Compared with other common primary malignant bone tumors, including osteosarcoma and chondrosarcoma, Ewing sarcoma is more likely to extend into the extraskeletal tissue because of its histological origination. Another hypothesis proposed by some experts was that tumors with an increased non-spindle cell component tend to have an increased frequency of extrapulmonary metastases, including lymph node metastases (17, 20, 21).

Based on the results from the present study, patients with primary malignant bone tumors and regional lymph node involvement have inferior overall survival outcomes.

Regional nodal involvement was previously reported to be an adverse prognostic factor for several histological subtypes of primary bone malignancies, such as osteosarcoma and chondrosarcoma (15, 16). Our study confirmed the adverse effect of regional lymph node involvement patients with primary malignant bone tumors on overall survival, including all common histological subtypes. Although the presence of regional nodal involvement is rare, the effect on the prognosis of patients with all subtypes of bone malignancies should not be ignored. Since an examination of regional lymph nodes is not included in the routine evaluation of primary malignant bone tumors, we recommend PET/CT imaging as an effective method to screening for lymph node involvement (22, 23). Biopsy of suspicious regional lymph nodes may be needed for confirmation when planning further treatment.

The analysis of data from the SEER database has several limitations. This study is limited by its retrospective approach. Second, the SEER database did not provide detailed information about the treatment of patients, including the management of regional lymph node metastasis and surgical methods. Therefore, bias may exist in the survival analysis. Additionally, a detailed analysis of recommendations for patients with regional lymph node involvement was impossible. Moreover, the status of lymph node involvement in patients included in the SEER database was determined by either clinical, surgical or pathologic adjudication. Therefore, the actual prevalence of regional lymph node involvement was unable to be determined.

We conclude that the prevalence of regional lymph node involvement in patients with primary malignant bone tumors included in the SEER database was 3.63%.

Patients with nodal involvement were more likely to have a large tumor size and distant metastasis. Ewing sarcoma was associated with a higher risk of regional lymph node involvement than other subtypes of bone malignancies. Patients with regional nodal involvement exhibit a poorer survival than patients without regional lymph node involvement. The importance of a regional lymph node evaluation in patients with primary malignant bone tumors might currently be underestimated. Based on the independent association between regional lymph node involvement and poor survival, we suggest a cautious assessment of the status of regional nodal involvement in patients with primary bone malignancies. The mechanism of lymph node involvement, association of this finding with a poor prognosis, and recommended management of invaded lymph nodes require further investigation.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

Availability of data and materials

The dataset(s) supporting the conclusions of this article is(are) available in the US National Cancer Institute Surveillance Epidemiology and End Results (SEER) database in https://seer.cancer.gov/.

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TABLES

TABLE 1 Characteristics of patients with primary malignant bone tumor, Surveillance, Epidemiology, and End Results Program database, 1988-2016

Characteristic	**Number (%)**
Age (years)	
<25	2776(28.97)
25-59	3536(36.9)
≥60	3270(34.13)
Sex	
Male	5579(58.22)
Female	4003(41.78)

Race	
White	7945(82.92)
Black	855(8.92)
Asian or Pacific Islander	615(6.42)
American Indian/Alaska Native	74(0.77)
Unknown	93(0.97)
Tumor size (cm)	
<5	2496(26.05)
≥5	5393(56.28)
Unknown or not applicable	1693(17.67)
Primary tumor location	
Lower extremity	3611(37.69)
Upper extremity	1245(12.99)
Head	765(7.98)
Spine	377(3.93)
Ribs/sternum	482(5.03)
Pelvis	940(9.81)
Other	2162(22.56)
Histologic type	
Osteosarcoma	2361(24.64)
Osteosarcoma, NOS	1557(16.25)
Chondroblastic osteosarcoma	323(3.37)

