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Prognostic Impact of Proximal *Versus* Distal Localization in Extremity Long Bone Osteosarcomas

KJETIL BERNER[1] and ØYVIND S. BRULAND[1,2]

[1]*Department of Oncology, Oslo University Hospital, The Norwegian Radium Hospital, Oslo, Norway;*
[2]*Institute for Clinical Medicine, Faculty of Medicine, University of Oslo, Oslo, Norway*

Abstract. *Background/Aim: This study aimed to identify the prognostic factors and outcomes of osteosarcoma (OS) located in proximal versus distal extremity long bones. Patients and Methods: A nationwide cohort comprising all Norwegian high-grade OSs in extremity long bones between 1982 and 2009 was investigated. Results: The univariate analysis results identified no significant differences in survival between patients with OS in proximal long bones (101 cases) as a group in comparison to patients with OS in the distal part of these bones (120 cases). However, proximal femur and primary metastasis were both independent adverse prognostic factors for sarcoma-specific survival in multivariate analyses, while elevated LDH and secondary OS were inferior prognostic factors for event-free survival. Adequate surgery and chemotherapy had a positive impact on survival. Conclusion: OS of the proximal femur had an unfavorable outcome in comparison to OS in other anatomical locations in extremity long bones.*

It is well established that axial tumor locations of osteosarcoma (OS) result in a worse outcome than primary disease located in the appendicular skeleton (1-5). Proximal osteosarcoma in extremity long bones (POS) has also been associated with poor outcome (4, 6-8), although the prognostic impact of the anatomical location of such tumors is still debated (6, 8, 9). Hence, this study aimed to evaluate the clinical features and outcomes of POS *versus* distal osteosarcoma in extremity long bone (DOS) in a nationwide Norwegian OS population. To the best of our knowledge, clinical epidemiology and treatment outcomes of POS *versus* DOS have not been previously reported in such a complete and population-based cohort.

Correspondence to: Kjetil Berner, MD, Ph.D., Department of Oncology, Oslo University Hospital, The Norwegian Radium Hospital, P.O. Box 4953, Nydalen, N-0424 Oslo, Norway. Tel: +47 22934000, Fax: +47 22525559, e-mail: kjetil.berner@ous-hf.no

Key Words: Prognostic factors, overall survival, population-based, osteosarcoma, pathological fracture.

Materials and Methods

Patient cohort. We analyzed 221 cases of extremity long bone OS identified among the 335 histologically-verified high-grade OS patients diagnosed in Norway between 1982 and 2009. The gross cohort included all subgroups of OS, even secondary OS (10), according to the current World Health Organization criteria (11). The following variables were relevant to this study: retrospectively validated cases based on multiple and partly overlapping data from registry sources, including all cases reported to the Norwegian Cancer Registry (NCR), supplemented with clinical records from all Norwegian hospitals involved in sarcoma management (10).

The starting year of 1982 was in line with the introduction of modern, multi-agent chemotherapy in Norway (12). The ending year of 2009 was the last available year of registration of primary diagnosis according to the NCR when the current project began. All follow-up data were updated to the second half of 2013.

Demographic and tumor-related variables. The demographic and tumor-related variables are presented in Table I. Tumor size was defined as the maximum length of the tumor in centimeters (cm); duration of symptoms was defined as the interval in months between the first symptom and the time of biopsy. Tumor size above 11 cm and duration of symptoms longer than three months were defined as elevated values in the analyses, and metastasis that was evident within six weeks of primary diagnosis was defined as primary metastatic disease. Serum alkaline phosphatase (ALP) and serum lactate dehydrogenase (LDH) were measured in international units at the time of diagnosis. Data on the date and cause of death were primarily retrieved from the Cause of Death Registry (10).

Treatment variables. Adequate treatment was defined as having undergone surgery for all detectable disease in addition to chemotherapy. Adequate surgery implied surgical removal of the primary tumor with wide or marginal margins as described by Enneking *et al*. (13), while adequate chemotherapy was defined as having received at least six courses of chemotherapy. The latter definition with its justification, is more thoroughly presented in a previous study (5). Patients with metastatic disease at the time of diagnosis were in need for a surgical remission for both primary tumor and metastases in order to be classified as having undergone adequate surgical treatment.

