The final diagnosis in patients with a suspected primary malignancy of bone

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We investigated the eventual diagnosis in patients referred to a tertiary centre with a possible diagnosis of a primary bone malignancy.

We reviewed our database from between 1986 and 2010, during which time 5922 patients referred with a suspicious bone lesion had a confirmed diagnosis. This included bone sarcoma in 2205 patients (37%), benign bone tumour in 1309 (22%), orthopaedic conditions in 992 (17%), metastatic disease in 533 (9%), infection in 289 (5%) and haematological disease in 303 (5%). There was a similar frequency of all diagnoses at different ages except for metastatic disease. Only 0.6% of patients (17 of 2913) under the age of 35 years had metastatic disease compared with 17.1% (516 of 3009) of those over 35 years (p < 0.0001). Of the 17 patients under 35 years with metastatic disease, only four presented with an isolated lesion, had no past history of cancer and were systematically well.

Patients under the age of 35 years should have suitable focal imaging (plain radiography, CT or MRI) and simple systemic studies (blood tests and chest radiography). Reduction of the time to biopsy can be achieved by avoiding an unnecessary investigation for a primary tumour to rule out metastatic disease.

Bone and soft-tissue sarcomas represent less than 1% of all malignant tumours.1,2 Delays in diagnosis and a wide range of differential diagnoses are common.3 These include infections, benign tumours, normal variants, degenerative or metabolic processes and other malignant tumours. Reaching the correct diagnosis in the quickest time possible is essential for the patient and important for resource allocation.4-7

Current guidelines from the National Institute for Clinical Excellence (NICE)2 recommend that any patient presenting with bone pain or swelling (in particular, pain not aggravated by activity) should be referred for radiography.8 Any suspicious lesion with bone lysis, formation of new bone, periosteal elevation or soft-tissue swelling, should be investigated further. If a bone sarcoma is considered to be a possibility, the patient should be referred directly to a specialist bone-tumour unit, whereas, if metastasis is suspected, investigation locally is appropriate.9

For more than 30 years, our centre has accepted referrals from patients who might have a primary malignant bone tumour. Our aim in this study was to analyse the correct diagnosis in all such patients and to define patterns which might lead to clearer guidelines for referral.

Patients and Methods

We searched our database for all patients referred with a possible primary malignant bone tumour between 1986 and 2010. Patients with a known diagnosis of a bone metastasis or benign tumour were excluded. Most were thought to have had a possible primary malignant bone tumour before referral, but in most cases no definite diagnosis had been made and the patients were referred for investigation, diagnosis and advice on treatment. In almost all a ‘suspicious’ plain radiograph had been obtained before referral, but the extent of further investigations varied widely, with some having had none and others having had CT of the chest and abdomen, bone scanning and MRI of the primary site.

All the patients were investigated according to a protocol designed to reach a diagnosis as quickly as possible. In some cases targeted investigations could reach a diagnosis without a biopsy, for example, CT revealing a typical osteoid osteoma. In most, however, the investigations included a full history and examination followed by local and systemic imaging. Local imaging was usually CT before 1993 and MRI afterwards. Systemic imaging included bone scanning and chest radiography and in some cases of possible metastatic disease, CT of the...
chest and abdomen to try to identify a primary tumour. Routine blood tests included a full blood count, measurement of the ESR, a biochemical profile and, when indicated, screening for myeloma and the prostate-specific antigen test.

The patients were reviewed for age, gender, site and final diagnosis. Final diagnosis was divided into broad categories as follows: bone sarcoma, such as osteosarcoma, chondrosarcoma, Ewing’s sarcoma and chordoma; benign lesions, such as fibrous dysplasia, chondroma and aneurysmal bone cysts; orthopaedic lesions, such as fracture callus and avascular necrosis; metastatic disease; infection; haematological oncology, including lymphoma and myeloma; giant-cell tumours; and stress fractures. Patients with incomplete data or recurrence after treatment for a primary bone malignancy were excluded.

Statistical analysis. In addition to analysis of demographic trends, the data were examined for associations between age at diagnosis, site and final diagnosis, using the chi-squared test. A p-value ≤ 0.05 was deemed to be significant.

Results
A total of 5922 patients with complete records was identified. There were 2637 women and 3285 men with a mean age of 38 years (1 to 95), with a predominance of cases in the 10- to 20-year-old group (Fig. 1).

The most common diagnosis was that of primary bone sarcoma in 2205 patients, followed by a benign bone tumour or lesion in 1309 (Table I) and a giant-cell tumour in 197. Therefore, of the 5922 patients referred, 3711 (62.7%) had a primary bone tumour requiring specialist treatment at a regional centre. The remainder (37.3%) had the following diagnoses: orthopaedic (922, 16.8%), metastatic deposits (533, 9.0%), infection (289, 4.9%), haematological conditions (303, 5.1%) and stress fracture (94, 1.6%). The relative proportion of patients with a primary malignant bone tumour decreased over the period of study since surgeons were increasingly encouraged to refer any patient with a suspected primary malignant bone tumour before investigation. In the 1980s almost 92% of patients referred had a primary bone tumour. This decreased to 76% in the 1990s and further still to 34% after 2000.

The most common sites for the presenting bone lesions were the femur in 2246 patients (37.9%), the tibia in 1031 (17.4%), the humerus in 666 (13.0%), but 1207 (20.4%) arose elsewhere. There was a trend towards an increasing proportion of pelvic and sacral lesions with increasing age (8% (98 of 1243) of cases in the 1- to 15-year group, rising to 20% (82 of 409) in those patients > 75 years old.

