Paediatric high-grade osteosarcoma and its prognostic factors: a 10-year retrospective study

Grace PY Tong *, WF Hui, KC Wong, Benjamin ST Fong, CW Luk, CK Li

ABSTRACT

Introduction: This retrospective study was conducted to identify the characteristics of paediatric high-grade osteosarcoma and define its prognostic factors.

Methods: We identified paediatric patients (aged <19 years at diagnosis) diagnosed with high-grade osteosarcoma from 1 January 2009 to 31 December 2018 in two hospitals in Hong Kong, then retrospectively evaluated their medical records to identify prognostic factors.

Results: In total, 52 patients were included in this study (22 girls, 42.3%). Femoral tumour was the most common form of osteosarcoma. Most patients (78.8%) had localised disease at diagnosis. The lung was the most common site of metastasis. Almost half (n=23, 46.9%) of the patients showed a good response to chemotherapy (ie, chemonecrosis >90%). Most patients (n=40, 80%) underwent limb-salvage surgery. The event-free survival and overall survival rates were 55.8% and 71.2%, respectively. Prognostic factors independently associated with poor event-free survival and poor overall survival were the presence of metastasis at diagnosis, poor tumour chemonecrosis, and the need for amputation.

Conclusion: This multicentre review of paediatric high-grade osteosarcoma showed that the baseline patient demographics, event-free survival, and overall survival in Hong Kong were similar to previous findings in other countries. Patients with metastatic disease at diagnosis and poor chemonecrosis had worse survival outcomes. Molecular analyses of genetic abnormalities may help to identify targeted therapies in future studies.

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New knowledge added by this study

- The need for amputation was a prognostic factor independently associated with poor event-free survival and poor overall survival.
- Many conventional biochemical markers were not useful as prognostic factors for event-free survival or overall survival.

Implications for clinical practice or policy

- An updated protocol is needed for the management of paediatric high-grade osteosarcoma. Factors that can be incorporated for early risk stratification include local tumour aggressiveness and the need for amputation; genetic mutations in the tumour may also be useful.

Introduction

Osteosarcoma arises from primitive bone-forming mesenchymal cells.[1] It is the most common primary malignant bone tumour worldwide,[1,2] with an annual incidence of 4.8 per million population in the US.[2] Moreover, it was one of the most common types of childhood malignancy in Hong Kong in 2017 to 2019.[3]

In Hong Kong, paediatric patients with high-grade osteosarcoma are treated in accordance with the Hong Kong Paediatric Haematology and Oncology Study Group Treatment Protocol for High-Grade Osteosarcoma (Fig 1), which consists of neoadjuvant chemotherapy, followed by tumour resection and subsequent adjuvant chemotherapy. Histological response to neoadjuvant chemotherapy, defined as tumour chemonecrosis according to the Huvos system,[4] is used to stratify patients into good responders (patients with ≥90% tumour chemonecrosis) and poor responders (patients with <90% tumour chemonecrosis). These two groups receive different chemotherapy regimens.

A few prognostic factors for survival have been recognised; these factors include the presence

兒童骨肉瘤及其預後因素：10年回顧性研究

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引言：此回顧性研究旨在探討兒童骨肉瘤的特性及其預後因素。

方法：研究團隊對2009年1月1日至2018年12月31日期間於香港兩所醫院確診骨肉瘤的19歲以下兒童的醫療紀錄進行回顧性分析，以找出預後因素。

結果：共有52名兒童患者（22名女性，42.3%）被納入研究。股骨骨肉瘤為最常見類別。大部分患者（78.8%）於確診時並沒有擴散。肺轉移屬最常見轉移類別。近半數（n=23，46.9%）患者對化療反應良好（即腫瘤細胞壞死>90%）。大部分（n=40，80%）病人接受腫瘤切除手術而不需要截肢。無事件存活率為55.8%，整體存活率為71.2%。影響存活率的獨立預後因素包括確診時已有轉移、化療反應不良及有截肢需要。

結論：這項多中心兒童骨肉瘤研究顯示香港患者年齡、性別、腫瘤位置等特徵以及存活率均與外國研究相近。有轉移及化療效果不良的患者存活率較差。日後研究應着重於就基因異常進行分子分析，從而找出有效處理骨肉瘤的標靶治療。

of metastasis at diagnosis[5-7] and poor tumour chemonecrosis.[5-9] However, no specific studies have examined the validity of these factors for patients with osteosarcoma in Hong Kong. Moreover, the presence of lung nodules in computed tomography (CT) scans is a common finding at diagnosis and reassessment. In this study, we reviewed paediatric patients with osteosarcoma at two of the largest paediatric oncology centres in Hong Kong. We sought prognostic factors for event-free survival (EFS) and overall survival (OS), and we assessed lung nodules and metastasis in these patients.