Table I. *Characteristics of patients with proximal osteosarcoma in long bones (POS) and distal osteosarcoma localization (DOS).*

	All patients (%)	POS (%)[1]	DOS (%)[1]	*p*-Value[2]
All patients	221 (100)	101 (46)	120 (54)	
Gender				0.371
Male	134 (61)	58 (43/57)	76 (57/63)	
Female	87 (39)	43 (49/43)	44 (51/37)	
Anatomic site				<0.001
Femur	125 (57)	18 (14/18)	107 (86/89)	
Tibia	58 (26)	50 (86/50)	8 (14/7)	
Fibula	10 (4)	10 (100/10)	0 (0/0)	
Humerus	24 (11)	22 (92/22)	2 (8/2)	
Radius/ulna	4 (2)	1 (25/1)	3 (75/3)	
Age				0.566
≤20 years	138 (62)	66 (48/65)	72 (52/60)	
20-40 years	44 (20)	17 (39/17)	27 (61/23)	
>40 years	39 (18)	18 (46/18)	21 (54/17)	
Tumor size[3,4]				0.476
≤11 cm	112 (57)	49 (44/54)	63 (56/59)	
>11 cm	86 (43)	42 (49/46)	44 (51/41)	
Duration of symptoms[3,5]				0.319
≤3 months	83 (52)	35 (42/47)	48 (58/55)	
>3 months	78 (48)	39 (50/53)	39 (50/45)	
Pathological fracture				0.742
No	184 (83)	85 (46/84)	99 (54/83)	
Yes	37 (17)	16 (43/16)	21 (57/17)	
Primary metastasis[3]				0.388
No	169 (77)	75 (44/74)	94 (56/79)	
Yes	51 (23)	26 (51/26)	25 (49/21)	
Secondary osteosarcoma				0.635
No	213 (96)	98 (46/97)	115 (54/96)	
Yes	8 (4)	3 (38/3)	5 (62/4)	
LDH[3]				0.794
Normal	82 (54)	41 (50/55)	41 (50/53)	
Elevated	71 (46)	34 (42/45)	37 (52/47)	
ALP[3]				0.162
Normal	90 (56)	48 (53/62)	42 (47/51)	
Elevated	71 (44)	30 (42/38)	41 (58/49)	
Histologic type[3]				0.216
Osteoblastic	106 (49)	48 (45/49)	58 (55/49)	
Chondroblastic	25 (12)	8 (32/8)	17 (68/14)	
Fibroblastic	20 (9)	8 (40/8)	12 (60/10)	
Mixed	57 (26)	28 (49/28)	29 (51/25)	
Other	9 (4)	7 (78/7)	2 (22/2)	
Years of diagnosis				0.327
1982-1989	68 (31)	30 (44/30)	38 (56/32)	
1990-1999	70 (32)	28 (40/28)	42 (60/35)	
2000-2009	83 (38)	43 (52/42)	40 (48/33)	
Surgical procedure[3]				0.064
Amputation	74 (36)	26 (35/29)	48 (65/41)	
Other	132 (64)	64 (48/71)	68 (52/59)	
Adequate surgery				0.193
Yes	183 (83)	80 (44/79)	103 (56/86)	
No surgery	13 (6)	9 (69/9)[6]	4 (31/3)	
Inadequate surgery	25 (11)	12 (48/12)	13 (52/11)	
Adequate chemotherapy				0.324
Yes	182 (82)	86 (47/85)	96 (53/80)	
No	39 (18)	15 (38/15)	24 (62/20)	
Adequate treatment				0.846
Yes	163 (74)	76 (47/75)	87 (53/73)	
No	58 (26)	25 (43/25)	33 (57/27)	

[1]Both row percentage (nominator) and column percentage (denominator). [2]χ^2. [3]Missing values equal the difference between the summarized numbers in the second column and the total patients in the study. [4]Median tumor size was 11 cm. [5]Median duration of symptoms before biopsy was 3 months. [6]Eight cases located to proximal femur and one in proximal humerus, mainly due to primary metastatic disease.

