



## Original Article

## Bone tumors distribution in diagnostic and excisional biopsies

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## ABSTRACT

**Objectives:** Bone tumors are uncommon. Nevertheless, bone is a common site for metastasis. Due to limited data regarding bone tumors in Jordan, this study aims to understand better bone tumor epidemiology and distribution in the Jordanian population.**Methods:** A part of a retrospective, single-center study, all biopsy reports confirming the diagnosis of a bone tumor between January 2017 and December 2019 were abstracted from Princess Iman Research Center records. The patients' age, gender, anatomical location, and histopathological type of the tumors were obtained and analyzed.**Results:** Two hundred eighty-four diagnostic and excisional biopsies were reviewed. Most of the patients (60.2%) were males. The mean age for the patients was 26.74(±16.29) years. Malignant bone tumors were diagnosed in 15.6%. The femur was the most common site of biopsy diagnosed tumor followed by the tibia.

Osteochondroma was the most commonly diagnosed benign tumor and accounted for 39.4%, followed by aneurysmal bone cysts (14.8%), and enchondroma (10.2%). The metastatic bone tumors were the most frequent malignant bone pathology (6.7%), while osteosarcoma was the most common primary sarcoma, diagnosed in 5.6% of the sample. Increasing age, pelvic, and spine location of bone tumors were found to be significantly associated with malignancy.

**Conclusion:** In our 284 samples, osteochondromas were the most commonly diagnosed tumors (39.4%), followed by aneurysmal bone cysts (14.8%), and enchondromas (10.2%). Metastatic tumors were the most common malignant bone pathologies, while osteosarcomas were the most common primary bone sarcomas. Femur and tibia were the most common tumor-located sites. Breast and lung deposition were the most common metastasis primaries. Additionally, increasing age, pelvic, and spine-located bone tumors were significantly associated with malignancy.**Keywords:** Benign, Biopsy, Bone tumor, Jordan, Malignant

## INTRODUCTION

Bone neoplasms are uncommon tumors; bone sarcomas account for less than 0.2% of overall tumors.<sup>[1]</sup> However, bone is considered the third most common metastasis site, just after lung and liver.<sup>[2]</sup> Common sources of metastasis to bone include breast, lung, thyroid, kidney and prostate. The spine is the most common target for metastasis.<sup>[3]</sup>

According to the World Health Organization (WHO) classification of soft tissue and bone tumors, bone tumors are classified according to the differentiation of neoplastic cells and their

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similarity to normal matches.<sup>[4]</sup> Accordingly, bone tumors are grouped into 15 categories. Cartilage producing, osteogenic producing, fibrogenic producing, giant cell, and notochordal origin are examples of this classification.<sup>[5,6]</sup> Currently, bone tumor classification is more complex and includes a combination of morphology, phenotype, and genotype parameters.<sup>[7,8]</sup>

Bone tumors may be detected incidentally or may be presented after a pathological fracture. Pain and palpable lump are common presenting features of bone tumors.<sup>[9]</sup> Bone pathology could be diagnosed based on clinical and radiological features. Nevertheless, a biopsy is a definitive test to confirm the diagnosis. However, not all bone-tumor cases required a biopsy for consecutive management.<sup>[10]</sup>

Estimating the annual incidence and prevalence of bone tumors is challenging since not all cases need investigation or treatment. Many tumors are diagnosed according to their radiological features and the fact that some of them are incidentally detected. Therefore, it is necessary to understand the distribution of bone tumors and their histopathological allocation. There are no sufficient resources about bone tumors in Jordan; most of them are hospital-based or concerning certain age groups or histopathological types. According to Jordan Cancer Registry, malignant bone tumor accounts for 0.9% of overall cancer in Jordan.<sup>[11]</sup> Regional resources are limited as well. Therefore, this study aimed to review the histopathological type of bone tumors and their distribution regarding age, gender, and anatomical locations to help in a better understanding of bone tumors and aid in diagnosis.

## MATERIALS AND METHODS

This is a retrospective, single-center study conducted at Princess Iman Research Center (PIRC) at King Hussein Medical City (KHMC), one of the limited oncology-laboratory centers in Jordan. All biopsy reports confirming a bone tumor's diagnosis between January 2017 and December 2019 were abstracted from PIRC's records.