Methods

This study included paediatric patients (aged <19 years at diagnosis) with biopsy-proven high-grade osteosarcoma, who were diagnosed from 1 January 2009 to 31 December 2018 at Queen Elizabeth Hospital and Prince of Wales Hospital. The patients' medical records were reviewed and the following information was collected: demographic data (sex, age at diagnosis, ethnicity, and time from symptom onset to presentation), clinical characteristics (location of tumour, largest dimension of tumour, staging, maximal alkaline phosphatase [ALP] level, calcium and phosphate levels before the start of treatment, and presence of pathological fracture), treatment-related characteristics (time from diagnosis to start of chemotherapy, surgical treatment approach, and histological results of the resected tumour [including tumour chemonecrosis and surgical margin]), and details of metastasis (timing, location, size, and treatment). Radiological reports for the primary tumour were reviewed to determine the presence of local anatomical aggressiveness, which was defined as intra-articular tumour involvement or neurovascular bundle involvement. These risk factors made surgical resection with a negative tumour margin difficult or impossible. Thus, amputation was expected to provide the best local control. There were three indications for limb-salvage surgery (ie, tumour resection and reconstruction). First, clinical and radiological responses were observed during neoadjuvant chemotherapy. Clinical responses

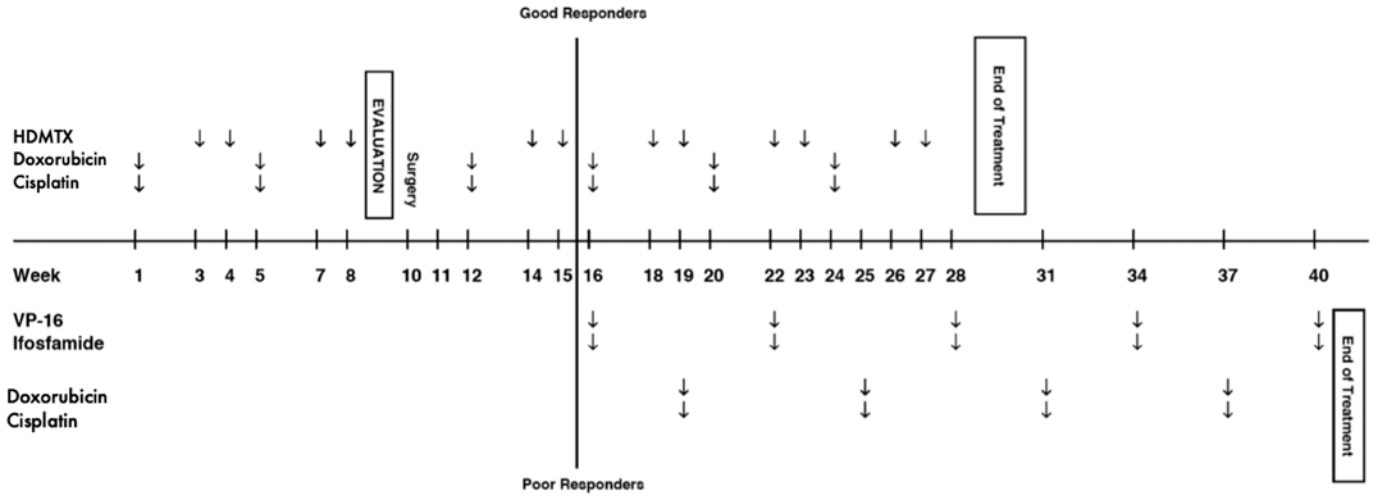

FIG 1. Roadmap of the Hong Kong Paediatric Haematology and Oncology Study Group treatment protocol for high-grade osteosarcoma*

Abbreviations: HDMTX = high-dose methotrexate; VP-16 = etoposide

* HDMTX: 12 g/m² on day 1; doxorubicin: 30 mg/m²/day on days 1-2; cisplatin: 100 mg/m² on day 1; VP-16: 100 mg/m²/day on days 1-3; ifosfamide: 2.5 g/m²/day on days 1-3. Arrows (↓) represent a week when the drug was given

were reduction or stabilisation of tumour size and a significant decrease in pain. Radiological responses were an increase in consolidated calcification of the tumour on plain radiographs, reduction or stabilisation of tumour size, and decreased peritumoral oedema on magnetic resonance images. Second, magnetic resonance images showed no neurovascular involvement. Third, there was no need for extensive muscle resection that would render the limb non-functional. Amputation was considered when patients did not meet the above criteria for limb-salvage surgery. It was also considered as a palliative treatment for patients who had large painful tumours with metastatic disease.

The characteristics of lung nodules identified in chest CT scans were recorded from CT reports. The initial and final sizes, laterality, timing of appearance, and mediastinal lymph node involvement were analysed to determine whether their characteristics were sufficiently different for clear distinction. Non-specific lung nodules were either small or remained stable in subsequent scans; they were not biopsied or surgically excised for histological diagnosis. Lung metastases were either large when first observed, had radiological features of metastasis, or demonstrated enlargement in subsequent follow-up scans.

Statistical analysis

Descriptive data were expressed as median (interquartile range) or frequency (percentage). The Pearson Chi squared test or Fisher's exact test was used for comparisons of categorical variables. The Mann-Whitney *U* test was used for comparisons of continuous variables.

