SHORT COMMUNICATION

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Indeterminate nodules in osteosarcoma: what's the follow-up?

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Background: Indeterminate pulmonary nodules in patients diagnosed with osteosarcoma present a challenge for accurate staging and prognosis. The aim of this study was to explore the significance of this finding.

Methods: A retrospective cohort study of 120 patients with osteosarcoma was performed in the North East of England. Chest computed tomographies (CTs) at presentation were reviewed and the incidence of 'indeterminate' nodules recorded. Follow-up scans were reviewed and survival as well as prognostic features were analysed.

Results: 25% of our cohort presented with indeterminate nodules. Of these, 33% were subsequently confirmed as metastases, the majority within a year. Kaplan–Meier survival analysis showed that patients with indeterminate nodules fared better than those with frank metastatic disease, and similar to those who presented with a normal chest CT. We found no radiographic features that predicted survival.

Conclusions: Indeterminate nodules remain a clinical and diagnostic dilemma. Close monitoring of patients is advised during the first year from presentation, and there is potential for indeterminate nodules to develop into frank metastases later than five years from presentation.

Sarcomas metastasise most frequently to the pulmonary parenchyma. Computed tomography (CT) has become the standard for detecting and monitoring pulmonary lesions, but frequently identifies nodules of uncertain clinical significance. Often the assumption is that, especially in children, these nodules represent metastatic disease. However, up to 60% of pulmonary nodules found in adults and 33% in children may be non-malignant (Bearcroft and Davies, 1999; Picci *et al*, 2001).

Differentiating benign and malignant lesions is essential for planning treatment and determining prognosis. When nodules are detected, invasive procedures may be necessary to establish the histopathologic diagnosis, but in many cases the nodules are simply monitored with repeat CT scans. From the patients' perspective, such nodules cause stress and concern as their significance remains uncertain.

Osteosarcoma is the most common malignant bone tumour arising in children and adolescents. Up to 20% of patients will have synchronous metastatic pulmonary disease detectable radiologically at initial presentation (Goorin *et al*, 1991). However, the positive predictive value of radiographic criteria for pulmonary nodules using CT has been estimated at 53% (Robertson *et al*, 1988). Among patients with normal chest CTs on presentation, 20–25% will relapse, usually in the lungs (metachronous metastatic pulmonary disease). A cohort of these patients will have indeterminate pulmonary nodules (IPNs) at presentation, the majority of which will turn out to be malignant (Fernandez-Pineda *et al*, 2012).

Indeterminate pulmonary nodules are those that have some risk of cancer. There remains controversy around their definition, but in general IPNs fall under the category of non-calcified nodules. Their diameters can vary but based on recent studies nodules arising from a range of solid cancer types with a diameter < 10 mm have caused greatest discussion (Robertson *et al*, 1988; Rissing *et al*, 2007; Nakamura *et al*, 2009, 2017).

Our institution performed a retrospective cohort study to determine the significance upon survival of IPNs reported at initial presentation on chest CT in patients diagnosed with osteosarcoma.

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Furthermore, we tried to characterise features of these nodules for patients at risk. Our null hypothesis was that the presence of such nodules had no effect on long-term survival when compared to a non-metastatic group.

MATERIALS AND METHODS

Approval for this study was obtained by our NHS trust clinical effectiveness committee, Caldicott number 7707. A retrospective cohort study of 120 consecutive osteosarcoma patients treated between 1998 and 2015 was performed using a regional database. Patients underwent a CT scan as part of their initial staging studies (Scanner Somatom Definition AS by Siemens, Erlangen, Germany—3 mm slices).

Data entered included age, anatomical site and histological type of osteosarcoma.

The minimum follow-up was 2.5 months (average, 78 months; median, 54 months; range, 2.5–243 months).

Computed tomography scans and reports were reviewed by two authors (KMG and LL), who were blinded to the clinical outcome of the patients. Patients were grouped into non-metastatic, metastatic (synchronous) and indeterminate nodules. Indeterminate pulmonary nodules were defined as non-calcified nodules <10 mm in maximal diameter (Rissing *et al*, 2007).

Follow-up CT scans usually performed every 4–6 months were examined for the subgroup of patients with either no metastasis or IPNs to record their radiological outcome as either stable or metachronous disease (Figure 1).