Fibroblastic osteosarcoma	112(1.17)
Telangiectatic osteosarcoma	88(0.92)
Osteosarcoma in Paget disease of bone	16(0.17)
Small cell osteosarcoma	23(0.24)
Central osteosarcoma	82(0.86)
Intraosseous well differentiated osteosarcoma	4(0.04)
Parosteal osteosarcoma	107(1.12)
Periosteal osteosarcoma	33(0.34)
High grade surface osteosarcoma	16(0.17)
Chondrosarcoma	2406(25.11)
Chondrosarcoma, NOS	1710(17.85)
Juxtacortical chondrosarcoma	27(0.28)
Chondroblastoma, malignant	20(0.21)
Myxoid chondrosarcoma	356(3.72)
Mesenchymal chondrosarcoma	81(0.85)
Clear cell chondrosarcoma	36(0.38)
Dedifferentiated chondrosarcoma	176(1.84)
Giant cell tumor of bone	180(1.88)
Giant cell tumor of bone, malignant	131(1.37)
Malignant giant cell tumor of soft parts	17(0.18)
Malignant tenosynovial giant cell tumor	32(0.33)
Ewing sarcoma	1305(13.62)

Adamantinoma of long bones	39(0.41)
Malignant fibrous histiocytoma	2634(27.49)
Chordoma	657(6.86)
Chordoma, NOS	604(6.30)
Chondroid chordoma	49(0.51)
Dedifferentiated chordoma	4(0.04)
Regional lymph node involvement	
NO	9236(96.39)
YES	346(3.61)
Distant metastasis	
NO	7395(77.18)
YES	1131(11.8)
Unknown or not applicable	1056(11.02)
Grade	
I	860(8.98)
II	1194(12.46)
III	1420(14.82)
IV	2318(24.19)
Unknown	3790(39.55)
Status	
Alive	6229(65.01)
Dead	3353(34.99)

390 **Abbreviations:** NOS, not otherwise specified

391

392 **TABLE 2** Comparison of characteristics of patients with and without regional lymph

393 node involvement

Characteristic	No regional lymph node involvement (n =9236,96.39%)	Regional lymph node involvement (n = 346,3.61%)	p value
Age (years)			0.002
<25	2650(28.69%)	126(36.42%)	
25-59	3410(36.92%)	126(36.42%)	
≥60	3176(34.39%)	94(27.17%)	
Sex			0.051
Male	5360(58.03%)	219(63.29%)	
Female	3876(41.97%)	127(36.71%)	
Race			0.703
White	7664(82.98%)	281(81.21%)	
Black	818(8.86%)	37(10.69%)	
Asian or Pacific Islander	594(6.43%)	21(6.07%)	
American Indian/Alaska Native	70(0.76%)	4(1.16%)	
Unknown	90(0.97%)	3(0.87%)	
Tumor size (cm)			<0.001

<5	2442(26.44%)	54(15.61%)	
≥5	5152(55.78%)	241(69.65%)	
Unknown or not applicable	1642(17.78%)	51(14.74%)	
Primary tumor location			0.379
Skeletal	6503(70.41%)	236(68.21%)	
Extraskeletal	2733(29.59%)	110(31.79%)	
Histologic type			<0.001
Osteosarcoma	2288(24.77)	73(21.10)	
Osteosarcoma, NOS	1499(16.23%)	58(16.76%)	
Chondroblastic osteosarcoma	312(3.38%)	11(3.18%)	
Fibroblastic osteosarcoma	110(1.19%)	2(0.58%)	
Telangiectatic osteosarcoma	87(0.94%)	1(0.29%)	
Osteosarcoma in Paget disease of bone	16(0.17%)	0(0%)	
Small cell osteosarcoma	23(0.25%)	0(0%)	
Central osteosarcoma	81(0.88%)	1(0.29%)	
Intraosseous well differentiated osteosarcoma	4(0.04%)	0(0%)	
Parosteal osteosarcoma	107(1.16%)	0(0%)	
Periosteal osteosarcoma	33(0.36%)	0(0%)	
High grade surface osteosarcoma	16(0.17%)	0(0%)	
Chondrosarcoma	2358(25.53)	48(13.87)	
Chondrosarcoma, NOS	1689(18.29%)	21(6.07%)	
Juxtacortical chondrosarcoma	27(0.29%)	0(0%)	