Princess Iman Research Center receives specimens from KHMC and all-district military hospitals in Jordan, which insures many Jordanian population sectors. All biopsies were evaluated at PIRC by two histopathologists, first by a specialist for the diagnosis, then confirmed by a consultant.

The patients' age, gender, anatomical location, and histopathological types of the tumors were obtained and analyzed. Tumors are classified into benign and malignant tumors; metastatic tumors were assessed with malignant ones. Additionally, benign and malignant tumors were

assessed according to anatomical location, tumor origin, gender, and age group.

A total of 284 confirmed bone tumor specimen were evaluated. The study included all diagnostic or excisional biopsies confirming bone tumors, limbs and trunk location of bone tumor, and a single diagnosis biopsy. Skull bone tumors and reports with more than one possible diagnosis were excluded.

## Statistical data analysis

Descriptive analysis with the mean and standard deviation was applied to continuously measured variables and the frequency and percentages for categorical variables. In addition, the statistical normality assumption was tested with the histograms, and the statistical Kolmogorov–Smirnov test and the equal variance assumption was tested with Levene's test.

The unpaired samples' t-test was used to assess the statistical significance of mean difference on metric variables across patients' binary dichotomous variables levels. The chi-squared test of independence ( $\chi^2$ -test) was used to evaluate the statistical value of associations between categorically measured variables. However, the residual analysis with the adjusted standardized residuals was used along with the chi-squared test of association to identify influential cells within the contingency tables for their clinical implications. Cells within the contingency (chi-squared) test tables with a standardized adjusted residual above or below (+1.96) were considered the influential cells with a more or less predicted likelihood for the analyzed outcomes like malignancy association with patients age and gender.

The chi-squared Goodness-Of-Fit test ( $\chi^2$ -G.O.F) was used to assess the statistical significance of the distribution of soft tissue tumors across the patients' body locations and age groups.

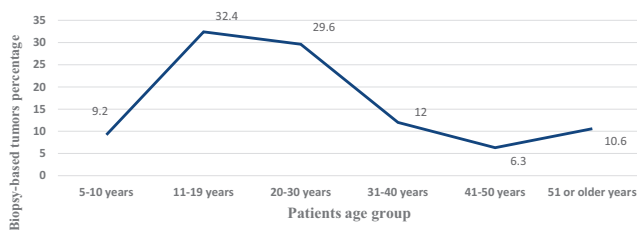
The Statistical Package for the Social Sciences (SPSS) IBM Version 21 (Chicago) was used for the statistical data analysis, and the alpha significance level was considered at the 0.050 level.

## RESULTS

Two hundred eighty-four patients' biopsy results were reviewed retrospectively. Table 1 summarizes findings for the patients' sociodemographic, tumor body location, and histopathological characteristics. Males represented most of the study sample (60.2%). The majority of the patients were younger than 30 years. The mean age for the patients was 26.74( $\pm$ 16.29) years. Figure 1 demonstrates the distribution of biopsy-based tumor percentage across age groups.

**Table 1:** Patients sociodemographic characteristics and distribution of bone tumor by body locations, histopathological specimens, and metastatic sources. (N = 284)

