ORIGINAL ARTICLE

Initial presentation and management of osteosarcoma, and its impact on disease outcome

CME

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Objective To evaluate the initial presenting symptoms and management of osteosarcoma in Hong Kong Chinese children, in relation to any possible impact on disease outcomes.

Design Retrospective study.

Setting A tertiary referral centre of bone cancer in a university teaching hospital in Hong Kong.

Patients All children aged younger than 18 years with a diagnosis of osteosarcoma who received treatment from March 1994 to October 2005.

Results A total of 51 children were studied. The median age of onset was 13 (range, 3-20) years; 61% were males. The tumours were located in the distal femur and proximal tibia, which accounted for 45% and 22% of the cases, respectively; 24% of patients had metastatic disease at presentation. Swelling (76%) and pain (90%) were the most common presenting complaints. Approximately one third of the patients had a preceding history of trauma. The median duration of initial symptoms to first medical consultation of any sort was 30 (range, 0-360) days. The median time from the first consultation to a definitive diagnosis was 21 (range, 0-350) days; 25% were diagnosed more than 52 days after presentation. Bonesetters were initially consulted by 37% of these patients. From presentation to diagnosis, the median duration was 61 (range, 4-361) days. Analysis of the duration of pre-diagnosis symptoms did not correlate significantly with the development of metastatic disease, response to chemotherapy, feasibility of limb salvage surgery, relapse rates, or survival rates.

Conclusions In Hong Kong, initial consultation to bonesetters was common. A relatively long delay in between symptom onset and diagnosis of osteosarcoma was encountered. The public and medical practitioners should be made aware of this disease, especially in adolescents.

Key words
Bone neoplasms; Diagnosis, differential; Osteosarcoma; Pelvic neoplasms; Treatment outcome

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Introduction

Osteosarcoma is the most common malignant bone tumour in childhood, with the peak incidence occurring between the age of 10 and 20 years. It is characterised by the proliferation of malignant mesenchymal cells that produce osteoid or immature bone.[1] It is the sixth commonest malignant neoplasm in children, and the fourth most common in adolescents and young adults. In Hong Kong, about 11 new cases are diagnosed every year.[2]

According to cancer statistics of the Hong Kong Paediatric Haematology and Oncology Study Group (HKPHOSG), osteosarcoma was diagnosed in 84 children in local public hospitals from 1 November 1993 to 31 December 2006. All of them received neoadjuvant chemotherapy according to a unified standard protocol, with the aim of reducing the tumour size, clearing micro-metastasis, and facilitating better margination of the primary tumour to enable limb salvage surgery if possible. The total duration of treatment varied from 6 to 10 months depending on the response to the chemotherapy. The 5-year overall survival and event-free survival rates achieved with the current HKPHOSG protocol was about 70% and 58%, respectively (unpublished results), which was comparable to results reported by most centres in North America and Europe.[3,4] However, patients presenting with metastatic disease still have poor outcomes; their overall 5-year survival being 34%, which is also similar to results reported in other published series.[4,5]

There are several known prognostic factors for osteosarcoma. They include: the

presence of metastatic disease, young age (<10 years), high bone alkaline phosphatase, p-glycoprotein expression, and degree of chemonecrosis after initial chemotherapy.[6,7] The duration of symptoms may be an indirect measure of tumour growth rate. There is an indolent variant of osteosarcoma, the parosteal type, which usually arises on the surface of the metaphysis of long bones, represents 1 to 6% of all osteosarcomas, and is commonly associated with a longer duration of symptoms and better patient survival.[8,9]

In Hong Kong, some patients present quite late after the onset of symptoms, with or without metastases at diagnosis. Many had sought medical advice from several doctors, and not uncommonly from bonesetters. Management by the latter could involve manipulation or topical treatment over a prolonged period before the diagnosis was established. Often, parents question whether the delay in diagnosis affects disease outcome, to which the literature provides scant answers.

We therefore set out to perform a retrospective study to investigate the presenting patterns of osteosarcoma in Hong Kong children and its management and evaluate any possible corresponding impact on disease outcomes.