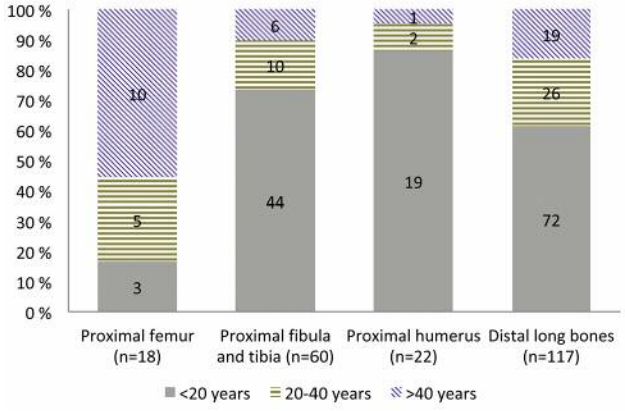

Figure 1. *Distribution of age and primary site in extremity long bone osteosarcomas at diagnoses (femur, humerus, tibia and fibula).*

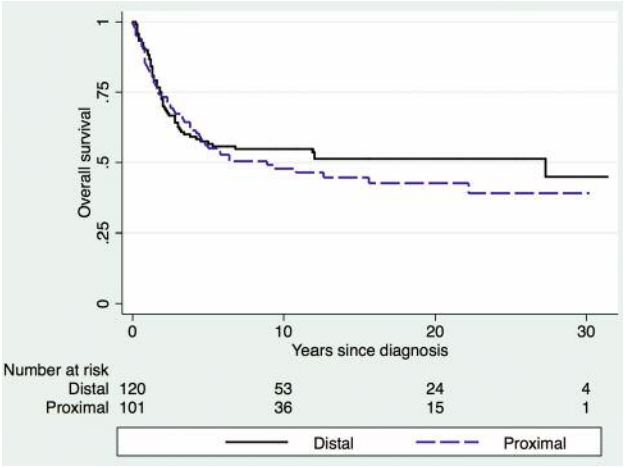

Figure 2. *Overall survival of patients with osteosarcoma in proximal and distal long bones (p=0.418).*

Statistical analyses. Chi square analyses (χ^2) were used to compare unrelated samples, when appropriate. Survival analyses using Kaplan–Meier estimates, the log-rank test, and Cox regression were used to analyze overall survival, sarcoma specific survival (SSS), and event-free survival (EFS), using SPSS version 21 (SPSS Inc., Chicago, IL, USA) and Stata version 13.1 (Stata corporation, College Station, TX, USA) software. The endpoint for all survivors in the entire cohort was set at July 2013. Overall survival was calculated from the date of diagnosis until the date of death from any cause, while sarcoma-specific death or treatment-related death was the endpoint of SSS. EFS was calculated from the date of diagnosis until the date of the first metastasis, local recurrence, sarcoma-specific death, or treatment-related death, whichever occurred first. Patients with primary metastatic OS were not included in the EFS analyses. The statistically significant prognostic variables in the univariate analysis were included in the multivariate backward Cox-regression analyses. The Cox proportion hazard assumption was evaluated using Kaplan–Meier plots. We did not account for multiple imputations of missing values in this report, since their effects were considered to be modest (5).

Ethical approval. The Regional Ethical Committee was informed about this project, although the study did not require formal ethical approval since the data registration was in line with the legitimate mandate of the NCR.

Results

Anatomical localization. This study included 101 (46%) POS patients and 120 (54%) DOS patients (Table I). Proximal anatomical locations were more common in the fibula (100%), humerus (92%), tibia (86%), and radius/ulna (25%) than in the femur, where only 14% of the tumors were proximally located ($p<0.001$). We observed a substantially higher percentage of OS located in the proximal femur among elderly patients in contrast to other anatomical locations in long bones (Figure 1).

Clinicopathological data. As seen in Table I, there were no significant differences between the POS and the DOS groups regarding gender, age, tumor size, duration of symptoms, pathological fracture, secondary OS, LDH, ALP, and histologic type. Approximately 23% (51 patients) of all patients had metastatic disease at the time of OS diagnosis, nearly equally distributed among groups of POS and DOS, respectively. In contrast, as many as 44% (8 cases) of the patients with OS in the proximal femur had primary metastatic disease.

Treatment. Amputations were more often performed in DOS patients (65%) in comparison to the POS patients (35%) (Table I). We have previously demonstrated a significant increase in limb salvage procedures since the 1980s for high-grade OS in Norway during this time period, although amputation still remains a valid and justified procedure in selected OS cases (5). In the current study, we documented a higher percentage of adequate surgery among patients with DOS (86%) as compared to those having POS (79%) (Table I). Interestingly, only 39% (7 patients) of the cases with a primary tumor in the proximal femur received adequate surgery in comparison to all (10 patients) of the cases with a primary tumor in the fibula, 88% (44 patients) of the cases with a primary tumor in the tibia and 82% (18 patients) with a primary tumor in the humerus. This discrepancy was due to the fact that eight patients in the previously mentioned POS subgroup did not undergo surgery, mainly due to disseminated disease at the time of diagnosis and/or higher age (Figure 1). We observed no significant differences in receiving adequate treatment among the patients in the POS *versus* the DOS on a group basis ($p=0.846$), as presented in Table I.

