

## Epidemiology of bone tumors in children and adolescents: a retrospective study of 266 patients in the south of Tunisia

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Although bone tumors (BT) are relatively uncommon among the human neoplasm, they constitute the most frequent tumors in children and adolescents (CAA). Little information is available about the epidemiologic features of BT in CAA. We aimed to present and discuss epidemiological characteristics of BT in CAA in southern Tunisia, regarding the different histological types. This is a retrospective study including cases of BT in CAA collected in the pathology department at the Habib Bourguiba university hospital over a period of 15 years (2006- 2020). A total of 266 BT was diagnosed in our institution (42,7% among all BT in Southern Tunisia) divided into 200 benign bone tumors (BBT) (75,2%) and 66 malignant bone tumors (MBT) (24,8%). The mean age for all BT was 14,2 years (3-20 years) with male predominance (sex ratio: 1,48). The most common tumor was osteochondroma (42.2%) followed by osteosarcoma (14.6%) and Ewing sarcoma (6.4%). For BBT, the most affected age group was the 16 to 20 year - old - group (50,7%) with a male predominance (59.8%) and a predilection for lower limb (66.8%) then the upper limb (16,8%). Osteochondroma was the most common histological type (56.5%) followed by aneurysmal cyst (8,5%) and osteoid osteoma (6,5%). For MBT, the mean age was 12,5 years (5-20 years) and the most affected age group was the 11 to 15 year -old -group (59%). Boys were more affected (60.6%), with a preference for the lower limb (57%) followed by the pelvis (15,6%). Osteosarcoma was the most common MBT (60%) followed by Ewing sarcoma (24%). Given their rarity and heterogeneity, the diagnosis of BT is particular in CAA and requires a multidisciplinary approach. The reporting of epidemiological studies remains essential in order to expand our knowledge regarding these uncommon tumors.

**Keywords:** Bone tumors, benign, malignant, epidemiology, children, adolescent.

### INTRODUCTION

Although bone tumors (BT) are relatively uncommon among the wide array of human neoplasms, they constitute the most frequent tumors in children and adolescents (CAA)<sup>1</sup>. They are very heterogeneous and include a wide variety of clinico-pathological entities<sup>2</sup>. Their management requires knowledge of their epidemiological profile. Most of BT are benign which account for 85-90% of cases. However, the frequency of benign BT is likely underestimated because these lesions are usually asymptomatic<sup>3</sup>. Osteochondroma is the most common BBT in CAA<sup>4</sup>. Malignant BT (MBT) are rare, representing 10-15% of BT in children and 5% of all pediatric cancers<sup>5</sup>. However, they are among the most common malignant tumors at this age and constitute the third leading cause of death in patients younger than 20 years<sup>6</sup>. Unlike those of adults, MBT

are almost primitive in CAA and are dominated by osteosarcoma and Ewing sarcoma<sup>7</sup>.

Currently, epidemiological data of childhood BT are still limited in the literature. Therefore, the aim of our study was to present and discuss epidemiological characteristics of BT in CAA in southern Tunisia, regarding the different histological types.

### MATERIALS AND METHODS

This is a retrospective study including cases of BT in CAA collected in the pathology department at the Habib Bourguiba university hospital, over a period of 15 years from 2006 through 2020. We enrolled in this study patients aged less than 20 years, with benign or malignant tumors, confirmed on biopsy samples or surgical resection specimens.

The patients 'age, sex, location and histological type of the tumor were retrieved.

The included BT were those diagnosed by fulfilling the 2020 WHO classification of soft tissue and bone tumors.

Data was collected and entered into a spreadsheet and analyzed using Excel software. Descriptive statistics was performed to calculate the percentages of qualitative variables and the mean of quantitative ones. Age was stratified into various groups of 5-year intervals.

**RESULTS**

From a total of 623 BT reviewed during the study period, 266 cases (42,7%) were seen in CAA and divided into 200 BBT (75.2%) and 66 MBT (24,8%), representing 51,5% and 23,5% respectively of all BT during this period. There were 159 boys (59,8%) and 107 girls (40,2%) with a male-female ratio of 1,48. The mean age at diagnosis was 14,2 years (3-20 years). The most affected age group was between 16 and 20 years; 82% of all patients were over 10 years old. The most common involved site was the lower limb (65%), upper limb (15,2%), head (7,1%), pelvis (4,7%), scapula (3,2%), vertebra (2%), clavicle (1,6%) and rib (1,2%). The most common histologic type was osteochondroma (42,2%) followed by osteosarcoma (14,6%) and Ewing sarcoma (6,4%). Bone metastases accounted for only 0.8% (2 cases) of all BT (Figure 1).