Chondroblastoma, malignant	20(0.22%)	0(0%)	
Myxoid chondrosarcoma	340(3.68%)	16(4.62%)	
Mesenchymal chondrosarcoma	78(0.84%)	3(0.87%)	
Clear cell chondrosarcoma	35(0.38%)	1(0.29%)	
Dedifferentiated chondrosarcoma	169(1.83%)	7(2.02%)	
Giant cell tumor of bone	176(1.91)	4(1.16)	
Giant cell tumor of bone, malignant	129(1.4%)	2(0.58%)	
Malignant giant cell tumor of soft parts	15(0.16%)	2(0.58%)	
Malignant tenosynovial giant cell tumor	32(0.35%)	0(0%)	
Ewing sarcoma	1190(12.88%)	115(33.24%)	
Adamantinoma of long bones	39(0.42%)	0(0%)	
Malignant fibrous histiocytoma	2538(27.48%)	96(27.75%)	
Chordoma	647(7.01)	10(2.89)	
Chordoma, NOS	594(6.43%)	10(2.89%)	
Chondroid chordoma	49(0.53%)	0(0%)	
Dedifferentiated chordoma	4(0.04%)	0(0%)	
Distant metastasis			<0.001
NO	7254(78.54%)	141(40.75%)	
YES	976(10.57%)	155(44.8%)	
Unknown or not applicable	1006(10.89%)	50(14.45%)	
Grade			<0.001
I	855(9.26%)	5(1.45%)	

II	1184(12.82%)	10(2.89%)
III	1348(14.6%)	72(20.81%)
IV	2209(23.92%)	109(31.5%)
Unknown	3640(39.41%)	150(43.35%)

394 **Abbreviations:** NOS, not otherwise specified

395

396 **TABLE 3** Frequency of regional lymph node involvement by histologic subtype

Histologic subtype	Number (%) of patients with regional lymph node involvement
Ewing sarcoma	115 (8.81)
Myxoid chondrosarcoma	16 (4.49)
Dedifferentiated chondrosarcoma	7 (3.98)
Osteosarcoma, NOS	58 (3.73)
Mesenchymal chondrosarcoma	3 (3.7)
Malignant fibrous histiocytoma	96 (3.64)
Chondroblastic osteosarcoma	11 (3.41)
Clear cell chondrosarcoma	1 (2.78)
Giant cell tumor of bone	4 (2.22)
Fibroblastic osteosarcoma	2 (1.79)
Chordoma, NOS	10 (1.66)
Telangiectatic osteosarcoma	1 (1.14)
Chondrosarcoma, NOS	21 (1.23)

Central osteosarcoma	1 (1.22)

Abbreviations: NOS, not otherwise specified

FIGURE LEGEND

Figure 1 This flowchart shows the patient selection process, based on the SEER dataset.

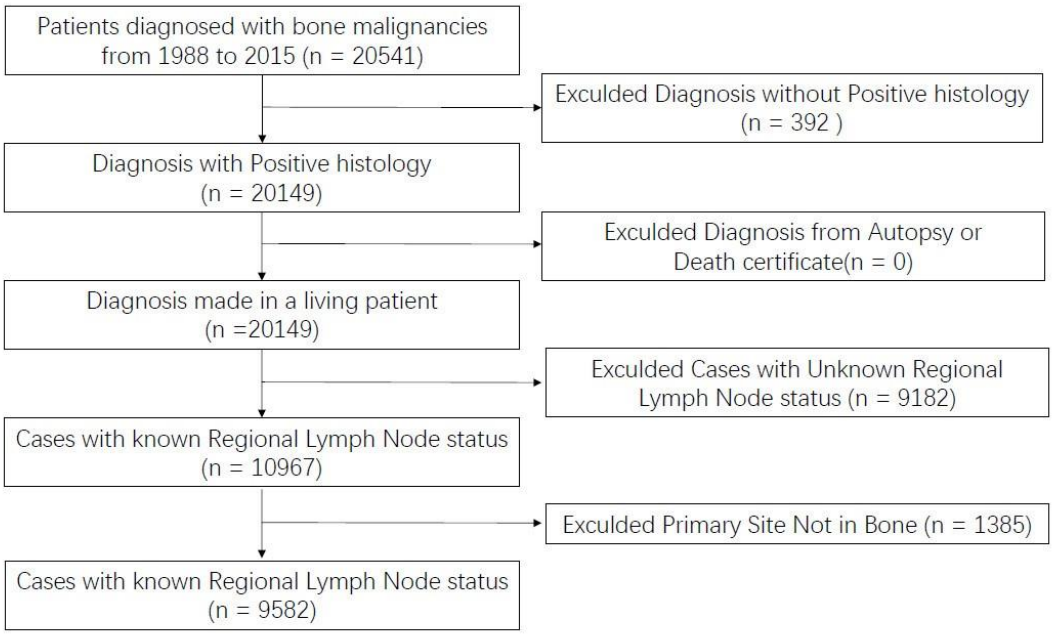


Figure 2A-F The graph shows Kaplan-Meier survival curves according to the presence or absence of regional lymph node involvement in **(A)** all included patients with primary malignant bone tumor; **(B)** patients without distant metastatic disease; **(C)** patients with distant metastatic disease; **(D)** patients with osteosarcoma; **(E)** patients with Ewing sarcoma; **(F)** patients with malignant fibrous histiocytoma.