Table II. *Univariate Kaplan–Meier and Cox-regression analyses of five-year sarcoma specific survival and event-free survival based on different characteristics of long bone osteosarcoma.*

	Sarcoma specific survival				Event-free survival			
	Patients (%)	5 years in % (95%CI[1] in %)	RR[2] (95%CI[1])	*p*-Value[3]	Patients (%)	5 years in % (95%CI[1] in %)	RR[2] (95%CI[1])	*p*-Value[3]
Gender				0.455				0.031
Male	134 (61)	56 (48-64)	1		109 (64)	51 (42-60)	1	
Female	87 (39)	59 (47-68)	0.9 (0.6-1.3)		60 (36)	68 (55-78)	0.6 (0.4-1.0)	
Anatomic site				0.001				0.072
Distal femur	107 (48)	58 (47-66)	1		82 (49)	61 (48-70)	1	
Proximal femur	18 (8)	22 (7-43)	3.7 (2.1-6.8)	<0.001	9 (5)	33 (8-62)	2.5 (1.1-5.7)	0.026
Proximal tibia	50 (23)	70 (55-81)	0.5 (0.5-1.4)	0.468	42 (25)	62 (45-74)	0.9 (0.5-1.5)	0.594
Distal tibia	8 (4)	63 (23-86)	1.1 (0.4-3.2)	0.803	7 (4)	14 (1-46)	2.5 (1.1-6.1)	0.035
Proximal fibula	10 (5)	48 (16-75)	1.0 (0.4-2.5)	0.994	7 (4)	69 (21-92)	0.8 (0.2-2.6)	0.707
Proximal humerus	22 (10)	55 (32-72)	1.3 (0.7-2.4)	0.417	16 (9)	56 (30-76)	1.2 (0.6-2.6)	0.567
Other	6 (3)	67 (20-90)	1.1 (0.3-3.4)	0.927	6 (4)	67 (20-90)	1.1 (0.3-3.6)	0.875
Age				0.003				<0.001
≤20 years	138 (62)	63 (54-71)	1		111 (66)	74 (65-81)	1	
20-40 years	44 (20)	56 (40-69)	1.2 (0.8-2.0)	0.394	30 (18)	73 (53-85)	1.2 (0.6-2.2)	0.585
>40 years	39 (18)	39 (24-53)	2.3 (1.4-3.6)	0.001	28 (17)	36 (19-53)	3.3 (1.9-5.6)	<0.001
Tumor size				0.011				0.090
≤11 cm	86 (43)	66 (57-75)	1		60 (39)	63 (53-72)	1	
>11 cm	112 (57)	45 (37-52)	1.7 (1.1-2.6)		95 (61)	48 (35-60)	1.5 (0.9-2.3)	
Pathological fracture				0.048				0.041
No	184 (83)	60 (53-67)	1		143 (85)	59 (51-67)	1	
Yes	37 (17)	43 (27-58)	1.6 (1-2.6)		26 (15)	46 (27-64)	1.8 (1.0-3.0)	
Primary metastasis				<0.001				
No	169 (77)	69 (61-76)	1					
Yes	51 (23)	17 (8-29)	4.2 (2.8-6.3)					
Secondary osteosarcoma				0.116				<0.048
No	213 (96)	58 (51-64)	1		163 (96)	58 (50-65)	1	
Yes	8 (4)	38 (9-67)	2.0 (0.8-5.0)		6 (4)	33 (5-68)	2.4 (1.0-6.0)	
LDH				0.005				0.037
Normal	82 (54)	69 (58-78)	1		68 (58)	63 (52-74)	1	
Increased	71 (46)	45 (33-56)	1.9 (1.2-3.1)		49 (42)	49 (35-62)	1.7 (1.0-2.9)	
ALP				<0.001				0.005
Normal	90 (56)	71 (60-79)	1		80 (65)	66 (55-75)	1	
Increased	71 (44)	39 (28-50)	2.3 (1.4-3.5)		43 (35)	42 (27-56)	2.1 (1.2-3.4)	
Histological subtype				<0.081				0.251
Osteoblastic	106 (49)	53 (43-62)	1		80 (48)	54 (42-64)	1	
Chondroblastic	25 (11)	76 (54-88)	0.6 (0.3-1.2)	0.117	21 (13)	62 (38-79)	0.8 (0.4-1.6)	0.765
Fibroblastic	20 (9)	75 (50-89)	0.5 (0.2-1.1)	0.486	15 (9)	60 (32-80)	0.9 (0.4-1.9)	0.869
Mixed	58 (27)	57 (43-69)	0.6 (0.7-1-3)	0.882	47 (28)	60 (44-72)	1.0 (0.6-1.6)	0.918
Other	9 (4)	11 (1-39)	3.8 (1.9-7.7)	<0.001	3 (2)	33 (1-77)	3.2 (1.0-10.3)	0.056
Years of diagnosis				0.039				0.057
1982-89	68 (31)	47 (33-57)	1.8 (1.1-2.9)	0.015	51 (30)	41 (28-54)	1.9 (1.1-3.2)	0.022
1990-99	70 (32)	59 (46-69)	1.2 (0.8-2.0)	0.396	54 (32)	59 (45-71)	1.3 (0.7-2.2)	0.416
2000-09	83 (37)	65 (54-74)	1		64 (38)	69 (56-79)	1	
Adequate treatment				<0.001				<0.001
Yes	163 (74)	72 (65-78)	1		139 (82)	67 (58-74)	1	
No	58 (26)	15 (7-25)	6.7 (4.5-10)		30 (18)	11 (3-25)	9.2 (5.6-15.2)	