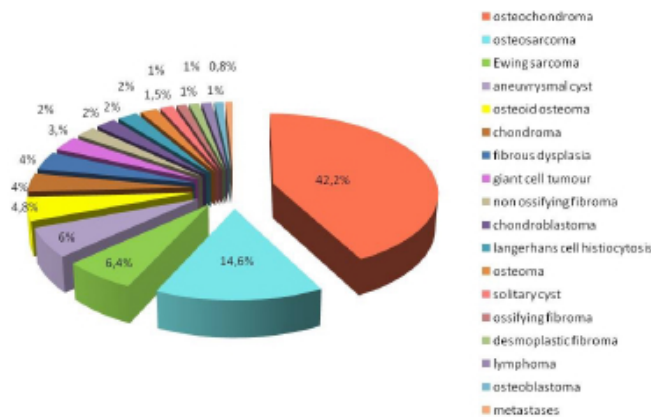


Figure 1. — Distribution of tumors by histological type.

**Benign bone tumors**

From a total of 200 BBT, 59,8% occurred in boys (119 cases) and 40,2% in girls (81 cases) with a mean age of 14,7 years (3-20 years). The most commonly affected age group was the 16 to 20 year-old-group (50,7%); 84% of cases were over the age of 10. Most

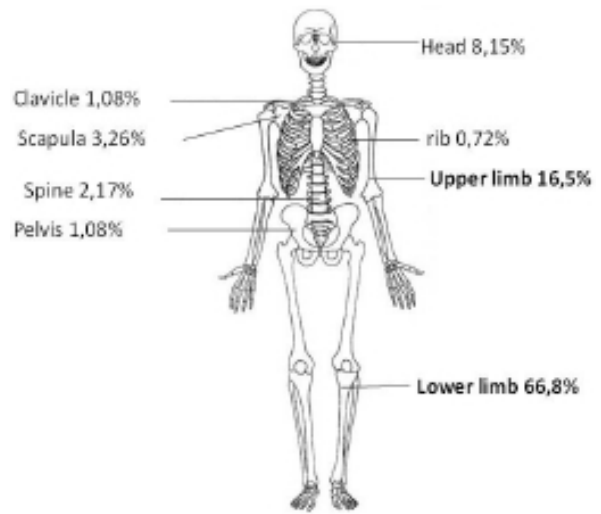


Figure 2. — Anatomical distribution of benign bone tumors.

Table I. — Distribution of benign bone tumors

	Number	Rate
<i>Chondrogenic tumors</i>		
Osteochondroma	113	56.5%
Chondroma/Enchondroma	10	5%
Chondroblastoma	6	3%
<i>Osteogenic tumors</i>		
Osteoid osteoma	13	6.5%
Osteoma	5	2.5%
Osteoblastoma	2	1%
<i>Other tumors</i>		
Aneurysmal cyst	17	8.5%
Fibrous dysplasia	10	5%
Giant tumor cell	8	4%
Non ossifying fibroma	6	3%
Solitary cyst	4	2%
Ossifying fibroma	3	1.5%
Demoplastic fibroma	3	1.5%
<b>Total</b>	<b>200</b>	<b>100%</b>

of the benign tumors arose in the lower limb (66,8%), followed the upper limb (16,8%) then head bones (8,15%) (Figure 2). The most common BBT was osteochondroma (56,5%) followed by aneurysmal bone cyst (8,5%) and Osteoid Osteoma (6,5%) (Table I).

The distribution of BBT by age categories revealed a peak in the 16 to 20-year old-group for most of histological types (Table II). Aneurysmal bone cyst was more frequent in the 11- to 15-year age group.

**Table II.** — Benign bone tumors according to age categories

	[1-5]	[6-10]	[11-15]	[16-20]	Total
<i>Chondrogenic tumors</i>					
Osteochondroma	4	12	27	<b>70</b>	113
Chondroma/Enchondroma	0	1	4	<b>5</b>	10
Chondroblastoma	0	0	1	<b>5</b>	6
<i>Osteogenic tumors</i>					
Osteoid osteoma	1	1	3	<b>8</b>	13
Osteoma	0	1	0	<b>3</b>	5
Osteoblastoma	0	1	1	0	2
<i>Other tumors</i>					
Giant cell tumour	1	1	2	<b>4</b>	8
Aneurysmal cyst	1	3	7	6	17
Solitary cyst	0	1	1	<b>2</b>	4
Fibrous dysplasia	1	0	3	<b>6</b>	10
Ossifying fibroma	0	0	1	<b>2</b>	3
Non-ossifying fibroma	1	1	2	2	6
Desmoplastic fibroma	1	0	0	<b>2</b>	3
<b>Total</b>	<b>12</b>	<b>23</b>	<b>52</b>	<b>115</b>	<b>200</b>