	Frequency	Percentage		Frequency	Percentage
<b>Gender</b>			<b>Frequency of bone tumors in the histopathological specimen</b>		
Female	113	39.8	<b>Benign tumors</b>		
Male	171	60.2	Osteochondroma	112	39.4
<b>Age (years) mean (SD)</b>			Aneurysmal bone cyst	42	14.8
26.74(±16.29)			Enchondroma	29	10.2
<b>Age groups</b>			Giant cell tumor of bone	19	6.7
5–10 years	26	9.2	Osteoid osteoma	17	6
11–20 years	92	32.4	Chondroblastoma	10	3.5
21–30 years	84	29.6	Fibrous dysplasia	6	2.1
31–40 years	34	12	Non-ossifying fibroma	3	1.1
41–50 years	18	6.3	Solitary bone cyst	2	0.7
≥ 51 years	30	10.6	<b>Malignant tumors</b>		
<b>Tumor location</b>			Metastasis	19	6.7
Femur	76	26.8	Osteosarcoma	16	5.6
Tibia	67	23.6	Chordoma	6	2.1
Humerus	33	11.6	Ewing's sarcoma	2	0.7
Hand	28	9.9	Chondro sarcoma	1	0.4
Spine	20	7	<b>Metastatic source</b>		
Foot	16	5.6	Breast	7	36.8
Fibula	11	3.9	Lung	6	31.6
Radius	11	3.9	Kidney	2	10.5
Pelvis	9	3.2	Prostate	2	10.5
Scapula	8	2.8	Lymphoma	1	5.3
Chest wall	5	1.8	Pancreaticobiliary	1	5.3
<b>Tumor general classification</b>			<b>Age group collapsed based on 40 year</b>		
Benign	240	84.5	≤ 40 years	236	83.1
Malignant	44	15.5	> 41 years	48	16.9



**Figure 1:** The proportions of the biopsy-based tumor within different age groups.

Regarding the bone tumor distribution according to the body locations, the femur (26.8) was the most common site of the biopsy-diagnosed tumor, followed by the tibia. The majority of tumors were of a benign type found in 84.5% of the specimens. Considering the bone tumor origin, most of them (53.5%) had chondroid-producing tumors, followed by giant cell originated-tumors (21.5%). Osteoid-producing tumors accounted for 11.6% of the specimens, while metastatic deposition represented 6.7%.

Concerning the frequency of bone tumors according to biopsies' findings, osteochondroma was the most commonly (39.4%) diagnosed tumor in histopathological specimens. The metastatic bone tumors were the most frequent malignant bone pathology (6.7%), and osteosarcoma was the most common primary sarcoma (5.6%) [Figure 2]. Breast and lung

cancer deposition were the most common metastatic source to bone and accounted for 36.8% and 31.6%, respectively.

Table 2 gives a detailed distribution of specific tumors regarding their anatomical location. Most tumors occur in long bones. However, chest wall, scapula, and pelvis were uncommon sites for bone tumors.

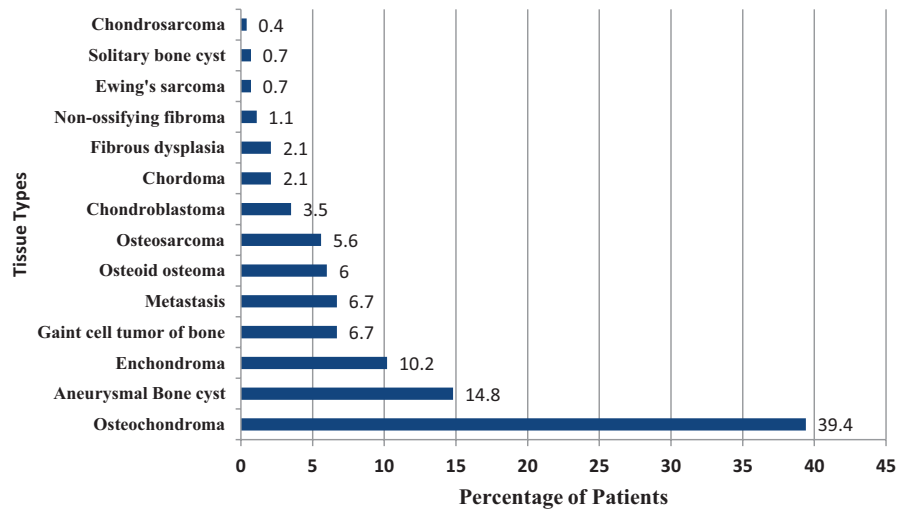


Figure 2: The percentage of patients with various bone tumor types.