[1]Confidence interval, [2]relative risk and [3]log rank.

Metastatic relapse or local recurrence during follow-up. Among the patients without primary metastatic disease, 30 of the POS patients (42%) and 41 of the DOS patients (44%) developed metastases from OS during follow-up (p=0.636). Approximately 90% of the patients in both metastatic subgroups developed recurrence in the lungs (first metastatic relapse). Among the patients with no primary metastatic disease, four patients experienced local relapse during

Table III. *Multivariate Cox-regression analyses of prognostic factors and treatment-related variables for sarcoma specific survival and event-free survival.*

	Sarcoma specific survival		Event-free survival	
Variables[1]	RR[2] (95%CI[3])	*p*-Value	RR[2] (95%CI[3])	*p*-Value
Gender			1.7 (0.9-3.3)	0.087
Anatomic site				
Proximal femur	5.5 (2.3-13.1)	<0.001		
Proximal tibia	1.1 (0.6-2.1)	0.776		
Distal tibia	0.7 (0.2-3.1)	0.623		
Proximal fibula	1.3 (0.4-3.9)	0.618		
Proximal humerus	1.4 (0.6-3.1)	0.427		
Other	2.3 (0.5-10.0)	0.276		
Primary metastasis	3.9 (2.3-6.6)	<0.001		
Secondary osteosarcoma			11.1 (2.4-52.6)	0.002
Elevated LDH	1.6 (1.0-2.7)	0.068	1.8 (1.0-3.0)	0.034
Years at diagnosis				
1982-1989	2.1 (1.1-3.7)	0.015		
1990-1999	1.7 (0.9-3.3)	0.112		
2000-2009	1			
Adequate treatment				
Yes	1		1	
No	4.3 (2.3-7.7)	<0.001	4.4 (2.4-7.9)	<0.001

[1]References values in line with Table II. [2]Relative risk and [3]confidence interval.

follow-up in both the POS (5%) and the DOS (4%) subgroups, respectively (p=0.743). The median time to the first metastatic event, or local recurrence, was 2.2 years (range=0.2-11.6 years) and 2.3 years (range=0.3-7.6 years) from diagnosis, respectively.