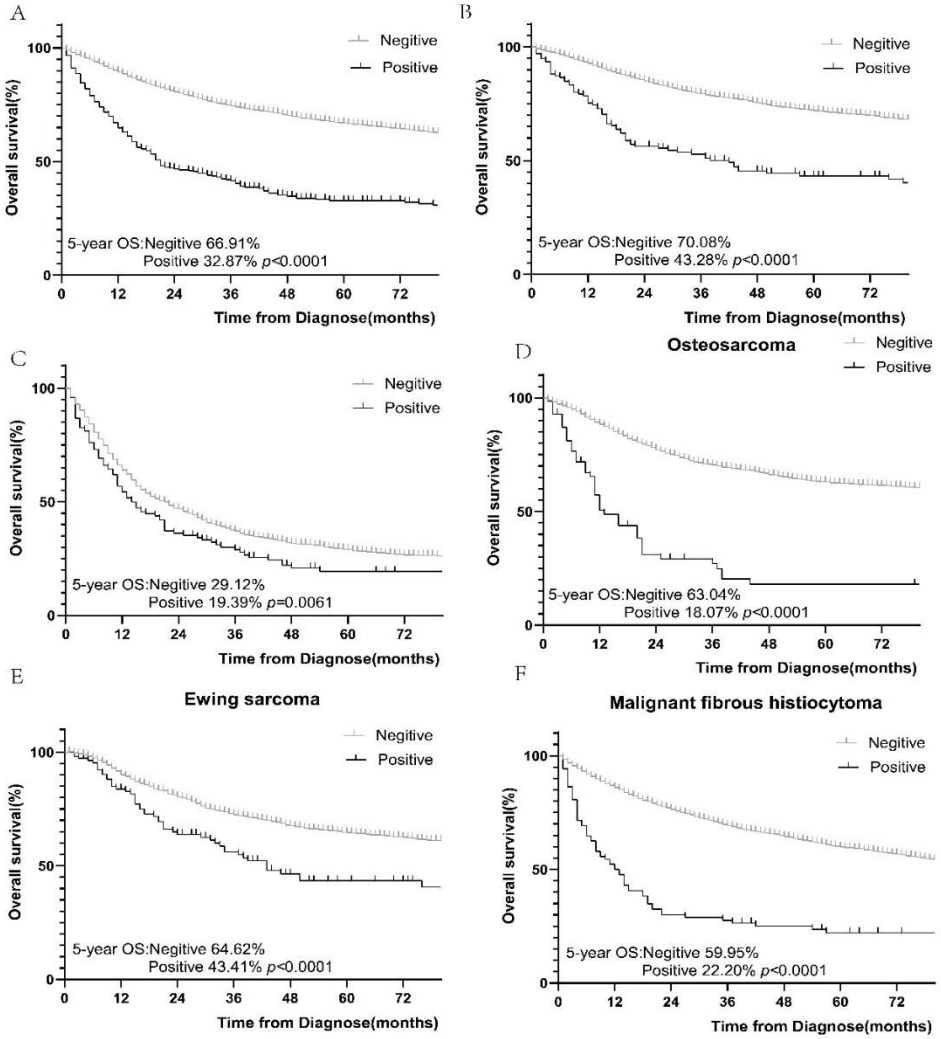
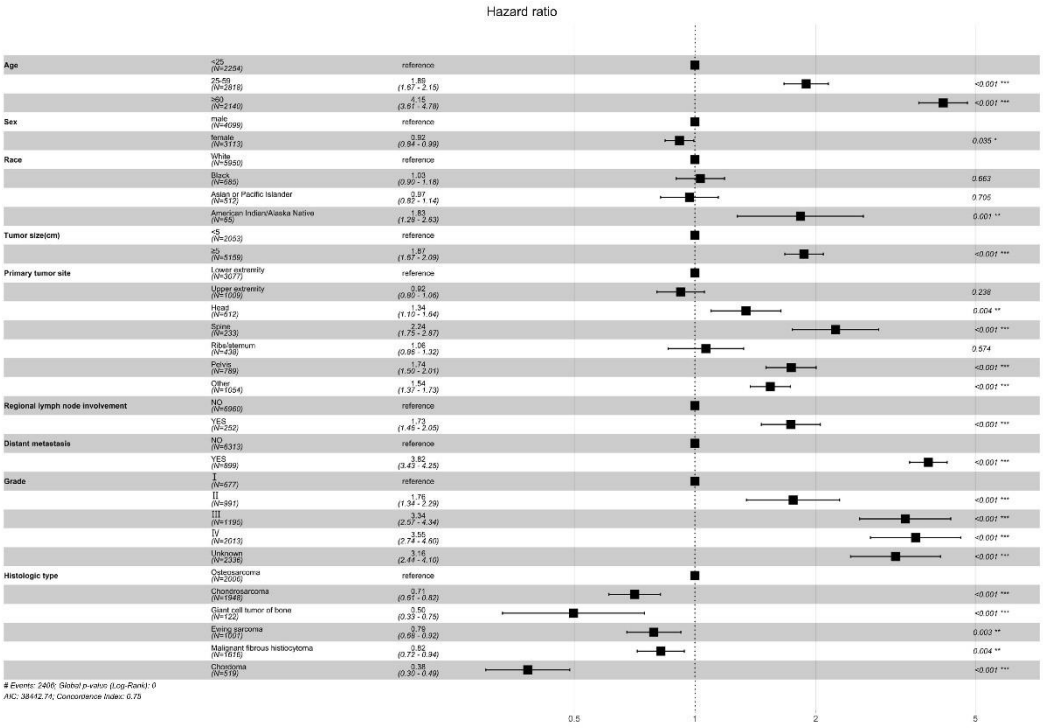