Table 2: The distribution of bone tumors across body locations. (N = 284)

	Femur	Tibia	Humerus	Hand	Spine	Foot	Fibula	Radius	pelvis	Scapula	Chest Wall
Osteochondroma	36(32.1)	35(31.3)	10(8.9)	5(4.5)	0	5(4.5)	6(5.4)	4(3.6)	2(1.8)	8(7.1)	0
Aneurysmal bone cyst	13(31)	8(19)	8(19)	2(4.8)	1(2.4)	3(7.1)	4(9.5)	2(4.8)	1(2.4)	0	0
Enchondroma	2(6.9)	1(3.4)	0	20(69)	0	2(6.9)	1(3.4)	1(3.4)	0	0	2(6.9)
Giant cell tumor of bone	1(5.3)	7(36.8)	5(26.3)	1(5.3)	1(5.3)	2(10.5)	0	2(10.5)	0	0	0
Osteoid osteoma	1(50)	1(50)	0	0	0	0	0	0	0	0	0
Chondroblastoma	3(30)	3(30)	2(20)	0	0	1(10)	0	1(10)	0	0	0
Fibrous dysplasia	1(16.7)	1(16.7)	0	0	0	0	0	0	1(16.7)	0	3(50)
Non-ossifying fibroma	0	2(66.7)	0	0	0	0	0	1(33.3)	0	0	0
Solitary bone cyst	6(35.3)	4(23.5)	2(11.8)	0	2(11.8)	2(11.8)	0	0	1(5.9)	0	0
Metastasis	3(15.8)	0	5(26.3)	0	10(52.6)	0	0	0	1(5.3)	0	0
Osteosarcoma	9(56.3)	4(25)	1(6.3)	0	0	0	0	0	2(12.5)	0	0
Chordoma	0	0	0	0	6(100)	0	0	0	0	0	0
Ewing's sarcoma	0	1(50)	0	0	0	0	0	0	1(50)	0	0
Chondrosarcoma	1(100)	0	0	0	0	0	0	0	0	0	0

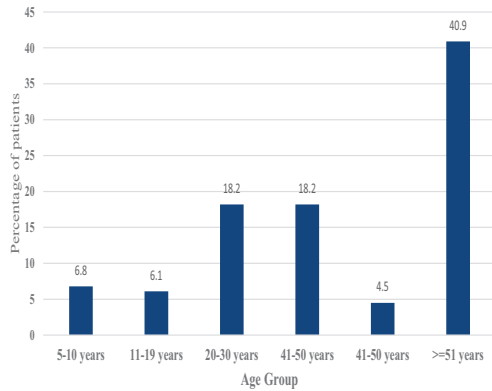
The numbers between brackets are the percentage of patients in relation to the tumor type.

By analyzing bone tumors' correlation with sociodemographic characteristics [Table 3], biopsy-based bone tumors were most commonly diagnosed from femur, tibia, humerus, and hand. There was no statistical correlation between

patients' gender with the malignancy ( $p = 0.869$ ). Nevertheless, patients with bone sarcomas were older than those with benign tumors; the mean age for bone sarcomas was 28.12 years compared to 23.78 years in the benign group.

**Table 3:** Bivariate analysis of the patients' bone tumor.

	Tumor classification		Test statistic	p-value
	Benign	Malignant		
<b>Gender</b>				
Female	95(39.2)	18(40.9)	$\chi^2(1)=0.03$	0.869
Male	145(60.4)	26(59.1)		
<b>Age (years) mean (SD)</b>	23.78(12.99)	42.89(22.17)	$t(48.56) = 5.55$	0.009
<b>Age group</b>				
5–10 years	23(9.6)	3(6.8)	$\chi^2(5) = 44.60$	< 0.001
11–19 years	87(36.2)	5(11.4)		
20–30 years	76(31.7)	8(18.2)		
41–50 years	26(10.8)	8(18.2)		
41–50 years	16(6.7)	2(4.5)		
≥ 51 years	12(5)	18(40.9)		
<b>Age group collapsed based on 40 year</b>				
≤ 40 years	212(88.3)	24(54.5)	$\chi^2(1) = 30.22$	< 0.001
≥ 41 years	28(11.7)	20(45.5)		
<b>Tumor location</b>				
Femur	63(26.2)	13(29.5)	$\chi^2(10) = 76.11$	< 0.001
Tibia	62(25.8)	5(11.4)		
Humerus	27(11.2)	6(13.6)		
Hand	28(11.7)	0		
Spine	4(1.7)	16(36.4)		
Foot	16(6.7)	0		
Fibula	11(4.6)	0		
Radius	11(4.6)	0		
Pelvis	5(2.1)	4(9.1)		
Scapula	8(4.6)	0		
Chest wall	5(2.1)	0		
<b>Tumor origin general types</b>				
Chondroid producing	151(62.9)	1(2.3)	$\chi^2(7) = 187.14$	< 0.001
Giant cell origin	61(25.4)	0		
Osteoid producing	17(7.1)	16(36.4)		
Secondary tumor	0	19(43.2)		
Fibrous tissue producing	9(3.8)	0		
Giant cell	61(25.4)	0		
Notochord origin	0	6(13.6)		
Tumor-like lesion	2(0.8)	0		
Unknown origin	0	2(4.5)		