Survival analysis. Univariate survival analyses revealed no difference in survival between all POS and DOS patients (Figure 2; SSS, p=0.430; EFS, p=0.808). Nevertheless, a significant discrepancy was observed in both overall survival and SSS within the respective groups of patients with OS in extremity long bones, with the poorest prognosis for patients with a primary tumor located in the proximal femur (Table II and Figure 3A). The poor prognosis of the latter subgroup regarding overall survival and SSS was independent of primary metastatic disease (Figure 3B, SSS, p=0.037) or not (Figure 3C, SSS, p=0.022; EFS, p=0.086). We did not identify any corresponding difference in survival among the groups; neither in patients below 20 years at time of diagnosis (Figure 3D; SSS, p=0.702; EFS, p=0.422) nor among patients that were adequately treated (Figure 3E; SSS, p=0.539; EFS, p=0.227).

Table II presents the results of the univariate analyses as five-year SSS and EFS based on different OS characteristics, including time periods and adequate *versus* inadequate treatment. The non-significant impact of the duration of symptoms observed (p=0.913/0.947) is not included in Table II.

Prognostic factors. The results of the final step in the multivariate cox analyses are presented in Table III. OS in proximal femur and primary metastatic disease were both adverse prognostic factors for SSS while elevated LDH and secondary OS were inferior prognostic factors for EFS. As expected, patients that received adequate treatment had significantly better SSS and EFS than patients that received inadequate treatment. No improvement in SSS was identified for all patients since the 1990s.

Discussion

No previous nationwide studies have analyzed the prognostic relevance of POS *versus* DOS. The current cohort of extremity long bone OS was extracted from an unselected cohort that comprised all subgroups and histopathological entities of OS, including secondary OS, between 1982 and 2009 in Norway.

We observed no difference in survival between all patients dichotomized between POS and DOS primary disease in extremity long bones (Figure 2). This finding is in accordance with the results reported in a previous study from the United Kingdom (9). However, several prior studies found poorer outcomes for POS than DOS (4, 6, 14, 15). Nevertheless, we documented inferior survival among all patients with OS in the proximal femur in comparison to OS in other anatomical locations in extremity long bones (Figure 3a, Table II, Table III). Previous reports have also documented the proximal femur as an unfavorable anatomical site for OS (4, 6, 8, 16).

The dismal outcome of proximal tumor sites documented in previous studies has been linked to several hypotheses, such as variations in chemosensitivity (8) or differences in other biological factors, such as regional blood flow (6). There is, however, no sound evidence for these hypotheses (6). The prognostic effect of the anatomical location of OS within a long bone can be influenced by methodological inequalities between various studies. For example, the proximal tibia and fibula were considered to be a distal site of origin in some prior studies (4, 8), while one study defined the correct anatomical location (6). Furthermore, in comparison to population-based studies, the results of prior studies may also depend on the clinical and demographic characteristics of the OS population being analyzed, which may be biased, for example, depending on the referral patterns, pediatric and adolescents *versus* including also adult OS patients and/or reporting systems of the various hospitals involved.

We believe that the strength of the present study is the reliability of the database, which is validated by multiple and partly overlapping data and registry sources. As expected in