The primary outcomes were OS and EFS. Overall survival was defined as the time from diagnosis to death. Event-free survival was defined as the time from diagnosis to the appearance of a new metastasis, progression of an existing metastasis, or death (whichever occurred first). The study end date was 31 December 2020. Patients who had no events were censored at the time of the last follow-up (if they had been lost to follow-up) or at the study end date. Kaplan-Meier curves and log-rank tests were used for survival analysis. To identify prognostic factors for OS and EFS, unadjusted hazard ratios (with 95% confidence intervals) were determined for each potential factor by using Cox proportional hazards models. Significant factors in univariate analyses were included in subsequent multivariate analyses; adjusted hazard ratios (with 95% confidence intervals) were generated in the multivariate analyses.

The secondary outcome was the differentiation of lung nodules. Their initial and final sizes, initial and final lateralities, timing of appearance, and mediastinal lymph node involvement were compared to identify statistical differences.

The SPSS software (Windows version 23.0; IBM Corp, Armonk [NY], US) was used for statistical analysis. P values <0.05 were considered statistically significant.

Results

Patient characteristics

In total, 52 paediatric patients (22 girls and 30 boys; age 5-18 years) with high-grade osteosarcoma were included in this study. Their baseline demographics are shown in Table 1. Two patients (3.8%) had a predisposing condition: one had Rothmund–Thomson syndrome and the other had osteofibrous

TABLE 1. Baseline demographics (n=52)*

Demographics	
Female sex	22 (42.3%)
Age at diagnosis, y	13.5 (10.0-16.0)
Ethnicity (Chinese)	48 (92.3%)
Time from symptom onset to presentation, mo	8.0 (4.0-12.0)
Follow-up interval, mo	53.0 (30.0-104.5)
Tumour characteristics	
Location	
Femur	33 (63.5%) [Distal 32, mid-shaft 1]
Tibia	13 (25.0%) [Proximal 12, mid-shaft 1]
Fibula	4 (7.7%) [Proximal 3, distal 1]
Others	2 (3.8%)
Largest dimension of tumour, mm	87 (53.0)
Staging at diagnosis	
Localised disease	41 (78.8%)
Metastatic disease	11 (21.2%)
Maximal alkaline phosphatase before diagnosis, IU/L	228.5 (156.0-419.5)
Maximal serum calcium before diagnosis, mmol/L	2.4 (2.4-2.5)
Maximal serum phosphate before diagnosis, mmol/L	1.5 (1.3-1.7)
Presence of pathological fracture at diagnosis	7 (13.5%)
Presence of pathological fracture at any time point	10 (19.2%)
Treatment-related characteristics	
Time from diagnosis to start of chemotherapy, d	9.0 (8.0-14.0)
Good tumour chemonecrosis† after neoadjuvant chemotherapy (n=49)	23 (46.9%)
Underwent surgery	50 (96.2%)
Clear surgical margin	50 (100% of patients receiving surgery)
Mode of surgery (n=50)	
Limb-salvage	40 (80%)
Amputation	10 (20%)

* Data are shown as No. (%) or median (interquartile range)

† Good tumour chemonecrosis: tumour chemonecrosis >90%, as defined by the Huvos system[4]

dysplasia, from which the high-grade osteosarcoma developed.

For the histological diagnosis, 45 patients (86.5%) had conventional high-grade osteosarcomas. The other subtypes of osteosarcoma were: two giant cell-rich osteosarcomas, one telangiectatic osteosarcoma, one chondrosarcomatous-predominant osteosarcoma, one osteoblastoma-like osteosarcoma, and one chondroblastic osteosarcoma. One patient had features suggestive of small round-cell sarcoma; the tumour was subsequently treated as a conventional high-grade osteosarcoma.

Treatment

All patients received neoadjuvant chemotherapy with doxorubicin, cisplatin, and high-dose methotrexate (Fig 1). After two courses of chemotherapy, the patients underwent surgical resection of tumours. Almost all patients (n=50, 96.2%) underwent resections of primary tumours. Most patients (n=44, 84.6%) completed the whole course of treatment with adjuvant chemotherapy. Five patients (9.6%) experienced disease progression during treatment. They had terminated chemotherapy early, received palliative care, and eventually died. One patient (1.9%) had disease progression and left Hong Kong to seek a second opinion. In one patient (1.9%), the last course of chemotherapy was omitted because previous chemotherapy had induced clinically significant renal impairment. In one patient (1.9%), the last course of chemotherapy was omitted because of disease progression while receiving treatment.

TABLE 2. Metastasis characteristics (n=25)*

Timing of metastasis	
At diagnosis (synchronous)	11 (44.0%)
During or after completion of treatment (metachronous)	14 (56.0%)
Location of initial metastasis (n=11)	
Lung alone	9 (81.8%)
Bone alone	1 (9.1%)
Lung, pleura, and bone	1 (9.1%)
Location of metachronous metastasis/recurrence (n=15)	
Lung only	7 (46.7%)
Lung and pleura	4 (26.7%)
Bone	1 (6.7%)
Multiple sites	3 (20.0%)
Treatment of lung metastasis (n=22)	
Treatment of synchronous lung metastasis (n=10)	
Standard chemotherapy	4 (40.0%)
Standard chemotherapy and second-line chemotherapy	3 (30.0%)
Standard chemotherapy, surgery, and second-line therapy	
(zoledronic acid-based)	2 (20.0%)
Standard chemotherapy and surgery	1 (10.0%)
Treatment of metachronous lung metastasis (n=12)	
Surgery alone	4 (33.3%)
Surgery and zoledronic acid-based therapy	3 (25.0%)
Second-line chemotherapy alone	1 (8.3%)
Surgery and second-line therapy	1 (8.3%)
None or terminated chemotherapy	2 (16.7%)
Pending decision	1 (8.3%)