Figure 3 Results and forest plot of Cox proportional hazard regression analysis with hazard ratio (HR) and 95% confidence intervals (CIs).


Hazard ratio
Age
<25 (N=2254) reference
25-59 (N=2818) 1.86 (1.67 - 2.15) <0.001 ***
>60 (N=2140) 4.16 (3.61 - 4.78) <0.001 ***
Sex
male (N=4099) reference
female (N=3113) 0.92 (0.84 - 0.99) 0.035 *
Race
White (N=5950) reference
Black (N=595) 1.03 (0.90 - 1.18) 0.663
Asian or Pacific Islander (N=512) 0.97 (0.82 - 1.14) 0.705
American Indian/Alaska Native (N=55) 1.83 (1.29 - 2.63) 0.001 **
Tumor size(cm)
<5 (N=2053) reference
≥5 (N=5159) 1.87 (1.67 - 2.09) <0.001 ***
Primary tumor site
Lower extremity (N=3077) reference
Upper extremity (N=1009) 0.92 (0.80 - 1.06) 0.238
Head (N=612) 1.34 (1.10 - 1.64) 0.004 **
Spine (N=233) 2.24 (1.75 - 2.87) <0.001 ***
Ribs/sternum (N=438) 1.06 (0.85 - 1.32) 0.574
Pelvis (N=789) 1.74 (1.50 - 2.01) <0.001 ***
Other (N=1054) 1.54 (1.37 - 1.73) <0.001 ***
Regional lymph node involvement
NO (N=6960) reference
YES (N=252) 1.73 (1.45 - 2.05) <0.001 ***
Distant metastasis
NO (N=6313) reference
YES (N=899) 3.82 (3.43 - 4.25) <0.001 ***
Grade
I (N=677) reference
II (N=991) 1.76 (1.34 - 2.29) <0.001 ***
III (N=1195) 3.34 (2.57 - 4.34) <0.001 ***
IV (N=2013) 2.55 (2.14 - 4.60) <0.001 ***
Unknown (N=2236) 3.16 (2.44 - 4.10) <0.001 ***
Histologic type
Osteosarcoma (N=2006) reference
Chondrosarcoma (N=1948) 0.71 (0.61 - 0.82) <0.001 ***
Giant cell tumor of bone (N=122) 0.50 (0.33 - 0.75) <0.001 ***
Ewing sarcoma (N=1007) 0.76 (0.66 - 0.92) 0.003 **
Malignant fibrous histiocytoma (N=1616) 0.82 (0.72 - 0.94) 0.004 **
Chordoma (N=519) 0.38 (0.30 - 0.49) <0.001 ***
Events: 2406; Global p-value (Log-Rank): 0
AIC: 38442.74; Concordance Index: 0.79
0.5
1
2
5