There were differences noted between sex and histologic type; male involvement was predominant in osteochondroma (62%), osteoid osteoma (72,2%), osteoma (100%), aneurysmal cyst (64,7%), and chondroblastoma (83,3%), and was slightly predominant in desmoplastic fibroma and ossifying fibroma compared to females. While girls were most affected in non-ossifying fibroma (83%), fibrous dysplasia (60%), chondroma (70%), giant cell tumor (62,5%), osteoblastoma (100%) and solitary bone cyst (75%).

Anatomical distribution of BBT by histologic type is given in Table III; lower limb was more affected in case of osteochondroma, osteoid osteoma, giant cell tumor, aneurysmal cyst, solitary bone cyst, non ossifying fibroma and chondroblastoma. Chondroma was mainly seen at the upper limb (70% of cases). Head bones were mostly affected in osteoma, ossifying fibroma and desmoplastic fibroma in 60%, 70% and 100% of cases respectively. The two cases diagnosed as osteoblastoma were localized in the head bones and lower limb.

### **Malignant bone tumors**

Of 66 patients with MBT, 60,6% (40 cases) occurred in boys and 39,4% (26 cases) in girls, with a mean age

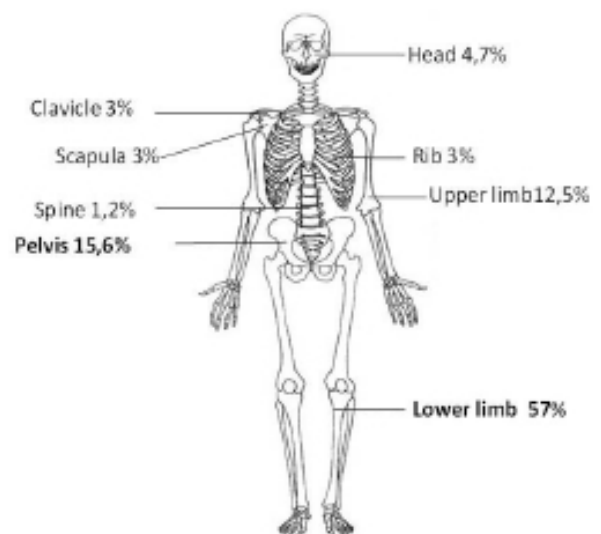
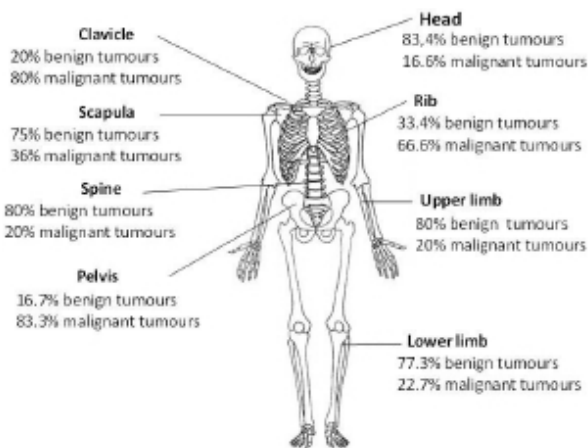


Figure 3. — Anatomical distribution of malignant bone tumors.

**Table III.** — Anatomical distribution related to diagnosis of benign bone tumors

	Lower limb	Upper limb	Head	Vertebra	Pelvis	Clavicle	Scapula	Rib
<i>Chondrogenic tumors</i>								
Osteochondroma	77%	14%	-	1%	2%	-	6%	-
Chondroma/Enchondroma	30%	70%	-	-	-	-	-	-
Chondroblastome	84%	16%	-	-	-	-	-	-
<i>Osteogenic tumors</i>								
Osteoid osteoma	83%	5,6%	5,8%	5,6%	-	-	-	-
Osteoma	-	-	60%	20%	-	20%	-	-
Osteoblastoma	50%	-	50%	-	-	-	-	-
<i>Other tumors</i>								
Giant cell tumor	50%	25%	12,%	12,5%	-	-	-	-
Aneurysmal cyst	86,%	9%	-	-	-	4,7%	-	-
Solitary cyst	75%	25%	-	-	-	-	-	-
Fibrous dysplasia	60%	-	30%	10%	-	-	-	-
Ossifying fibroma	30%	-	70%	-	-	-	-	-
Non Ossifying fibroma	83%	-	17%	-	-	-	-	-
Desmoplastic fibroma	-	-	100%	-	-	-	-	-



*Figure 4.* — Distribution of benign and malignant bone tumors in each location.

of 12,5 years (5-20 years). The most affected age group was the 11 to 15 year-old-group (59%); 83,3% of cases were under the age of 15. The most common sites were lower limb (57%) followed by pelvis (15.6%) and upper limb (12,5%) (Figure 3). It should be pointed out that reaching the pelvis, ribs and clavicle suggests MBT rather than BBT, while the latter predominates in the lower limb, upper limb, head, scapula, and spine (Figure 4).