骨肉瘤的首發病徵和處理方法，及其對治療結果的影響

目的 探討香港華籍兒童骨肉瘤患者的首發病徵和處理方法，及其對治療結果的影響。

設計 回顧研究。

安排 香港一所大學教學醫院的骨癌轉介中心。

患者 1994年3月至2005年10月期間，所有接受骨肉瘤治療的18歲以下的兒童。

結果 共51名兒童的發病年齡中位數為13歲（介乎3至20歲）；61%為男性。45%的腫瘤發生在股骨遠端位置，22%在脛骨近端；24%病人來診時已有轉移性腫瘤。腫脹（76%）及疼痛（90%）是最普遍的病徵。約三分一病人有創傷的病史。病徵初發至首次求診的時間中位數為30日（介乎0至360日）。首次求診至確診為骨肉瘤的時間中位數為21日（介乎0至350日）；其中有25%病人超過52日。有37%病人曾先向跌打醫師求診。由首發病徵至確診的時間中位數為61日（介乎4至361日）。分析顯示，確診前病徵的時間長短與下列結果沒有明顯相關：轉移性腫瘤的發展、對化療的反應、保肢治療的可行性、復發，以及生存率。

結論 遇上創傷時，香港病人普遍會先到跌打醫師求診。本研究發現從首發病徵至確診為骨肉瘤的時間有相對頗長的廷誤。大眾市民及醫生應對這種病提高警覺，尤其是對年青的病患者。

Methods

We conducted a retrospective review of 51 children diagnosed to have osteosarcoma, who received treatment at the Lady Pao Children's Cancer Centre between 1 March 1994 and 31 October 2005. The following parameters were studied: time from onset of symptoms to first medical consultation (to bonesetters, general practitioners, orthopaedic surgeons, paediatricians, and emergency departments), symptoms at presentation, number of doctors consulted before the diagnosis was made, time from first consultation to the diagnosis. The date of consultation with the first medical professional was retrieved from the medical records. The date of diagnosis was defined as the date of a confirmed histological diagnosis of osteosarcoma. The difference between these two dates was considered the 'time from first consultation to diagnosis'. We also explored factors that might correlate with disease outcome parameters: chemonecrosis factor, type of limb surgery (amputation versus limb salvage surgery), metastatic disease rates, relapse rates, and overall survival.

The patients were treated with the HKPHOSG osteosarcoma protocol. The response to chemotherapy after two courses of neo-adjuvant chemotherapy was determined by the Huvos chemonecrosis factor grading (grade I to IV). Grades III and IV (indicating good response) was defined as absence of viable tumour or less than 10% of viable tumour. Grades I and II (indicating poor response) was defined as the presence of more than 10% of viable tumour. The feasibility for limb salvage surgery was assessed by orthopaedic surgeons.

Statistical analysis

The diagnosis variables (duration, treatment, initial consultation) and disease characteristics (site, metastases) were correlated with treatment outcomes (chemonecrosis, limb salvage, and survival) using Student's *t* test, Chi squared test, or the Fisher's exact test as appropriate. Statistical significance was defined as a P value of less than 0.05.

Results

Demographic data

The age at diagnosis ranged from 3 to 20 years, with a median of 13 years. The male-to-female ratio was 3:2. The three commonest primary sites were the distal femur (45%), proximal tibia (22%), and proximal humerus (14%). At diagnosis, 12 (24%) patients presented with metastatic disease, all with lung involvement and three with additional bone metastases (Table 1). Among the 38 survivors, the duration of follow-up ranged from 29 to 170 (mean, 91;

TABLE 1. Disease characteristics at presentation

	Male (n=31)	Female (n=20)	Total (n=51)
Extent of disease			
Localised	26 (84%)	13 (65%)	39 (76%)
Metastatic	5 (16%)	7 (35%)	12 (24%)
Primary site			
Proximal femur	2 (6%)	1 (5%)	3 (6%)
Distal femur	12 (39%)	11 (55%)	23 (45%)
Proximal tibia	6 (19%)	5 (25%)	11 (22%)
Proximal fibula	1 (3%)	1 (5%)	2 (4%)
Distal tibia	1 (3%)	0	1 (2%)
Distal fibula	1 (3%)	0	1 (2%)
Proximal humerus	5 (16%)	2 (10%)	7 (14%)
Others	3 (10%)	0	3 (6%)

median, 78) months. In all, 12 patients were followed up for less than 5 years.

Presenting symptoms

The most common presenting symptom was pain (90%). Swelling of the affected region occurred in 76%, while decreased range of movement was noted in 39%. Pathological fracture was uncommon (8%). One of the patients incurred a fracture after a road traffic accident, and another two after sports injuries (badminton and wrestling). At presentation (Table 2), none of the patients had systemic symptoms (fever, weight loss), and none with pulmonary metastatic disease had respiratory symptoms (chest pain, haemoptysis, shortness of breath or cough).

Duration of symptoms before seeking medical advice

The durations of symptoms before the patients sought medical advice (including from bonesetters) ranged from 0 to 360 days, with a mean of 48 and median of 30 days (Table 3). Four patients sought medical advice after they had had symptoms in excess of 180 days. Patients presenting with metastatic disease (n=12) had a similar duration of symptoms as those with non-metastatic disease (n=39): 42 (standard deviation [SD], 50) days versus 50 (68) days (P=0.710). The total duration of symptoms to diagnosis in the metastatic group (mean, 63 days) was also not significantly different from that in those with non-metastatic group (mean, 90 days) [P=0.3].