* Data are shown as No. (%)

Metastasis and lung nodules

The lung was the most common site of distant metastasis, both synchronous (n=10, 90.9%) and metachronous (n=12, 80.0%) [Table 2]. Lung nodules in chest CT scans were observed in 39 patients (75.0%). Seventeen nodules (43.6%) were non-specific, while 22 nodules (56.4%) were lung metastases. Factors that could potentially be used to differentiate lung metastases from non-specific lung nodules included laterality of nodules in serial follow-up scans (P=0.004), number of initial nodules (P=0.006), maximal number of nodules (P<0.001), size of initial nodule (P<0.001), and size of the largest nodule (P<0.001) [Table 3].

For the 15 patients who had no lung nodules throughout the course of treatment, OS was very good (93%) [Fig 2]. Only one patient died of local recurrence. For the 17 patients with non-specific lung nodules (Figs 2 and 3), OS was excellent (100%), regardless of the timing of nodule appearance (ie, at diagnosis or later). Among these 17 patients, survival ranged from 2 years 4 months to 11 years 9 months from diagnosis. For the 10 patients with synchronous lung metastasis (Fig 3), OS was 60%, whereas for the 12 patients with metachronous lung metastasis (Fig 2), OS was 33.3%. This difference was not statistically significant (P=0.666).

Survival analysis

All patients were followed up until 31 December 2020; thus, the follow-up interval for the last recruited patient was 2 years from diagnosis. The median follow-up interval for all patients was 53 months from diagnosis (range, 4 months to 11 years 11 months). The EFS and OS were 55.8% and 71.2%, respectively. The EFS for patients with localised disease at diagnosis was significantly better than the EFS for patients with metastatic disease at diagnosis (65.9% vs 18.2%; P=0.007). The OS for patients with localised disease was better than the OS for patients with metastatic disease (75.6% vs 54.5%), but the difference was not statistically significant (P=0.26). Similarly, patients with good tumour chemonecrosis had better EFS and OS, compared with poor responders. These values were 78.3% versus 42.3% (P=0.019) and 82.6% versus 65.4% (P=0.209), respectively. Notably, patients with localised disease and good tumour chemonecrosis

had very good outcomes, with EFS of 80% and OS of 86.7%. All deaths in this study were caused by disease progression. No patients died of treatment complications or other causes.

The prognostic factors identified for both EFS and OS included the presence of metastasis at diagnosis and throughout, as well as the need for amputation to manage the primary tumour. Local aggressiveness and a larger tumour dimension contributed to OS, while poor tumour chemonecrosis contributed to EFS (Table 4). The following factors did not have a statistically significant impact on EFS or OS: sex, age at diagnosis, primary tumour location in the femur, the presence of a pathological fracture, time from symptom onset to presentation, time from diagnosis to start of chemotherapy, and the histological subtype of the primary tumour.

Multivariate analysis (Table 5) revealed that the presence of metastasis at diagnosis, the need for amputation, and poor tumour chemonecrosis were prognostic factors independently associated with poor EFS, while the presence of metastasis at diagnosis and the need for amputation were prognostic factors independently associated with poor OS. Figure 4 shows the Kaplan-Meier analysis of the effects of the above three independent prognostic factors on EFS.

TABLE 3. Lung nodule characteristics (n=39)*

	Non-specific lung nodule (n=17)	Lung metastasis (n=22)	P value
Laterality of initial nodules			
Unilateral	15 (88.2%)	14 (63.6%)	0.140
Bilateral	2 (11.8%)	8 (36.4%)	
Laterality of all nodules			
Unilateral	13 (76.5%)	6 (27.3%)	0.004
Bilateral	4 (23.5%)	16 (72.7%)	
Timing of appearance			
At diagnosis	7 (41.2%)	10 (45.5%)	0.928
During treatment	2 (11.8%)	3 (13.6%)	
After completion of treatment	8 (47.1%)	9 (40.9%)	
Number			
No. of initial nodules	1.0 (1.0-1.0)	2.5 (1.0-3.0)	0.006
Maximal No. of nodules	1.0 (1.0-2.0)	5.0 (3.0-6.0)	<0.001
Size			
Size of initial nodule, mm	3.0 (2.0-3.5)	9.0 (3.0-20.0)	<0.001
Size of the largest nodule, mm	3.0 (2.0-4.0)	29.5 (13.0-52.0)	<0.001
Mediastinal lymph node involvement			
Mediastinal lymph node involved	0	4 (18.2%)	0.118

* Data are shown as No. (%) or median (interquartile range), unless otherwise specified