Finally, the characteristics of IPNs were recorded including site (central or peripheral), size (>5 mm), number (single or multiple) and histological subtype of primary tumour.

Disease-free survival was undertaken via Kaplan–Meier survivor analysis with failure defined as death. Censored observations were defined by continuous disease-free survival at last follow-up. Univariate analysis of factors affecting survival in those patients with IPNs based on their radiological characteristics was performed using Log-rank test (SPSS version 21, IBM Corporation, Armonk, NY, USA)

For this study, significance was set at 0.05 and power 0.8.

RESULTS

One hundred and four out of 120 patients presenting with osteosarcoma had full data sets available (86%). The median age at presentation was 20 years (range, 7–72). Sixty-five (62%) tumours were located in the lower limb, 14 (13%) upper limb, 11 (11%) axial skeleton, 9 (9%) head and neck and 5 (5%) extraskeletal.

At initial staging, 55 (53%) patients presented with no metastasis, nor IPNs, 19 (18%) patients presented with synchronous metastatic disease (Supplementary Table) and 30 (29%) patients presented with IPNs.

Of the patients who presented with IPNs, 20% (6 out of 30) progressed to metastatic disease at the same site as the nodules, mean age 15 (range, 7–20). 10% (3 out of 30) developed lung metastasis at a separate site, mean age 21 (range, 16–25). In the remaining 21 patients (70%), the radiological features remained static, mean age 26 (range, 7–67).

The median time for patients presenting with IPNs to be diagnosed with metastatic disease was 27 weeks (range, 9–297 weeks). Eighty per cent of this cohort was diagnosed within 1 year.

The 104 patients presenting with osteosarcoma were split into three groups: non-metastatic; indeterminate pulmonary nodules and frank pulmonary metastases. Overall, survival was significantly different between patients presenting with metastatic pulmonary disease *vs* those presenting with no evidence of metastases or IPNs (Figure 2). In the 55 patients presenting with no evidence of metastases, nor IPNs, 16 developed new frank metastatic pulmonary lesions with only one long-term survivor following metastasectomy.

For patients presenting with IPNs, the groups were too small for the time varying covariates to be calculated; therefore, the raw data are presented demonstrating two early deaths in the group with stable IPNs, both of which were due to extra-pulmonary disease progression (Table 1A). For patients with IPNs that developed into metastases, there was one survivor out of six patients. This survivor underwent extensive right full pneumonectomy (Table 1B). This group also contains a patient with IPNs that progressed into frank metastases six years from presentation. In the remaining group where patients developed frank metastases around the IPNs, there was one survivor out of three. This survivor underwent a right wedge resection for a rapidly growing single metastasis (Table 1C).

Univariate analysis of nodule characteristics (site, size, number and location) found no prognostic indicators for survival (Table 2). In a direct comparison of nodule size, three out of six patients who developed metastasis at the same site as the nodule had an initial size of over 5 mm, compared to the static nodule group that had a rate of 2 from 21 patients with IPNs that were over 5 mm ($P=0.014$).

DISCUSSION

The purpose of this study was to evaluate whether IPNs were associated with poorer survival in patients with osteosarcoma.

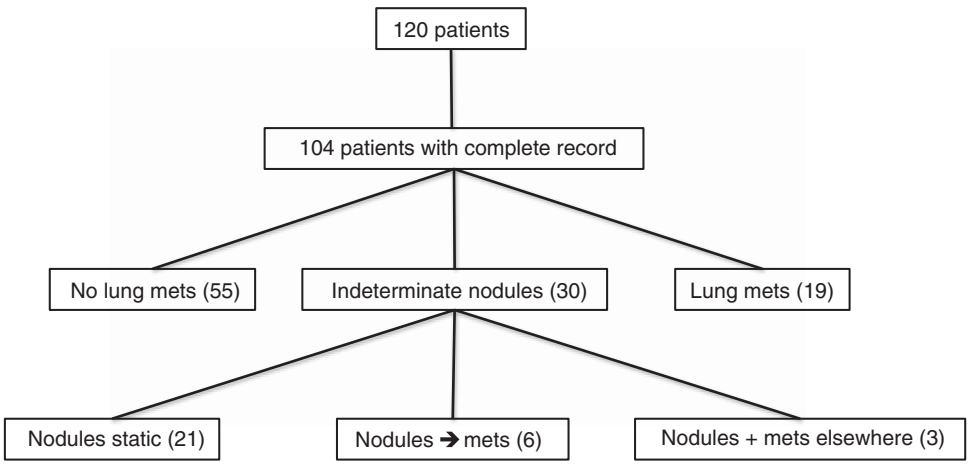

Figure 1. Patient distribution.