411

Figures

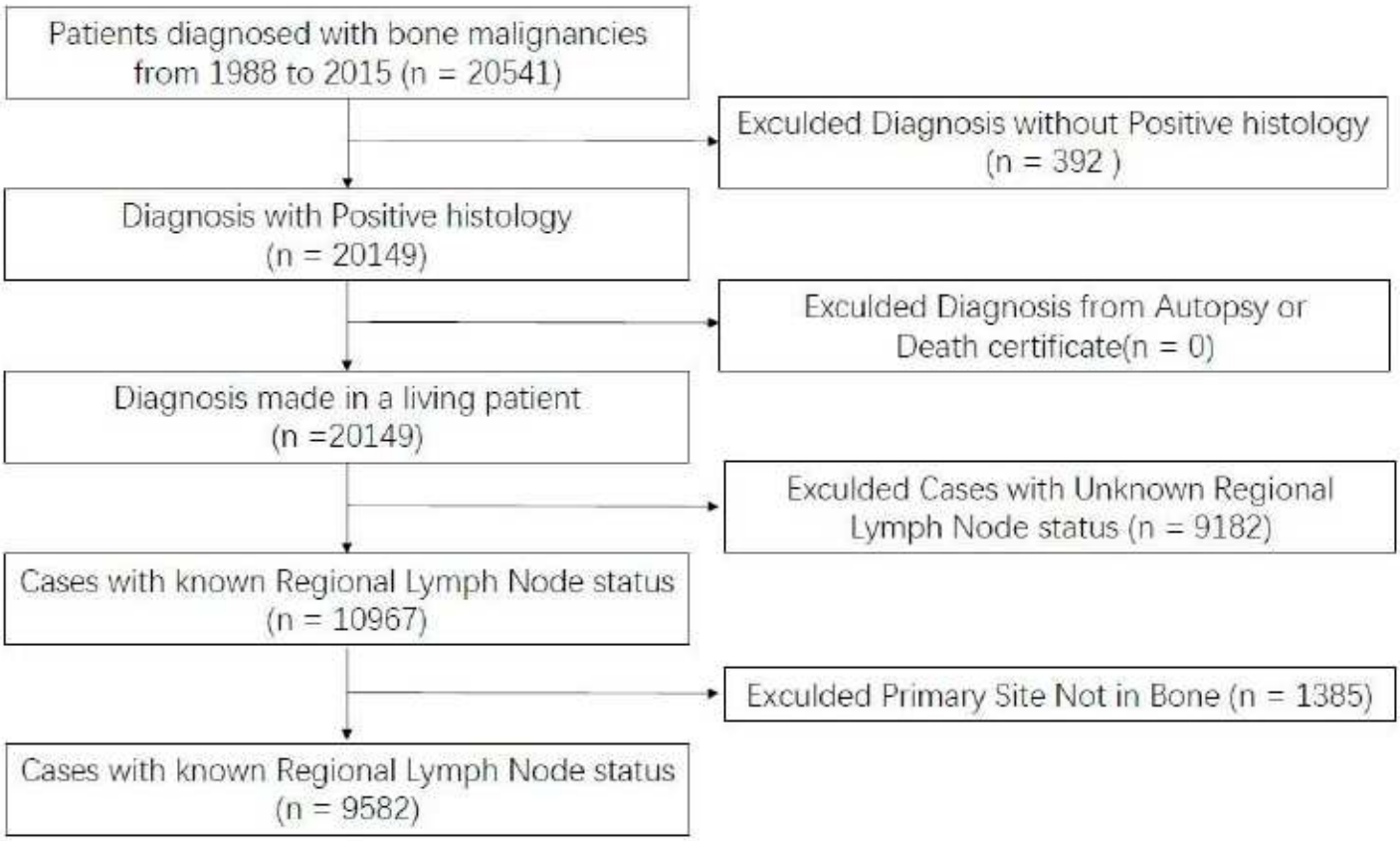


Figure 1

This flowchart shows the patient selection process, based on the SEER dataset.