**Figure 3:** Percentage of patients with definitive malignant tumors across patient's age groups.

The mean age for the metastatic tumors was 62.32, and the mean age for all malignant bone tumors was 42.89 years ( $p = 0.009$ ). Figure 3 demonstrates the percentage of patients with definitive malignant tumors across patients' age groups. Additionally, the tumor location had converged significantly on the malignancy potential. The patients with pelvic and spine located bone tumors were significantly more malignant than tumors of other body parts,  $p < 0.001$ .

Also, the patients' gender was statistically significantly associated with the bone tumor type, location, origin, and malignancy [Tables 4 and 5]. The analysis showed that the male patients were significantly younger than females ( $p < 0.001$ ). Moreover, the review revealed a statistically significant association between the tumor location and the patients' gender,  $p = 0.001$ . Male patients were found to be significantly less related for pelvic and hand tumors compared to females. However, they were found

**Table 4:** Bivariate analysis of the patients' gender for statistically significant differences in bone tumors location and origin findings.

	Patients gender		Test statistic	p-value
	Female	Male		
<b>Age (years) mean (SD)</b>	31.03(18.20)	23.90(14.30)	$t(199.6) = 3.51$	$< 0.001$
<b>Age group collapsed based on 40 years</b>				
≤ 40 years	81(71.7)	155(90.6)	$\chi^2(1) = 17.42$	$< 0.001$
> 41 years	32(28.3)	16(9.4)		
<b>Tumor location</b>				
Femur	19(16.8)	57(33.3)	$\chi^2(10) = 30.96$	0.001
Tibia	21(18.6)	46(26.9)		
Humerus	18(15.9)	15(8.8)		
Hand	16(14.2)	12(7)		
Spine	11(9.7)	9(5.3)		
Foot	9(8)	7(4.1)		
Fibula	5(4.4)	6(3.5)		
Radius	5(4.4)	6(3.5)		
Pelvis	7(6.2)	2(1.2)		
Scapula	2(1.8)	6(3.5)		
Chest wall	0	5(2.9)		
<b>Tumor origins</b>				
Chondroid producing	54(47.8)	98(57.3)	$\chi^2(7) = 16.2$	0.023
Giant cell origin	33(29.2)	28(16.4)		
Osteoid producing	9(8)	24(14)		
Secondary tumor	12(10.6)	7(4.1)		
Fibrous tissue producing	2(1.8)	7(4.1)		
Notochord origin	2(1.8)	4(2.3)		
Tumor-like lesion	0	2(1.2)		
Unknown origin	1(0.9)	1(0.6)		

**Table 5:** Bivariate analysis of the patients' gender for statistically significant differences in bone tumors histopathological findings.

Histopathological returned tissue finding	Patients gender		Test statistic	p-value
	Female	Male		
<b>Benign tumors</b>				
Osteochondroma	33(29.2)	79(46.2)	$\chi^2(14) = 37.13$	0.001
Aneurysmal bone cyst	19(16.8)	23(13.5)		
Enchondroma	19(16.8)	10(5.8)		
Giant cell tumor of bone	14(12.4)	5(2.9)		
Osteoid osteoma	6(5.3)	11(6.4)		
Chondroblastoma	2(1.8)	8(4.7)		
Fibrous dysplasia	1(0.9)	5(2.9)		
Non-ossifying fibroma	1(0.9)	2(1.2)		
Solitary bone cyst	0	2(1.2)		
<b>Malignant tumors</b>				
Metastasis	12(10.6)	7(4.1)		
Osteosarcoma	3(2.7)	13(7.6)		
Chordoma	2(1.8)	4(2.3)		
Ewing's sarcoma	1(0.9)	1(0.6)		
Chondrosarcoma	0	1(0.6)		
<b>Metastatic source</b>				
Breast	7(58.3)	0	$\chi^2(5) = 14.60$	0.012
Kidney	1(8.3)	1(14.3)		
Lung	2(16.7)	4(57.1)		
Lymphoma	1(8.3)	0		
Pancreatic-biliary	1(8.3)	0		
Prostate	0	2(28.6)		