Trauma history

A considerable proportion of patients had a preceding history of trauma (33%), but there were no significant differences related to gender (P=0.4). Eight subjects incurred sports injuries (playing badminton [n=3]; basketball [n=2]; 1 each during soccer, swimming, and wrestling). Five slipped and fell, two were hit by hard objects, one fracture ensued after a road traffic accident, and one after an ankle sprain. Patients with a trauma history (n=17) sought medical advice earlier than those without such a history (n=34); the mean duration of symptoms to first medical consultation being 20 versus 62 days, respectively (P=0.025). However, there was no significant difference between the two groups in the time elapsing from onset of symptoms to final diagnosis (P=0.5).

Initial medical consultation

The pattern of the initial consultation was: bonesetter 19 (37%), family practitioner 9 (18%), orthopaedic surgeon 10 (20%), and Accident and Emergency doctor 13 (25%). Regarding the management offered at the first consultation, 17 patients received topical herbs, 7 local or oral analgesics, 1 was treated with plaster of Paris cast for a fracture, and 16 had roentgenograms. Eight (16%) were referred to a specialist immediately after the first consultation.

Time from first medical consultation to establishing diagnosis

The median time from first consultation to diagnosis was 21 days, but in 25% of the patients it took more than 52 days to make the diagnosis (Table 3). The mean time from first consultation to diagnosis was significantly longer after first consultations with bonesetters group as opposed to registered practitioners, 36 (SD, 33) days versus 14 (27) days (P=0.011). A median of two doctors were attended before diagnosis was made, but in 16 (31%) patients, the diagnosis was made after three or more doctors had been consulted; the extreme case entailed 10 consultations by different doctors before the final diagnosis was reached. In this patient cohort, the

TABLE 2. Symptoms at presentation

	Swelling	Pain	Decreased range of movement	Fracture	Trauma
Male (n=31)	21 (68%)	28 (90%)	12 (39%)	2 (6%)	12 (39%)
Female (n=20)	18 (90%)	18 (90%)	8 (40%)	2 (10%)	5 (25%)
Total (n=51)	**39 (76%)**	**46 (90%)**	**20 (39%)**	**4 (8%)**	**17 (33%)**

TABLE 3. Duration of initial symptoms and treatment, time elapsing to diagnosis from first consultation and number of doctors seen

	Duration of symptoms before 1st consultation (days)	Time from 1st consultation to diagnosis (days)	Duration of initial treatment (days)	No. of consultations before diagnosis
Mean	48	36	22	2
Median	30	21	7	2
Range	0-360	0-350	0-120	1-10
25th percentile	0	5	0	2
50th percentile	7	21	7	2
75th percentile	30	52	30	3

TABLE 4. Disease outcomes and duration of symptoms before first consultation

Presenting time	Outcome variables			
	Good chemonecrosis factor*	Limb salvage surgery	Relapse	Death
<30 days	49%	93%	41%	21%
>30 days	43%	81%	25%	35%
P value	0.8	0.3	0.5	0.3

* Chemonecrosis factor >90%

TABLE 5. Disease outcome and the initial medical consultation

Initial medical consultation	Good chemonecrosis factor*	Limb salvage operation	Relapse	Death
Bonesetter (n=19)	41%	83%	41%	34%
Family practitioner (n=9)	75%	100%	13%	18%
Orthopaedic surgeon (n=10)	40%	90%	44%	21%
Accident and emergency specialist (n=13)	42%	92%	40%	26%
P value	0.4	0.6	0.5	0.9

* Chemonecrosis factor >90%

median time from presentation to confirmation of the diagnosis was 61 (range, 4-361) days.

Response after neoadjuvant chemotherapy

Overall 47% of the patients had good chemonecrosis response of Huvo grading (ie III or IV). There was a trend towards a higher frequency of good responders in patients with localised as opposed to metastatic disease (54% vs 20%; P=0.08). One of the treatment aims for neoadjuvant chemotherapy was to facilitate limb salvage surgery. Among patients with localised disease, 92% received limb salvage surgery in the form of bone allografts, metallic prosthesis, or resection of tumour only (for the fibular tumour). Regarding the 12 patients with metastatic spread, two had very advanced disease with progression after initial treatment, and surgical treatment was not attempted. For the remaining 10 patients, limb salvage surgery was performed in eight.