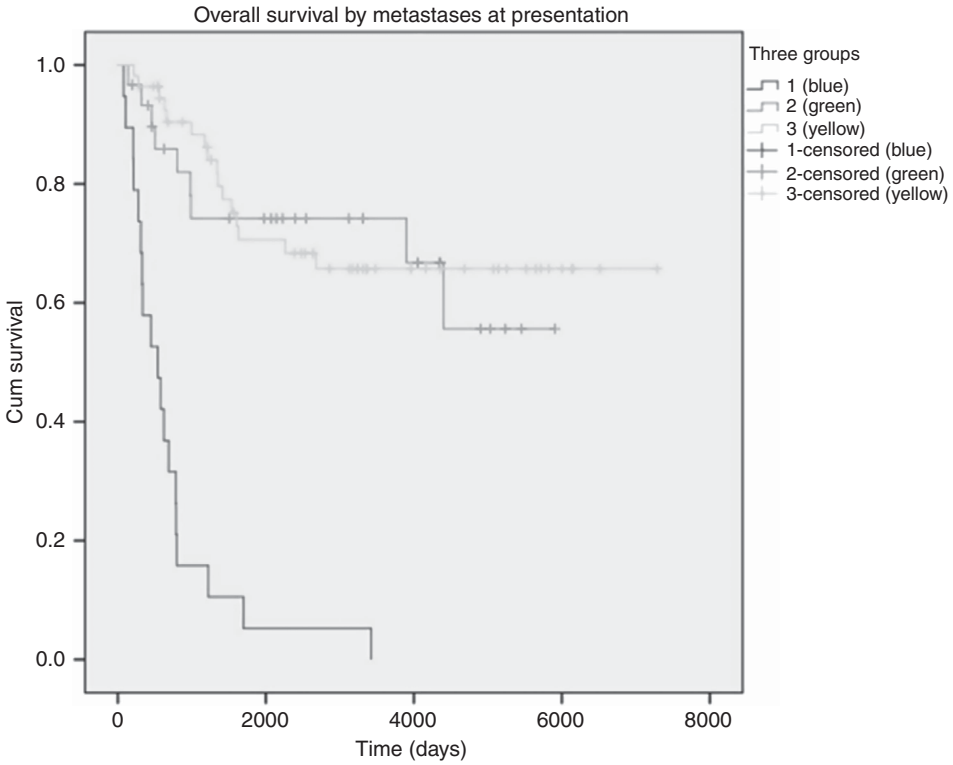

Figure 2. This graph shows three super-imposed Kaplan–Meier survivorship curves for patients with osteosarcoma. Green represents those patients who presented with no metastasis or indeterminate nodules. Yellow represents those patients with indeterminate nodules and blue are those patients with metastasis at presentation. No significant difference in survivorship was noted between those with indeterminate nodules and those without metastasis at presentation. Survivorship in the metastatic group was significantly worse ($P<0.001$). A full colour version of this figure is available at the *British Journal of Cancer* journal online.

Furthermore, we aimed to ascertain whether radiological characteristics of such nodules led to a poorer outcome. Our results showed that patients presenting with IPNs had significantly better survivorship to patients presenting with metastatic disease and similar survivorship to patients with no lung metastasis. Nodules that subsequently turned out to be metastasis tended to be larger (>5 mm).

