Chapter 8
Consequences of Delayed Diagnosis

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Abstract Background: To determine for pediatric patients with high grade metaphyseal osteosarcoma whether there are any correlations between delay in diagnosis (time between appearance of symptoms and start of treatment), tumoral spread across physis and outcome.

Procedure: The clinical records, imaging methods and histology reports of 157 patients with high grade metaphyseal pediatric osteosarcoma of a long bone were reviewed. The mean follow-up time was 102 months. Location, histological subtype, time from initial symptoms to start of treatment, major diameter, percentage of necrosis, whether the physis was crossed by the tumor, and outcome (recurrence, metastasis and status) were collated and statistically analyzed with SPSS v15.0.

Results: Compared to the group of patients with unbreached physis, the group with tumors that had crossed the physis (58 % of patients) was older (13.4 vs 11.9 years; $p=0.05$), had longer diagnostic delay (4 vs 2 months; $p<0.0001$), had almost twice the incidence of metastasis at diagnosis (38 % vs 22 %, $p=0.043$) and had poorer outcome (overall survival 49 % vs 67 %). Statistical analysis demonstrated an age-independent correlation between diagnostic delay and tumoral spread across the physis ($p<0.0001$).

Conclusion: Breach of the physis by a metaphyseal pediatric osteosarcoma is a matter of time. Outcomes for patients with tumors that had crossed the physis were worse than for patients with tumors that had not. Diagnostic delay of over 2 months

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was associated with poor prognosis. We urge that a major effort be undertaken to facilitate early diagnosis of all patients who might be suffering from this lesion.

Keywords Delay diagnosis • Osteosarcoma • Physis

8.1 Introduction

Pediatric osteosarcoma usually arises on the metaphysis of long bones, the most common site being around the knee (in the distal femur or proximal tibia). The standard treatment includes wide surgery and chemotherapy. The type of surgery differs according to such considerations as the age, extension of the tumor, the involvement of the joint, and the need for growth plate removal [1].

Tumors arising on the metaphysis sometimes proceed to invade the epiphysis by crossing the growth plate, which can be regarded as representing a temporary and somewhat imperfect barrier to tumoral spread. According to previous studies [1–7] such breaching of the growth plate and spread into the epiphysis occurs in between 50 and 70 % of cases. The large difference in these percentages can be explained in several ways: by variation in aggressiveness of tumors, by the age of patients (the younger the patient the thicker the growth plate), or by delay in starting treatment (the longer the tumor is allowed to develop the greater its chances of breaching the temporary barrier that the growth plate implies). In this respect it would be useful to establish whether tumors that cross the physis are qualitatively different from those that do not. The question arises: are tumors that invade the epiphysis more aggressive? Alternatively, do the cases with invasive tumors tend to be the cases that were diagnosed later? The outcomes for patients with tumors confined to the metaphysis are better than those for patients with epiphyseal involvement, is this attributable to differences in tumor aggressiveness or to earlier diagnosis?

The diagnostic and staging process for an osteosarcoma case includes obtaining the clinical history, imaging (x-ray, CT, MRI, bone scan) and a biopsy study. In the centers at which the authors work, all diagnostic tests, can be performed within 1 or 2 days. In non-reference centers, however, the diagnostic process can take up to several months.

The aim of this study of pediatric patients with high grade metaphyseal osteosarcoma is to determine whether there are any correlations between delay in diagnosis, tumoral spread across the physis, and final outcome. We define delay in diagnosis as the interval between appearance of initial symptoms and the beginning of treatment.

8.2 Patients and Methods

We reviewed the clinical data by patient records, imaging methods and histology reports for the pediatric osteosarcoma patients treated at two large tumor reference centers in two different countries (referred to here as hospitals A and B)

between 1980 and 2009. For inclusion, patients had to be of pediatric age (under 15 years old for girls and under 17 years old for boys), to have a diagnosis of classic high grade osteosarcoma with a metaphyseal location in a long bone, and to have been treated in standard manner, that is, with neoadjuvant chemotherapy, surgery and adjuvant chemotherapy. Patients with metastasis at diagnosis were included. Patients of adult age were excluded as were patients with tumors affecting flat bones, of low grade or located in the diaphysis. Data for location, histological subtype, time from initial symptoms to start of treatment, major diameter, percentage necrosis, whether the physis had been crossed by the tumor or not, and outcome (recurrence, metastases and status) were collated. Statistical analysis was by SPSS v15.0.

The study included 157 patients, with a mean follow-up of 102 months. The characteristics of these patients are given in Table 8.1.

8.3 Results

The tumor crossed the physis in 56 % (89/157) of patients. Comparison of patients in whom tumors crossed the physis and patients in whom tumors did not revealed statistically significant differences in age, time from initial symptoms to start of treatment, presence of metastases at diagnosis and outcome (Table 8.2).