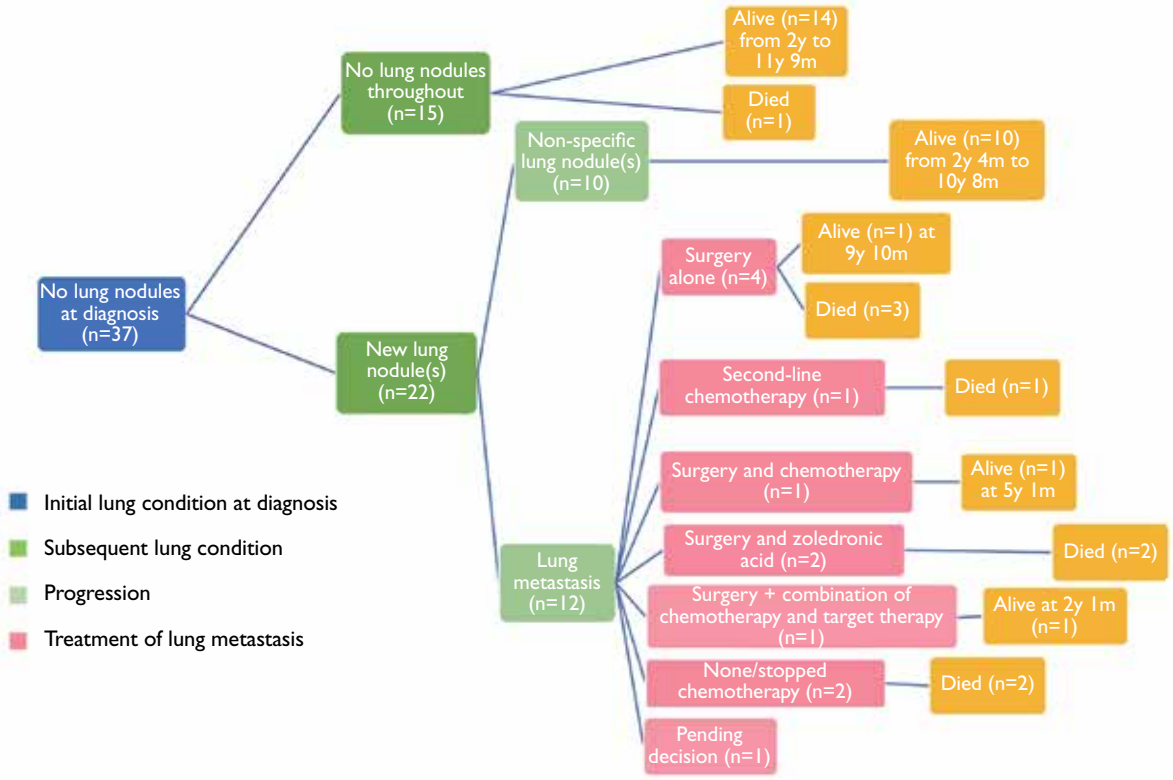

FIG 2. Lung nodules, nature, treatment, and outcomes for patients with no lung nodules at diagnosis