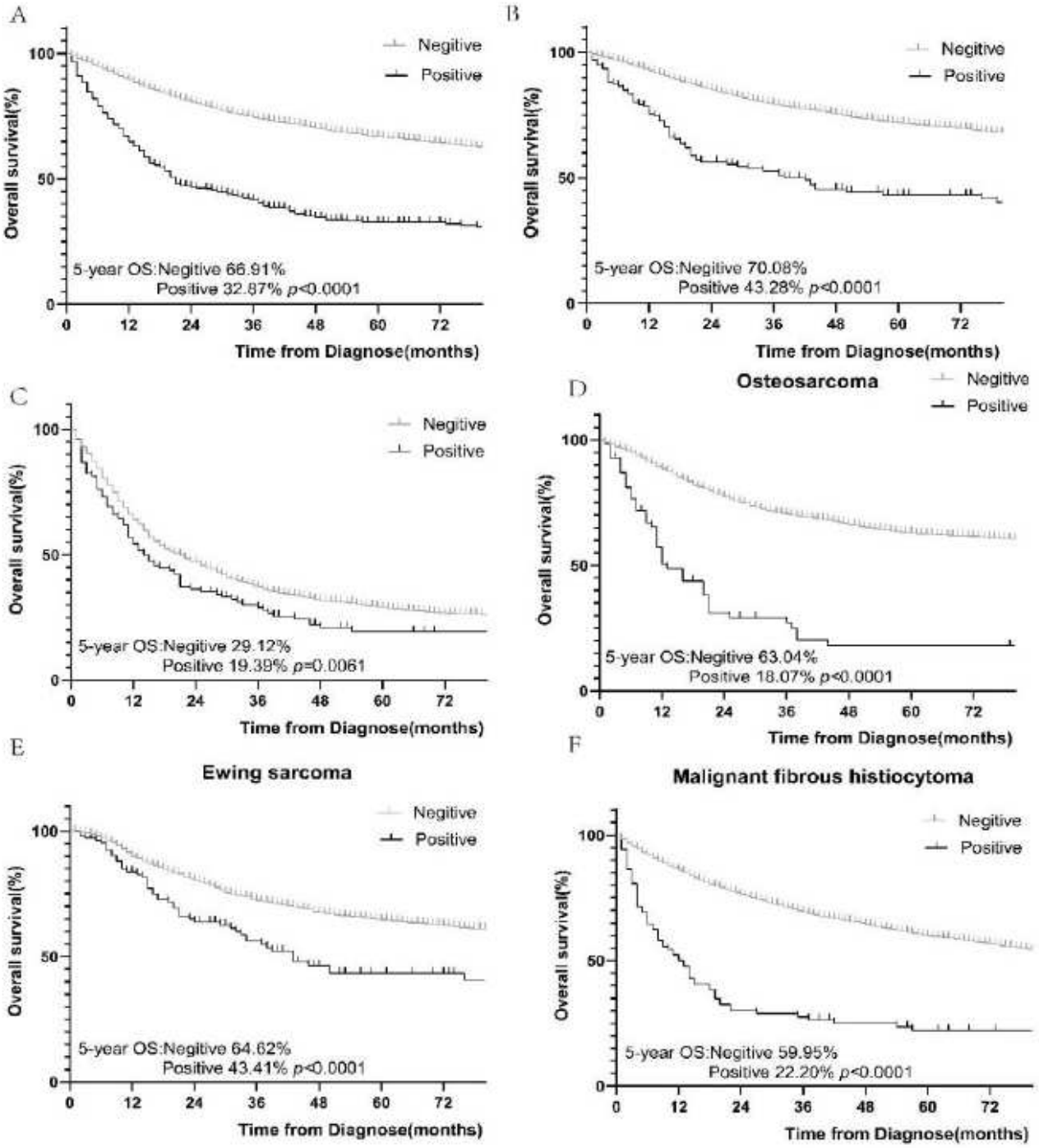


Figure 2

A-F The graph shows Kaplan-Meier survival curves according to the presence or absence of regional lymph node involvement in (A) all included patients with primary malignant bone tumor; (B) patients without distant metastatic disease; (C) patients with distant metastatic disease; (D) patients with osteosarcoma; (E) patients with Ewing sarcoma; (F) patients with malignant fibrous histiocytoma.