With the advent of fine slice CT, the incidence in detection of subcentimetre nodules is increasing. Hanamiya *et al* (2012) reported the rate of detection of non-calcified pulmonary nodules to be 75% in patients with extra-pulmonary malignant tumours. Understanding the significance of such nodules is difficult and only a handful of studies have aimed to try and quantify their impact on patient outcome. Rissing *et al* most notably performed a similar study but looking prospectively at 331 patients with a range of sarcoma types. In their cohort, 21% presented with IPNs (*vs* 29% in this study). Twenty-eight per cent of IPNs progressed to metastatic disease (*vs* 30% in this study). Metastatic disease tended to develop at the site of the original IPNs (90 *vs* 66% in this study). They also found that those IPNs that did progress to metastasis did so within the first year. In contrast, they found nodules >5 mm were associated with a poorer prognosis, whereas our study found no such association (Rissing *et al*, 2007). This may be as a result of fewer numbers as there was an association with larger nodules (>5 mm) being more prevalent at the site of subsequent metastatic disease.

Brader *et al* acknowledged that no algorithm existed for making the distinction between benign and malignant pulmonary nodules based on just radiological findings in paediatric patients with sarcomas. In their retrospective study of 30 paediatric osteosarcoma patients, radiologists correctly identified 94% of the malignant nodules. However, of the benign nodules, 11–30% were correctly classified and 54–65% were deemed indeterminate. They found only two radiological parameters consistently useful for predicting malignancy—calcification and size >5 mm (Brader *et al*, 2011). Other studies have focused more towards the significance of small or solitary nodules. Nakamura *et al* performed a retrospective cohort study on 206 patients with a range of sarcoma types. Their group found a statistically significant relationship between the size of the pulmonary nodules and cumulative overall survival. Patients with nodules <5 mm in size, showed overall survival similar to those that presented with a normal chest CT. However, neither nodule number, location nor tumour of origin was found to be of prognostic value. In their study, all nodules were classified as either metastatic or benign, with no mention of IPNs (Nakamura *et al*, 2009).

Indeterminate pulmonary nodules present a continued diagnostic dilemma for a large range of solid cancers and there is a clear paucity in the literature guiding best practice in their management. In terms of lung cancer, the American College of Chest physicians recommended follow-up scans *vs* PET-CT or tissue diagnosis of suspicious nodules on the basis of probability. These take into account amongst others, a number of time-dependent factors such as biomarkers, volumetric analysis and growth rate. Yet, such studies cannot provide the answer the patients want at the time of discovery (Pinsky *et al*, 2014; Massion and Walker, 2014; Gould *et al*, 2013).

Our study has a number of limitations. This is a retrospective study with a relatively small patient group, where incomplete data sets resulted in a large amount of censored data. Despite this, follow-up data were available for as far out as 14 years and our study represents the largest series we know of assessing the survival outcome of osteosarcoma patients presenting with IPNs. CT scans were reported by experienced musculoskeletal radiologists but may be prone to inter- and intra-observer error, which was not evaluated. Computed tomography scanning technology had

Table 1A. Stable indeterminate nodules

Age (years)	Primary site	Survival (days)	Histological subtype	IPN number	IPN distribution	Size over 5 mm	Pulmonary metastasectomy
10	Distal femur	Alive (5456)	Osteoblastic	Solitary	Peripheral	No	No
13	Clavicle	Alive (5031)	Chondroblastic	Solitary	Peripheral	No	No
17	Proximal tibia	Alive (4902)	Osteoblastic	Solitary	Peripheral	No	No
64	Great toe	Alive (4345)	Atypical high grade	Solitary	Central	No	No
13	Distal femur	Alive (4362)	Chondroblastic	Multiple	Peripheral	No	No
19	Distal femur	Alive (4053)	Chondroblastic	Solitary	Central	Yes	No
14	Distal tibia	Alive (3312)	Osteoblastic	Solitary	Peripheral	No	No
15	Distal femur	Alive (3123)	Osteoblastic and chondroblastic	Multiple	Central	No	No
35	Skull	Alive (2144)	Parosteal low grade	Solitary	Peripheral	No	No
35	Skull	Alive (2073)	Atypical high grade	Solitary	Peripheral	No	No
23	Ulna	Alive (2229)	Periosteal chondroblastic intermediate grade	Solitary	Peripheral	No	No
59	Maxilla	Alive (2541)	Osteoblastic and chondroblastic	Solitary	Peripheral	No	No
15	Proximal tibia	Alive (2398)	Osteoblastic	Multiple	Peripheral	No	No
19	Distal femur	Alive (1973)	Chondroblastic	Solitary	Peripheral	No	No
19	Proximal tibia	Alive (1508)	Periosteal chondroblastic intermediate grade	Multiple	Peripheral	No	No
19	Distal femur	Alive (461)	Osteoblastic and chondroblastic	Multiple	Peripheral	No	No
15	Proximal tibia	Alive (623)	Osteoblastic	Solitary	Peripheral	No	No
26	Proximal fibula	Alive (405)	Osteoblastic	Multiple	Central	No	No
24	Proximal humerus	Alive (195)	Chondroblastic	Multiple	Peripheral	No	No
56	Proximal femur	Death[a] (981)	Osteoblastic	Solitary	Peripheral	Yes	No
67	Kidney	Death[a] (139)	Atypical high grade	Solitary	Peripheral	Yes	No