significantly more related to femur tumors than females,  $p < 0.001$ . Secondary bone tumors were noticed more in female patients ( $p = 0.023$ ), which can be explained by the frequency of breast cancer in Jordan. Similarly, the patients' age groups were explored for a statistical association of bone tumors with anatomical locations, origins, types, and staging. Although the middle age period is somewhat arbitrary and varies from person to person, we used a 40-year cut point for analytical purposes. Table 6 showed that patients older than 41 years were significantly associated with spine tumors, secondary tumor depositions, notochord tumor origins, chondromas, fibrous dysplasias, giant tumors, and osteoid osteomas compared to younger age groups ( $p < 0.001$ ). Moreover, patients older than 41 years had lower

femoral and tibial tumor location frequency in addition to lower chondroid and osteoid producing tumor origins and aneurysmal bone cysts ( $p < 0.001$ ).

## DISCUSSION

In this study, we collected all bone tumor-biopsy results over three years; subsequently, just the tumors that were evaluated histopathologically were included. Secondary to this data collection design, the tumors not treated surgically nor investigated by diagnostic or excisional biopsies were not included. Therefore, this explains some findings in our study. For example, we found low numbers of non-ossifying fibroma in this study because this type of tumor is diagnosed

**Table 6:** Bivariate analysis of the patients' age groups for statistically significant differences in bone tumors findings.

	Patients age		Test statistic	p-value		
	≤ 40 years	> 41 years				
<b>Tumor location</b>						
Femur	70(29.7)	6(12.6)	$\chi^2(10) = 46.15$	< 0.001		
Tibia	61(25.8)	6(12.5)				
Humerus	26(11)	7(14.6)				
Hand	23(9.7)	5(10.4)				
Spine	7(3)	13(27.1)				
Foot	13(5.5)	3(5.2)				
Fibula	11(4.7)	0				
Radius	9(3.8)	2(4.2)				
Pelvis	4(1.7)	5(10.4)				
Scapula	8(3.4)	0				
Chest wall	4(1.7)	1(2.1)				
<b>Tumor origins</b>						
Chondroid producing	137(58.1)	15(31.2)			$\chi^2(7) = 67.54$	< 0.001
Giant cell origin	52(22)	9(18.8)				
Osteoid producing	32(13.6)	1(2.1)				
Secondary tumor	2(0.8)	17(35.4)				
Fibrous tissue producing	6(2.5)	3(6.2)				
Notochord origin	3(1.3)	3(6.2)				
Tumor-like lesion	2(0.8)	0				
Unknown origin	2(0.8)	0				
<b>Histopathological returned tissue finding</b>						
<b>Benign tumors</b>						
Osteochondroma	106(44.9)	6(12.5)	$\chi^2(13) = 87.94$	< 0.001		
Aneurysmal bone cyst	40(16.9)	2(4.2)				
Enchondroma	22(9.3)	7(14.6)				
Giant cell tumor of bone	12 (5.1)	7(14.6)				
Osteoid osteoma	16(6.8)	1(2.1)				
Chondroblastoma	8(3.4)	2(4.2)				
Fibrous dysplasia	4(1.7)	2(4.2)				
Non-ossifying fibroma	2(0.8)	1(2.1)				
Solitary bone cyst	2(0.8)	0				
<b>Malignant tumors</b>						
Metastasis	2(0.8)	17(35.4)	$\chi^2(13) = 87.94$	< 0.001		
Osteosarcoma	16(6.8)	0				
Chordoma	3(1.3)	3(6.2)				
Ewing sarcoma	2(0.8)	0				
Chondrosarcoma	1(4)	0				



incidentally and usually does not require treatment or biopsy evaluation. On the other hand, we found many osteochondromas in this study sample. Although their diagnosis can be made with accuracy by imaging only, but many surgeons prefer to confirm the pathology of the excised tumor, we found a high number of them. Similarly, although the hand is not usually a common location of bone tumors, the hand was the fourth common body tumor location in this study, secondary to many enchondroma diagnosed biopsies, which is a common benign hand tumor.