Osteosarcoma was the most frequent MBT, occurring in 39 cases (60%) followed by Ewing sarcoma (16

cases; 24%). These two tumors accounted for 83.3% of all MBT. Langerhans cell histiocytosis was the third MBT accounting for 6 cases (9%). Primary bone lymphomas were observed in 3 cases (4%) and were of type of Hodgkin lymphoma, Burkitt lymphoma and T-lymphoblastic lymphoma.

The two cases of bone metastases (3%) were metastasis of medulloblastoma and neuroblastoma, in a 6-year-old girl and in a 14-year-old boy respectively.

Distribution of MBT according to age categories is shown in Table IV. The 11 to 15 year -old -group showed an increased frequency of histiocytosis, osteosarcoma and Ewing sarcoma. These last two tumors constituted 61% and 26.8% respectively of all MBT in this age group.

Boys were significantly more affected than girls in cases of Ewing sarcoma (68,7%) and Langerhans cell histiocytosis (100%) and less affected in osteosarcoma (53,4%) and lymphoma (2/1). For bone metastases, there was no difference noted between genders.

As shown in Table V, lower limbs were more significantly affected in osteosarcoma, Ewing sarcoma, lymphoma and bone metastases in 67.4%, 55%, 66.6% and 100% of cases, respectively. Histiocytosis occurred mainly in head bones.

**Table IV.** — Malignant tumors according to age categories

	[1-5]	[6-10]	[11-15]	[16-20]	Total
Osteosarcoma	0	6	<b>25</b>	8	39
Ewing Sarcoma	2	2	<b>11</b>	1	16
Langerhans cell histiocytosis	1	2	<b>3</b>	0	6
Lymphoma	1	1	1	0	3
Metastases	0	1	1	0	2
<b>Total</b>	4	12	<b>41</b>	9	66

**Table V.** — Anatomical distribution related to diagnosis of malignant bone tumors

	<i>Lower limb</i>	<i>Upper limb</i>	<i>Head</i>	<i>Vertebra</i>	<i>Pelvis</i>	<i>Clavicle</i>	<i>Scapula</i>	<i>Rib</i>
Osteosarcoma	<b>67,4 %</b>	12%	-	-	11%	4,6%	-	5%
Ewing sarcoma	<b>55%</b>	13%	-	6%	20%	6%	-	-
Lymphoma	<b>66,6%</b>	-	33,3%	-	-	-	-	-
Histiocytosis	25%	-	<b>63%</b>	-	12%	-	-	-
Metastases	<b>100%</b>	-	-	-	-	-	-	-

## DISCUSSION

BT are rare and diverse. They occur more commonly in CAA compared to adults<sup>1</sup>. BBT are much more frequent than malignant ones representing 80-95% of all BT<sup>3</sup>. They show a higher incidence in males (52 to 66%) with a peak during the second decade<sup>1,4</sup>. Indeed these lesions are often asymptomatic with late and incidental discovery<sup>8</sup>. Some tumors did seem to show female predilection such as non-ossifying fibroma, osteoblastoma, aneurysmal cyst, solitary cyst and giant cell tumor<sup>2,6,9</sup>. The most common BBT occurring in CAA is osteochondroma, representing 10 to 15% of all BT and 20 to 50% of all BBT<sup>5</sup>. Osteochondroma is also the most frequent BBT (56,5%) in our study followed by aneurysmal bone cyst (8,5%) and Osteoid Osteoma (6,5%). This is consistent with Van den Berg et al study<sup>2</sup>, which obtained 1474 children with BT and found that Osteochondroma was the most prevalent tumor, followed by aneurysmal bone cyst. Nevertheless, this distribution is different with other reports. Senac et al<sup>10</sup> showed that solitary cyst was the second most common lesion (23,9%) following osteochondroma. Ozkan et al<sup>6</sup> conducted a retrospective review of 57 patients less than 18 years of age. Osteochondroma was the most frequent BBT (54,3%) followed by osteoid osteoma (15,7%) and fibrous dysplasia (7%). Traoré et al<sup>4</sup> reviewed 169 children with BBT and they found that solitary cyst (17,7%) and aneurysmal cyst (14,2%) are the most prevalent tumors after osteochondroma (20%).