Treatment outcome analysis

Using the median presenting time of 30 days as the cut-off, the analysis of the time elapsing from symptom onset to first medical consultation did not differ in patients with and without metastasis (24% in both groups). There were no significant correlations with respect to the feasibility of limb salvage surgery (P=0.3), chemonecrosis factors, relapse, and overall survival rates (Table 4). Another analysis using 60 days as the cut-off also revealed no difference in treatment with respect to these outcome variables. Nor did the type of first medical consultation correlate with the treatment outcomes (Table 5).

Discussion

This is the first local retrospective review for osteosarcoma in Chinese children and included about 60% (51 of 84) of all paediatric osteosarcoma cases in Hong Kong during the study period. Metastatic disease at diagnosis is known to have a significantly worse outcome compared to localised disease.[10,11] Poor chemonecrosis response was also known to be an independent prognostic factor, with a 5-year event-free survival of 49 versus 87%.[10,12,13]

Our patient cohort entailed a relatively large

proportion presenting with advanced disease. In all, 24% presented with metastatic disease at diagnosis, which is slightly higher than the 10 to 20% figure reported in other studies.[10,14] However, we could not demonstrate that this was secondary to a delay in diagnosis. There was no significant difference in the time from onset of symptoms to diagnosis in the metastatic and localised disease groups. Further analysis of the duration of presenting symptoms (patient delay) also confirmed that it had no direct adverse effect on treatment outcome. The presence of metastatic disease at presentation may be more related to the tumour biology of individual patients than the interval from symptoms to diagnosis.

This local retrospective study confirmed the special situation of Hong Kong, whereby parents tend to consult bonesetters rather than registered medical practitioners when their children had musculoskeletal symptoms (pain and/or swelling). The duration from initial symptoms (mean, 48 days; median, 30 days) was rather long. This may also reflect adolescent behaviour, namely self-determination that the symptoms must be trivial and temporary (due to sports injuries), and not due to serious underlying disease.

The history of preceding trauma or sports injury may mislead both parents and medical practitioners, and hence delay in making the correct diagnosis. Although our data showed that patients with a history of trauma tended to seek medical advice earlier, the total delay in making the correct diagnosis did not differ from those without a trauma history. In all, 31% of the patients had one or more roentgenograms at their first consultation (before the diagnosis). Four patients had a fracture identified but the history of trauma probably misled doctors about the underlying pathological aetiology. The diagnosis was made after months of treatment, when the fracture did not heal and pain and swelling progressed. In three patients having roentgenograms, the radiological fields did not include the affected bony lesions. One of the latter with an osteosarcoma in the proximal tibia had a roentgenogram of the spine instead of the knee, as the presumptive diagnosis was sciatica.

In patients with osteosarcoma, early recognition and diagnosis has probably led to a remarkable improvement in the survival rates, and increased the feasibility of limb salvage surgery. In this study, surprisingly analysis of the results could not demonstrate that a delay in diagnosis correlated with adverse outcomes. However, our study was limited by the small sample size, and no subgroup analysis of different histological subtypes that may affect outcome. We continue to believe that early medical attention and a correct diagnosis is beneficial, and should be improved in our local setting. Lack of awareness of this disease leads to inappropriate management including recourse to initial investigations and primary procedures that may impose a detrimental effect on outcome.[15] In order to achieve optimal presurgical treatment of osteosarcoma patients, good and effective communication among primary referring doctors, orthopaedic surgeons, radiologists, pathologists, and paediatric oncologists is necessary. This can only be achieved when all the relevant parties are aware of this relatively rare but important differential diagnosis. The long pre-diagnosis interval also elicits great parental anxiety and guilt feelings, after the diagnosis of such a serious disease. Therefore, the general public, and particularly adolescents and family practitioners, should be made aware of the presenting signs and symptoms of osteosarcoma. The important warning clinical features include severe pain (especially at night), bony hard swelling over the limbs, and unexplained or prolonged limping. In consideration of potentially fatal outcomes, osteosarcoma or bone tumours should be included in the differential diagnosis for a complaint of pain and swelling in the joint area in children. Family physicians should perform a careful physical examination and look for any palpable mass or swelling. If any of the above clinical features are present, clinicians should be alerted to initiate further investigations, such as radiography of the appropriate site even in the absence of trauma, and/or entertain early referral to a specialist.

This was a retrospective study and the data were retrieved from medical records of a children's cancer centre, after the diagnosis was already made by the referring specialty. The frequency of first consultations with bonesetters (37%) might have been an underestimate due to difficulties of recall. Nevertheless, a high proportion of our patient cohort had sought advice from bonesetters for their musculoskeletal symptoms.

Conclusion

Our study demonstrated that a significant number of osteosarcoma patients presented with metastatic disease. It is not unusual for there to be a long delay before the correct diagnosis is made. Measures to enhance public awareness of this malignant condition are needed.

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