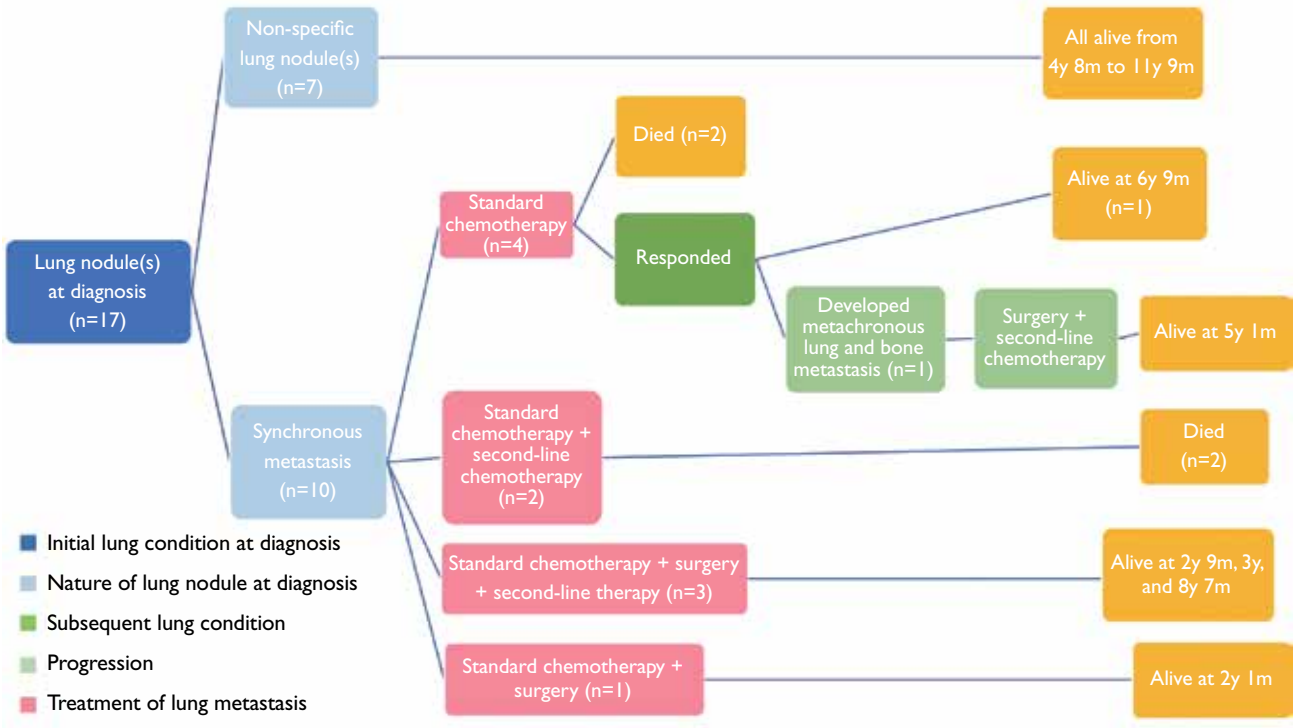

FIG 3. Lung nodules, nature, treatment, and outcomes for patients with lung nodules at diagnosis

TABLE 4. Factors associated with poor event-free survival and poor overall survival

	Event-free survival		Overall survival	
	Hazard ratio (95% confidence interval)	P value	Hazard ratio (95% confidence interval)	P value
Female sex	1.01 (0.44-2.30)	0.988	1.18 (0.43-3.24)	0.755
Age (years)	1.01 (0.90-1.14)	0.846	1.06 (0.91-1.22)	0.470
Time from symptom onset to presentation (weeks)	1.00 (0.93-1.07)	0.911	1.01 (0.93-1.09)	0.876
Time from diagnosis to start of chemotherapy (days)	1.01 (0.97-1.05)	0.715	1.02 (0.98-1.06)	0.321
Primary tumour in femur	1.04 (0.45-2.41)	0.926	1.39 (0.47-4.08)	0.547
High-grade conventional osteosarcoma*	1.78 (0.42-7.60)	0.436	0.92 (0.21-4.14)	0.915
Largest dimension of tumour (mm)	1.01 (1.00-1.02)	0.057	1.02 (1.00-1.03)	0.012
Maximal ALP ≥1000 IU/L before treatment	2.02 (0.47-8.63)	0.343	1.46 (0.19-11.2)	0.715
Pathological fracture	1.31 (0.49-3.53)	0.597	1.71 (0.54-5.42)	0.361
Metastatic disease at diagnosis	5.50 (2.33-13.02)	<0.001	4.39 (1.44-13.4)	0.009
Presence of metastasis throughout	211.73 (4.55-9855.59)	0.006	165.61 (1.66-16539.61)	0.030
Local aggressiveness†	2.12 (0.78-5.73)	0.141	4.15 (1.37-12.5)	0.012
Need for amputation‡	3.89 (1.59-9.54)	0.003	10.14 (3.20-32.08)	<0.001
Poor tumour chemonecrosis	3.44 (1.25-9.49)	0.017	2.47 (0.76-8.04)	0.134

Abbreviation: ALP = alkaline phosphatase

* Reference group: other histology

† Local aggressiveness: presence of intra-articular tumour involvement or neurovascular bundle involvement