Abbreviation: IPN = indeterminate pulmonary nodules.
[a]These patients died of extensive local recurrence.

Table 1B. Indeterminate nodules develop into metastases

Age (years)	Primary site	Survival (days)	Histological subtype	IPN number	IPN distribution	Size over 5 mm	Pulmonary metastasectomy
20	Distal femur (Li Fraumeni syndrome)	Alive (5905)	High grade	Multiple	Peripheral	Yes	Yes
11	Distal femur	Death (3901)	High grade	Solitary	Central	Yes	Yes
7	Distal femur	Death (803)	Osteoblastic	Solitary	Peripheral	Yes	Yes
19	Distal femur with skip lesion	Death (504)	Osteoblastic	Solitary	Peripheral	No	No
16	Distal femur	Death (987)	Osteoblastic	Multiple	Peripheral	No	Yes
15	Proximal humerus	Death (319)	Osteoblastic	Multiple	Peripheral	No	Yes

Abbreviation: IPN = indeterminate pulmonary nodules.

Table 1C. Metastases develop around indeterminate pulmonary nodules

Age (years)	Primary site	Survival (days)	Histological subtype	IPN number	IPN distribution	Size over 5 mm	Pulmonary metastasectomy
22	Distal femur	Alive (5238)	Chondroblastic	Multiple	Peripheral	No	Yes
25	Distal femur	Death (4401)	Osteoblastic	Solitary	Peripheral	No	Yes
16	Mandible	Death (874)	Atypical high grade	Multiple	Peripheral	No	No

Abbreviation: IPN = indeterminate pulmonary nodules.

improved over the study period and undoubtedly would have led to increased sensitivity and specificity when diagnosing IPNs. The effect of neo-adjuvant chemotherapy was not included in this analysis; however, standard treatment protocols were followed as per regional guidelines and in keeping with most surveillance studies (Daw *et al*, 2015).

In conclusion, IPNs remain a diagnostic dilemma for the clinician and patient. Lack of understanding with regard to the significance of these nodules at initial presentation makes for a difficult consultation. In our series, overall survival was significantly better for patient presenting with IPNs than those with metastatic disease. Most of those that progressed to metastatic

Table 2. Univariate analysis of prognostic variables for indeterminate nodules (Log-rank test)

Variable	Significance (*P* value)	Survival range (days)
>5 mm	0.530	803–4053
Multiple nodules	0.559	319–5905
Central location	0.873	405–4345
Chondroblastic	0.081	461–5238

disease did so within the first year although one patient did progress at a later stage, 6 years from presentation. Our series of IPN patients that developed metastases also contains two long-term survivors following metastasectomy. As such, we would recommend close observation with at least annual CT imaging for all patients for up to 10 years, particularly for larger nodules (>5 mm). Multicentre studies need to be performed and data pooled in order to provide better prognostic information and standardised care. Improved imaging techniques, such as MRI/PET, that may give radiologists the ability to enhance metastatic lesions to distinguish them from benign nodules is an important area for further research.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

INFORMED CONSENT

All patients in this study are made aware that their details are stored in a database and may be used for study purposes. Subsequent consent was therefore waived with approval for the study through the Trust clinical effectiveness committee and Caldicott guardian.

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Supplementary Information accompanies this paper on British Journal of Cancer website (http://www.nature.com/bjc)