BBT have more appendicular than axial involvement, and they predominate in lower limbs (50 to 62%) followed by the upper limbs (12 to 25%)<sup>11-13</sup>. On the other hand, chondroma and solitary bone cyst predominate in the upper limbs<sup>9,14</sup>. Head bones represent the preferred location for osteoma as well as desmoplastic fibroma (70%)<sup>15</sup>. Osteoblastoma predominates in axial skeleton particularly the spine, in 40% of cases<sup>2,15</sup>. In our study, osteoblastoma were localized in head bones and lower limbs.

MBT comprise 3 to 5% of all tumors in children under 14 years of age, while this figure rises to 7% in those between 15 and 19 years of age<sup>16</sup>. They are usually primitive and are dominated by osteosarcoma and Ewing sarcoma which represent 90% of all MBT in CAA<sup>17</sup>. The incidence increases with age until a peak in late childhood or adolescence ; they rarely present before age<sup>5,18</sup>. MBT are most common in males (52 to 75%)<sup>12,13,19</sup>. According to Stiller et al<sup>20</sup>, incidence rates were similar for boys and girls throughout childhood while boy's incidence was higher in adolescence.

Osteosarcoma represents the most common MBT in CAA, which constitutes around 40% to 70%<sup>12,16,19</sup>. The tumor shows a bimodal age peak, the first one during the second decade of life and the second one after the age of 50 years<sup>7,16</sup>. In our study, osteosarcoma accounted for 60% of MBT with predominance in patients between 11 and 15 years of age, followed by Ewing sarcoma (24%) and histiocytosis (9%). These results are consistent with most of the reports. On the other hand, the results in Senac et al report<sup>10</sup> are

different than our distribution in which histiocytosis is the most common MBT among 264 patients in the first decade of life.

Ewing sarcoma is the second most common MBT occurring in 20% to 45% of all MBT<sup>5,10,21</sup>. It is frequently diagnosed in young children and adolescents with a peak between 5 and 15 years of age<sup>22</sup>.

Osteosarcoma and Ewing sarcoma have contrasting skeletal site distributions. The vast majority of osteosarcoma arise in the long bones of lower limbs, particularly all around the knee (60% of cases)<sup>23</sup>. In contrast, Ewing sarcoma predominates in pelvis followed by lower extremities<sup>6,19</sup>. In our study, lower limb was the preferred site for both osteosarcoma and Ewing sarcoma in 67,4% and 55% of cases.

Langerhans cell histiocytosis is quite rare, with an incidence ranging from 2 to 5 cases/million/year for children under 15 years of age, and peaks between 5-10 years old<sup>24,25</sup>. It occurs mainly in the skull followed by the spine, limbs, pelvis and ribs in order of frequency<sup>26</sup>. In our study, histiocytosis was the third most common MBT (9%) with predominance in patients between 11 and 15 years of age and with a predilection for the head bones (63%).

Primary bone lymphoma accounts for 3-7% of all MBT<sup>27</sup>. Similarly to adults, majority of PBL are non-Hodgkin lymphomas; diffuse large B cell lymphoma being the most common (70-80%) and Hodgkin lymphoma the rarest<sup>28</sup>. IT affects mainly adolescent (10-12 years of old) with a predominance for the lower limb then axial involvement (spine and pelvis)<sup>29</sup>. Three cases of PBL were collected in our report, they consisted with Hodgkin lymphoma, Burkitt lymphoma and T-lymphoblastic lymphoma with an average age of 8,6 years and with a predominance the lower limb (66,6%).

Bone metastases in CAA are very rare, unlike adults. The most common metastatic tumor of pediatric skeleton is by far neuroblastoma<sup>17</sup>. It is mainly found in young children under the age of 5 with predominant spine involvement (80%)<sup>30</sup>. Furthermore, the case of bone metastasis of neuroblastoma in our report was diagnosed at the age of 14 at the lower limb.

## CONCLUSION

This article is a recent epidemiological study about BT in CAA over a 15-year span in Southern Tunisia. Our data was consistent with various studies in the international literature. On the other hand, other reports were heterogeneous. Given their rarity and heterogeneity, the diagnosis of BT is particular and requires a multidisciplinary approach. The reporting

of epidemiological studies remains essential in order to expand our knowledge regarding these uncommon tumors.

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