‡ Reference group: patients who underwent limb-salvage surgery

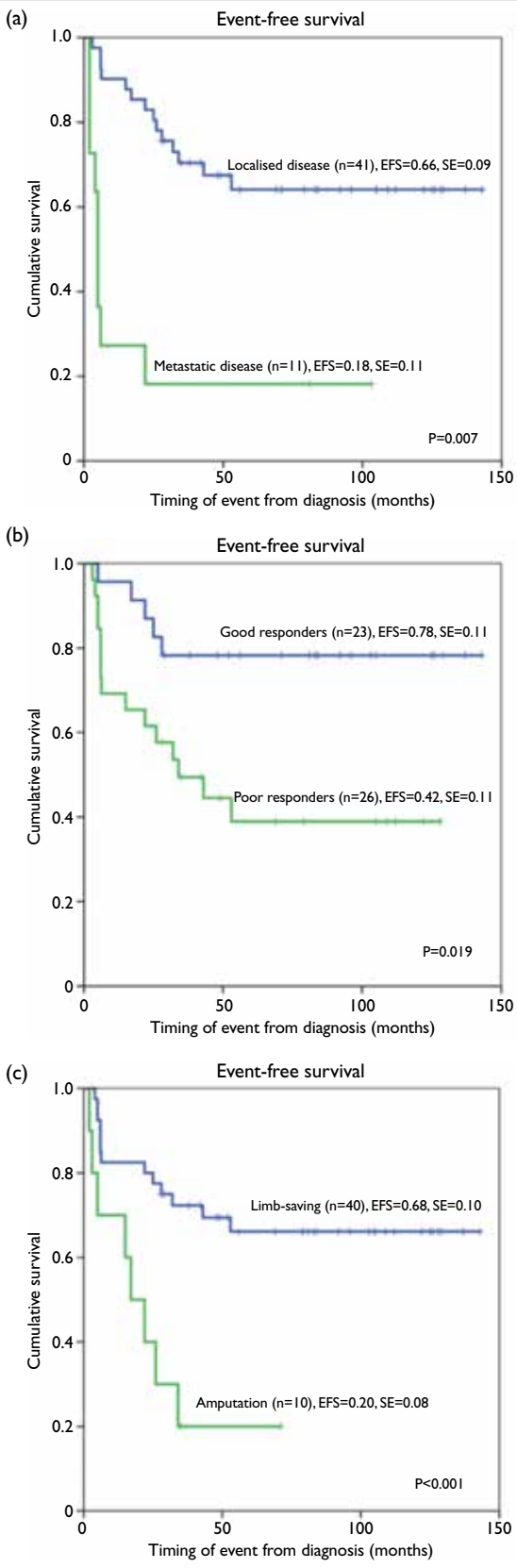

FIG 4. (a) Comparison of event-free survival between localised and metastatic disease groups. (b) Comparison of event-free survival between good and poor responder groups. (c) Comparison of event-free survival between limb-salvage surgery and amputation groups
Abbreviations: EFS = event-free survival; SE = standard error

TABLE 5. Multivariate analysis of factors associated with poor event-free survival and poor overall survival

	Adjusted hazard ratio (95% confidence interval)	P value
Event-free survival		
Presence of metastatic disease at diagnosis	12.94 (3.59-46.55)	<0.001
Need for amputation*	4.20 (1.50-11.74)	0.006
Poor tumour chemonecrosis	5.78 (1.76-19.00)	0.004
Overall survival		
Largest dimension of tumour (mm)	1.01 (0.99-1.02)	0.394
Presence of metastatic disease at diagnosis	11.75 (2.38-57.92)	0.002
Need for amputation*	17.55 (3.70-83.29)	<0.001

* Reference group: patients who underwent limb-salvage surgery

Discussion

Patient characteristics

To our knowledge, this is the first multicentre review of the demographic characteristics and prognostic factors of paediatric high-grade osteosarcoma in Hong Kong. The number of patients included in the study constituted 76.5% of children with osteosarcoma diagnosed in Hong Kong during the study period (unpublished data). Thus, our findings are likely to be representative of the courses of disease and treatment for children with osteosarcoma in Hong Kong. In this study, slightly more patients with high-grade osteosarcoma were boys, the median age at diagnosis was 13.5 years, and the femur was the most common site of involvement. All of these results are comparable to findings in western countries.[1,10] Only one patient had a high-grade osteosarcoma in the humerus; no patients had a primary nodule in the axial skeleton, demonstrating the rarity of such nodules. Although our study was limited by a short follow-up interval in some patients, the EFS and OS were comparable to the findings of large studies conducted in other countries,[6,8,10,11] as well as the results of a study performed in Hong Kong in 2009.[12] The shortest follow-up interval was 2 years from diagnosis. Most events occurred in the first 2 to 3 years, but some poor responders experienced late relapse at 4 to 5 years after initial diagnosis. Thus, a longer follow-up interval is necessary to better determine patient outcomes and more comprehensively assess the incidence of late toxicity.

Prognostic factors

In terms of prognostic factors, our findings in a cohort of Hong Kong patients confirm the validity of some important prognostic factors recognised

in studies performed elsewhere, including the largest dimension of the primary tumour,[8,13,14] presence of metastasis at diagnosis,[6,8,9,11] and poor tumour chemonecrosis.[6,8,9,13-15] Additionally, our study identified the need for amputation as an independent prognostic factor for EFS and OS. With respect to mortality, the prognostic effect of the need for amputation has varied among studies.[6,13-16] This variation is presumably because the decision to amputate depends on many factors, including the opinions of orthopaedic surgeons and parental acceptance. In our study, 10 patients underwent amputation; in two of these patients, the procedure was performed with palliative intent to achieve symptomatic control. Both of those patients had metastatic disease at diagnosis, which involved large and painful primary tumours. Thus, risk stratification of patients according to the need for amputation may enable the selection of patients with more advanced disease. Nonetheless, in our cohort, all surgical margins were negative in both limb-salvage surgery and amputation groups. Moreover, local recurrence was uncommon. Thus, our findings may provide insights that can be used to update risk stratification protocols for paediatric patients with osteosarcoma. In the current treatment protocol, there is a considerable delay between initial diagnosis and risk stratification (at week 16), which is performed after tumour resection and when tumour chemonecrosis data are available. However, the surgical approach is usually determined after approximately 4 to 5 weeks of treatment, when reassessment imaging is conducted. If aggressive features are observed at diagnosis (eg, a massive tumour, early intra-articular tumour involvement, or early neurovascular bundle involvement), the discussion of possible amputation may have already begun. Thus, the presence of such features, or the early recognition of the need for amputation, may be suitable for risk stratification after validation in larger-scale studies.

Surrogate markers of aggressiveness

In recent decades, there has been extensive research into surrogate markers for aggressiveness in osteosarcoma. In some studies, the levels of ALP[8,9,14,15,17] and lactate dehydrogenase[18-20] were identified as significant prognostic factors. Although the maximal ALP level was not associated with EFS or OS in our study, some studies have demonstrated a positive association between the serum ALP level and tumour volume.[21] This association is presumably related to the increased rate of bone remodelling in the tumour. However, the serum ALP level is also elevated in teenagers because of increased bone remodelling during periods of rapid growth. Thus, a universal cut-off for all paediatric patients may not provide the greatest prognostic accuracy.[22] Some studies[23] have explored methods to increase the age specificity of serum ALP levels. However, more validation and larger-scale studies are required before these methods can be widely adopted. Whereas the serum lactate dehydrogenase level showed a weaker association with tumour volume,[21] a change in this level is more likely to be associated with a non-specific increase in tumour metabolism. Currently, the serum lactate dehydrogenase level is not included in pretreatment staging and investigation protocols; thus, it is not routinely checked. For investigation purposes, it should also be included in baseline investigations.