Comparative studies are limited in Jordan. Therefore, regional studies were utilized to match our findings. Sevimli in 2017, retrospectively evaluated 710 patients who were hospitalized at Inonu University Turgut Ozal Medical Center in Turkey, with pre-diagnosis of a tumor, over 7 years. Osteochondroma was the most common benign tumor, whereas the most commonly seen malignant bone tumor was chondrosarcoma followed by multiple myeloma and osteosarcoma.<sup>[12]</sup> Although the distribution of benign tumors in our study was similar, the distribution of bone sarcoma was different.

Öztürk *et al.* retrospectively evaluated 3133 patients with presumed musculoskeletal tumors in a tertiary clinic from different Turkey regions between January 2002 and July 2013. Osteochondromas, enchondroma, and simple bone cysts were the most common benign tumors, while osteosarcoma, Ewing's sarcoma, and chondrosarcoma were the most common malignant tumors, according to Öztürk's study.<sup>[13]</sup> In another study in a military hospital in Turkey, similar comparative findings were found by Neyisci *et al.* on 317 bone localized tumors.<sup>[14]</sup>

Another regional comparative study from Iran by Solooki *et al.*, 426 pathologic reports from 1997 to 2008 were reviewed. The findings were as follows: the commonest malignant bone tumors were osteosarcoma, metastasis, Ewing's sarcoma, and chondrosarcoma. The most frequent benign bone tumors were osteochondroma, enchondroma, giant cell tumor, and osteoid osteoma. The femur was the most commonly involved site in musculoskeletal tumors, followed by the tibia in benign tumors and the humerus in malignant ones.<sup>[15]</sup>

Despite similar results in our study compared to regional ones, it is still challenging to know the actual bone tumor prevalence secondary to many factors, including that many tumors are incidentally diagnosed, many others still in subclinical presentation. Furthermore, different design studies are required as well as radiological diagnosis-based studies. Nevertheless, having data based on local studies gives clues about the prevalence of bone tumors and aids in diagnosis. In addition, for the better outcome of tumor management, the diagnosis and management should be centralized. In Jordan, there are a few referral centers for

cancer management. Although many tumor cases are treated outside these centers, mutual and collaborative studies between these centers would improve our understanding of tumor prevalence in Jordan.

## CONCLUSION

In our 284-sample, osteochondroma was the most commonly diagnosed tumor (39.4%), followed by aneurysmal bone cysts (14.8%), and enchondromas (10.2%). Metastatic tumor was the most common malignant bone pathologies, while osteosarcoma was the most common primary bone sarcomas. Femur and tibia were the most common tumor-located sites. Breast and lung deposition were the most common metastasis primaries. Additionally, increasing age, pelvic, and spine-located bone tumors were significantly associated with malignancy.

## RECOMMENDATIONS

Bone tumor data are limited in Jordan and require further studies. Therefore, collaborative studies between all tumor centers in Jordan and different design studies are recommended to understand bone tumor distribution better.

## AUTHORS' CONTRIBUTIONS

AKM, BZD, MAG conceived and designed the study. AKM, OMA, HAA conducted research, provided research material, and collected and organized data. AKM and OMA analyzed and interpreted data. AKM, BZD and MAG wrote the initial and final draft of the article. All authors have critically reviewed and approved the final draft and are responsible for the manuscript's content and similarity index.

## ETHICAL APPROVAL

This study has been approved by the local ethical committee of the Jordanian Royal Medical Services under study ID: RMS 1-2021:19 on January 19th 2021.

## Declaration of patient consent

The authors certify that they have obtained all appropriate patients consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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## Conflicts of interest

There are no conflicts of interest.

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