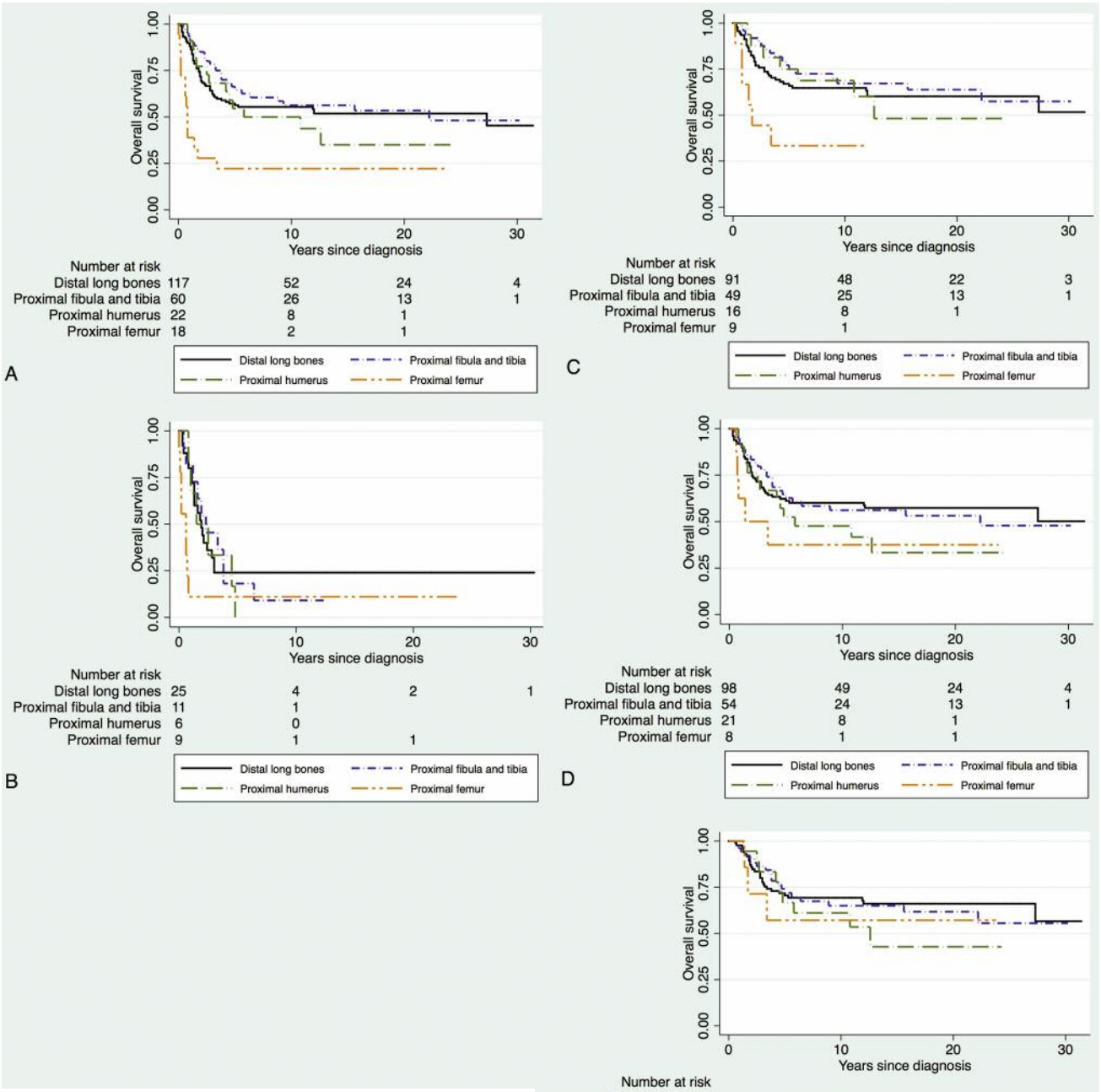

Figure 3. *Overall survival of patients with osteosarcoma related to extremity long bone localizations (femur, humerus, tibia, and fibula); A) for all patients (p<0.001); B) patients with metastasis at time of diagnosis (p=0.037); C) patients without metastasis at time of diagnosis (p=0.030); D) patients below 20 years of age at time of diagnosis (p=0.207) and E) among all patients that were adequately treated (p=0.707).*

nationwide studies, we were unable to obtain complete clinical information for all the patients in the present study. Moreover, unlike prospective clinical trials or experiences from institutional series, in our approach, it was not possible to obtain the same degree of detail regarding certain clinical variables. As an example, we cannot rule out that excluding histologic response to preoperative chemotherapy (4, 17, 18) may have affected the prognostic factors presented in Table III. The latter would have necessitated a complete and uniform histological reexamination of all cases in the present

cohort. Consequently, a significant disadvantage of such an approach is the lack of available histological specimens for reexamination. Hence, we have chosen not to include histological response to chemotherapy in this paper since we believe the potential disadvantage will exceed the potential gain of such an approach.

Furthermore, we were not able to include patients diagnosed with OS later than 2009 in the present cohort. However, we believe this limitation has minor impact on the results of the present study since conventional chemotherapy in conjunction with surgery has reached a plateau phase since the end of the 1980s (2, 19), also confirmed in this publication.

Conclusion

In this first study to investigate the prognostic importance of the anatomical location of OS within long bones of the appendicular skeleton in a nationwide setting. OS of the proximal femur had a more unfavorable outcome than OS in other locations in extremity long bones.

Conflicts of Interest

The Authors report no conflicts of interest. The Authors alone are responsible for the content and writing of the paper.

Authors' Contributions

Both Authors have contributed equally to concept and design of the study, data interpretation and writing the manuscript. First Author was responsible for establishing the gross database, merging clinical data from overlapping and multiple register sources and all data, as well as statistical analyses. Both Authors have in selected cases scrutinized available clinical records to ensure correct clinical information and approved the final version of the manuscript.

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