Patients in whom tumors did not cross the physis were younger than those in whom the epiphysis was involved. The mean age at diagnosis was slightly lower in patients from hospital A (12.5 years vs 13.2 years), and the percentage of patients with tumors crossing the physis was correspondingly lower for hospital A than for hospital B (54 % compared to 61 %, respectively).

For the group of patients with epiphyseal involvement, the median time between initial symptoms and start of treatment was 4 months (range 1–16 months). For the group in which the physis was not crossed, the median diagnostic delay was 2 months (range 1–7 months). The difference is statistically significant ($p < 0.0001$).

In order to control for confounding factors, a regression analysis with age stratification was performed (Table 8.3 and Table 8.4). Regardless of the age at diagnosis, there was a statistically significant correlation ($p < 0.0001$) between delay in starting treatment and tumoral spread across the physis.

Clinical outcome in terms of survival, local recurrence and metastasis was impaired when the physis was crossed by the tumor ($p = 0.04$, 0.07 and 0.04, respectively). In the group of patients with tumors that crossed the physis, the number of cases with metastasis at diagnosis was almost twice that in the group with unbreached physis (42 % vs 22 %) (Table 8.2).

Metastasis at diagnosis was the prognostic factor ($p < 0.0001$) most indicative of poor survival (Figs. 8.1 and 8.2). Local recurrence was almost three times higher in patients with tumors that crossed the physis (14 % vs 5 %). Overall long-term survival in the group of patients with tumors that crossed the physis was almost 20 % worse than that in the group with unbreached physis.

Table 8.1 Clinical characteristics of the patients included in the study

	Osteosarcomas (n = 157)	
	No.	%
Age at diagnosis (years)		
Median	13.3	
Range	(0–44)	
Sex		
Female	68	43.3
Male	89	56.7
Location		
Proximal femur	9	5.7
Distal femur	79	50.3
Proximal tibia	39	24.8
Distal tibia	11	7
Proximal fibula	5	3.2
Proximal humerus	11	7
Distal humerus	2	1.3
Distal radio	1	0.6
Necrosis		
Good (>90 %)	59	37.6
Poor (<90 %)	86	54.8
Not available	12	7.6
Histologic subtype		
Osteoblastic	132	84.1
Chondroblastic	16	10.2
Fibroblastic	3	1.9
Telangiectasic	6	3.8
Metastasis at diagnosis		
No	105	66.9
Yes	52	33.1
Status		
Alive	101	64.3
Dead	48	30.6
Not available	8	5.1
Follow-up (months)		
Mean	102	
Median	69.5	
Range	(2.6–363.7)	

8.4 Discussion

We have studied the relationships between breach of the physis by metaphyseal pediatric osteosarcoma, delay in diagnosis and clinical outcome. Our main finding, that outcomes for patients with tumors that had crossed the physis were worse than for patients with tumors that had not, is, to the best of our knowledge, the first

Table 8.2 Differences between patients grouped according to whether the tumor crossed the physis or not. (Contingency tables)

	Physis crossed (%)	Physis not crossed (%)	
Number	89 (56 %)	68 (44 %)	
Mean age	13.4	11.9	p=0.05
Diagnostic delay[a]	4 months	2 months	p<0.0001
Metastasis at diagnosis	37 (42 %)	15 (22 %)	p=0.04
Local recurrence	12 (14 %)	3 (5 %)	p=0.07
Overall survival	44 (49 %)	46 (67 %)	p=0.04

[a]Mean time in months between initial symptoms and start of treatment

Table 8.3 Regression analysis with age stratification

	Diagnostic delay (months)	
	Crude mean (95 % CI)	Age-adjusted mean[a]
With physis-crossing	2.21 (1.90–2.53)	2.20 (1.58–2.82)
Without physis-crossing	4.05 (3.40–4.69)	4.06 (3.53–4.58)

Analysis of covariance (ANCOVA)
Model: the dependent variable is time; independent variables are physis-crossing (dichotomous) and age (continuous)
[a]Analysis of Covariance ANCOVA (equivalent to linear ordinary least-squares regression). p<0.0001

Table 8.4 Regression analysis with age stratification

Time	N	OR (95 % CI)	Age-adjusted OR* (95 % CI)
≤1	31	1 (ref)	1 (ref)
1.5–2	37	1.99 (0.71–5.53)	1.88 (0.67–5.29)
2.5–3	31	4.04 (1.38–11.86)	4.67 (1.54–14.14)
4–16	49	9.14 (3.13–26.69)	9.36 (3.16–27.7)

* Odds ratio (95 % CI) for physis-crossing according to time between initial symptoms and start of treatment

demonstration of the veracity of the supposition, based on experience with other pediatric cancers, that the earlier a pediatric osteosarcoma is diagnosed and treated, the better the oncological outcome.