Because most biochemical parameters are not accurate surrogate markers for the aggressiveness of osteosarcoma, technological advancements have enabled molecular and genetic profiling of osteosarcomas to become the focus of research in the past 10 to 15 years.[22,24,25] These studies may provide insights concerning the 'non-conforming' behaviour of certain tumours in our patients; examples include locally aggressive primary tumours that warrant amputation but demonstrate good tumour chemonecrosis, or tumours that show disease progression despite good tumour chemonecrosis. The current literature suggests that paediatric osteosarcoma is a heterogeneous disease,[21,26] although general knowledge of the disease remains incomplete. Despite advancements in surgical techniques for primary tumour resection,[27] improvements in the accuracy of staging imaging, and enhancements of supportive care, further revisions are needed concerning the medical treatment of paediatric osteosarcoma. Thus, molecular and genetic studies are essential and may facilitate further stratification of patients with osteosarcoma into different risk groups, which may require tailored treatment regimens for better outcomes. Future studies may also enable the identification of molecular nodules for targeted therapy or immunotherapy, which lead to considerable advances in the treatment of osteosarcoma.

Lung nodule analysis

Lung nodules were common in the initial staging and serial follow-up CT scans of our patients. The small size of some nodules hindered characterisation. They might represent benign lung pathologies. However, they may also represent micro-metastases which were responsive to chemotherapy. Thus, they remained stable in size and number on subsequent scans, suggesting that they persisted as scars. Patients with non-specific lung nodules had an excellent prognosis, with an OS rate of 100% in our study. However, repeated scans are needed for the follow-up and characterisation of such lung nodules. Additionally, the appearance of any new lung nodules on CT scans creates a considerable psychological burden for patients and their families.

Our study identified parameters that can help to differentiate true lung metastases from non-specific nodules, including the number of initial nodules, maximal number of nodules, initial nodule size, and largest nodule size. A study in Hong Kong in 2011[28] also identified number (≤5 vs >5), size, and laterality of lung nodules as important prognostic factors for survival, whereas a study in the US in 2011[29] found that survival was worse for central lung metastases than for peripherally located lung metastasis. Additional larger-scale risk stratification studies are needed to clearly delineate the cut-offs for size, number, laterality, and location of initial lung nodules. The establishment of a scoring system that considers parameters of lung nodules observed in chest CT scans may enable prediction of the risk of malignancy, thus improving early detection of lung metastasis and reducing unnecessary anxiety for patients and their families. Furthermore, standardised reviews of CT scans will help to ensure more uniform classification of lung nodules, particularly when the nodules are small.

With respect to confirmed lung metastasis, the situation becomes increasingly complicated. For a single synchronous or metachronous lung metastasis, metastasectomy was conducted whenever surgically feasible because it has been regarded as the primary treatment approach in multiple studies.[30-32] However, given the diversity of treatments, there was no consensus regarding treatment strategies for multiple metastases or local recurrence. This is presumably because the effects of different chemotherapy regimens and targeted therapies remain under investigation.[11,33-36] In our study, surgical resection of lung metastasis whenever possible, together with zoledronic acid, generally achieved durable clinical remission for >5 years. Long-term randomised controlled trials of different chemotherapy or targeted therapy regimens should be conducted to determine the most cost-effective regimens that improve survival for relapsed paediatric patients with high-grade osteosarcoma. Many centres in other nations are performing karyotyping and genetic analysis of osteosarcoma tumour cells to identify targetable mutations.[11,24,37] However, these tests are not routinely conducted for standard care in Hong Kong. Collaborations with centres in other nations should be pursued to facilitate the implementation of international standards in Hong Kong.

Conclusion

To our knowledge, this represents the first multicentre review of paediatric high-grade osteosarcoma in Hong Kong. Important prognostic factors, including metastatic disease at diagnosis and poor tumour chemonecrosis, were validated. The need for amputation may reflect local aggressiveness, which influences OS. Larger-scale studies of high-grade osteosarcoma in paediatric patients should be conducted over a longer period of time to better understand the characteristics, patterns, and prognostic factors.

Author contributions

Concept or design: GPY Tong, CK Li.
Acquisition of data: GPY Tong.
Analysis or interpretation of data: GPY Tong, WF Hui, CK Li.
Drafting of the manuscript: GPY Tong, WF Hui, KC Wong, CK Li.
Critical revision of the manuscript for important intellectual content: All authors.

All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

The authors have no conflicts of interest to disclose.

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Ethics approval

This study was approved by the Research Ethics Committee (Kowloon Central/Kowloon East Cluster and New Territories East Cluster), Hospital Authority Hong Kong (Ref: KC/KE-19-0301/ER-1, 2019.712). The requirement for patient informed consent was waived.

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