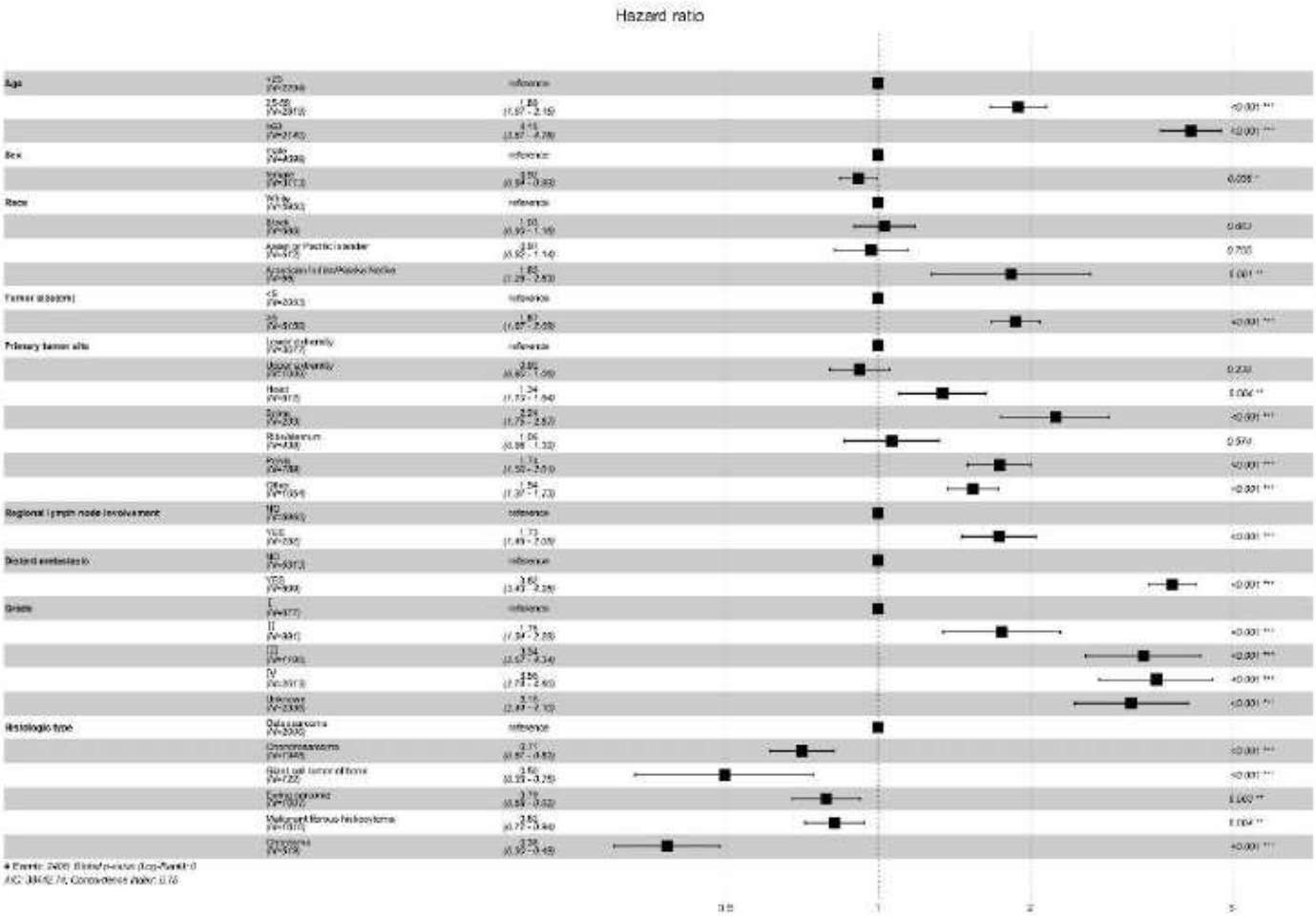


Figure 3

Results and forest plot of Cox proportional hazard regression analysis with hazard ratio (HR) and 95% confidence intervals (CIs).