The current study confirms the suggestion present in other published reports that invasion of the physis by a metaphyseal osteosarcoma is likely to be a matter of time [1, 3] osteosarcoma usually arises in the metaphysis of long bones, and the growth plate is thought to represent a temporary barrier to tumoral spread across the physis and into the epiphysisis. We found that for tumors that had crossed the physis, the mean time between initial symptoms and start of treatment was approximately twice the mean for tumors constrained in the metaphysis.

The physis can be regarded as representing a temporary barrier to tumoral spread from metaphysis to epiphysis. Because the thickness of the physis decreases with age, it is reasonable to hypothesize that breaching of the physis by a metaphyseal

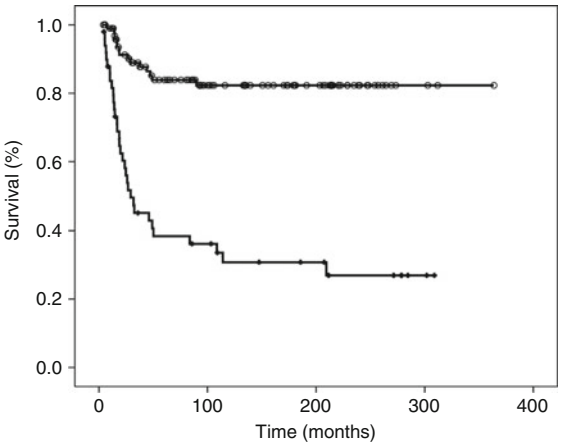

Fig. 8.1 Kaplan-Meier survival plot comparing patients in whom the tumor crossed the physis with patients in whom the tumor did not. The graph includes patients who were metastatic at diagnosis

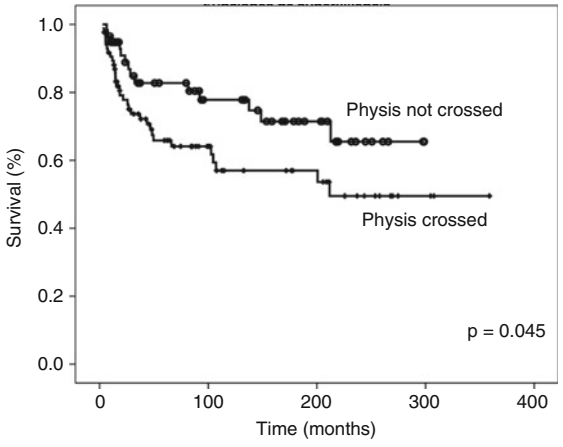

Fig. 8.2 Kaplan-Meier survival plot comparing patients with metastasis at diagnosis and those without ($p<0.0001$)

osteosarcoma may depend to some degree on a patient's age. One would expect that the younger the patient, the better the barrier to epiphyseal invasion posed by the physis. In view of the fact that diagnostic delay increases correspondingly a patient's age, could this putative age effect confound our results? After taking into account patient age by applying regression analysis with age stratification to our data, we found that patients in whom the tumor had crossed the physis were still associated with significantly longer diagnostic delay than patients in whom the tumor remained constrained in the metaphysis.

Patients with tumor crossing the physis had worse outcomes than those with a tumor that had not crossed the physis: the percentages with metastases at diagnosis and with local recurrence were higher, and overall survival was impaired (49 % vs 67 %).

From the point of view of surgical technique, surgery is simpler when the epiphysis is free of tumor. There is no need for joint resection, reconstruction is simpler,

and clinical results are usually better in terms of function [7–9]. Preserving the joint and, when possible, the potential for growth is the best way to avoid further complications and further surgery, especially in young children.

In children, tumor breaching of the physis is not only bad news in terms of post-treatment joint function, it is also a strong indicator of poor prognosis. As demonstrated by this study, whether a tumor breaches the physis depends on the speed with which treatment is started. It is of paramount importance to minimize the time interval between appearance of symptoms and start of treatment, because the consequences of a diagnostic delay of 2 months are, quite frankly, terrible.

It may not be possible to change the behavior and other characteristics of a tumor, but we can improve time intervals of the diagnostic procedures and avoid delays. The use of screening protocols in oncological centers is mandatory. In addition, we suggest implementation of educational measures so that general physicians and general orthopedic surgeons become the sufficiently aware of this pathology to send possible patients immediately to reference centers. This will improve prognosis and functional outcome in pediatric osteosarcoma.

8.5 Conclusion

Breaching of the physis by a metaphyseal pediatric osteosarcoma is a matter of time. Outcomes with tumors that have crossed the physis are worse than outcomes with tumors that have not. Regardless of age, a delay of 2 months between the appearance of symptoms and the start of treatment worsens the clinical outcome drastically. For this reason, we urge implementation of measures to guarantee early diagnosis of all patients who might be suffering from metaphyseal pediatric osteosarcoma.

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