When the final diagnosis was compared with the age at presentation there was variation in the proportion of final diagnoses. Bone sarcoma and benign lesions remained the most prevalent (Fig. 2). Infection was the most common diagnosis in children and adolescents, 11% (137 of 1243) in the 1- to 15-year-old group, decreasing to 1.6% (seven of 430) in those > 75 years of age, whereas a haematological lesion was more common in the fifth decade onwards (10%, 229 of 2226 patients > 50 years of age). The youngest patient diagnosed with myeloma was 33 years old, but lymphoma of bone arose at all ages. Metastatic bone lesions were increasingly common after the fifth decade, but were rare under the age of 35 years (Fig. 3).

Of the referred patients, 548 (9.3%) had a past history of malignancy. In many of these, the malignancy had occurred many years earlier and there was uncertainty as to whether the new lesion was metastatic. Of this group, 285 (52.0%) had a metastasis related to the original primary tumour, 69 (12.6%) had a primary bone sarcoma and 32 (5.8%) had a benign condition. Of the primary bone sarcomas, 18 (26.1%) could be related to the treatment of a previous cancer, usually a radiation-induced osteosarcoma. In six patients a chondrosarcoma was related to a past history of breast carcinoma.

Of the 2913 patients under the age of 35 years at the time of referral, only 17 were eventually found to have a diagnosis of...
metastatic tumour, representing 0.6% of this subset (95% confidence interval 0.3% to 0.9%). The metastasis was related to a past history of cancer in ten patients (58.5%) (three retinoblastoma, three pulmonary malignancy, two cervical carcinoma, one breast carcinoma and one soft-tissue sarcoma). A further three patients (17.6%) were found to have multiple lesions on nuclear bone scanning at presentation. Their final diagnoses were pulmonary carcinoma in two cases and a non-sarcomatous tumour, of unknown origin, in one.

The remaining four patients (23.5%) under 35 years, presenting with a solitary bone lesion and who were systemically well at presentation, had a normal chest radiograph and a solitary lesion on bone scanning. Two were later found to have metastatic disease, with the primary tumour being in the colon and kidney, respectively. There were two cases where the primary was not found, but histologically were not sarcoma: one malignant melanoma and one of an unknown primary tumour.

Metastatic disease became increasingly common over the age of 35 years. In 288 patients without a past history of cancer the most common primary sites were the lung, in 66 patients (23%), kidney in 37 (26%), breast in 32 (11%) and prostate in 20 (7%). The most common sites of presentation of the metastases in 533 patients were the femur in 204 (38%), pelvis in 137 (26%) and humerus in 64 (12%). Of the 2205 patients diagnosed with a primary malignant bone tumour, 286 (13%) had metastases at the time of presentation. Because of the increased use of more sophisticated CT the proportion of patients with detectable metastases at diagnosis has risen to 20% since 2000.
Discussion
We have investigated the eventual diagnosis in a highly selected group of patients who were referred to a tertiary referral centre with a possible primary malignant bone tumour. Some had radiography alone whereas others had undergone more extensive investigations.

Our review of practice over a period of 24 years not only shows that the age distribution and sites of presentation of bone tumours are similar to those of other published studies, but also that there is a wide range and frequency of other conditions which can be confused with a primary malignant bone tumour. It is notable that during this time, only 17 patients under the age of 35 years were found to have metastatic disease instead of a presumed primary bone tumour, and only four of these had no past history of cancer.

Because of the increasing awareness of the importance of referring patients with a suspected bone tumour to a specialist centre, there has been a rising number of referrals over the years. In the 1970s only patients with a definite or near definitive diagnosis were referred, but after the unit was designated as a supraregional unit in 1986, surgeons were encouraged to refer any patient with a suspected primary malignant bone tumour instead of investigating them locally.

We did not categorise the investigations carried out before referral, but increasingly more patients are being investigated locally and this fits with recent recommendations. These investigations, however, can be interpreted wrongly by inexperienced radiologists and the imaging may be incomplete and may need to be repeated. This may have to be accepted instead of recommending that all patients have to travel to a supraregional centre for every investigation. In general, however, discussion should be carried out with the specialist centre as soon as investigations suggest the presence of a possible primary malignant bone tumour either on radiography or MRI.

The limitation of our study is selection bias, since the patients were referred to a tertiary centre with the expectation that they might have a primary malignant bone tumour. Many patients would not have been referred, particularly those with metastatic disease or obvious benign conditions. Our proportion of patients with each diagnosis is not a true reflection of the absolute numbers in the population. For example, patients with haematological and infectious disorders are usually diagnosed and treated by the appropriate specialist.

Our study does not address the issue of false-negative cases, for example, when an abnormal radiograph is either not detected as such or is interpreted wrongly as showing some other conditions when a primary bone tumour is present. In general, most of these cases will eventually be referred when the true diagnosis declares itself. Fortunately the proportion of such cases thus misdiagnosed is relatively low, although in an earlier study it was found that 13 of 70 patients (19%) presenting with a primary bone tumour had had plain radiography which showed the undetected tumour. Our impression is that this situation has become less common, but patients with primary bone tumours still sometimes undergo inappropriate treatment before diagnosis, particularly if they present with a pathological fracture.

Despite these limitations, we believe that our findings confirm the algorithm recently published with the protocol we advocate for investigation of patients with a suspicious bone lesion. In a patient < 35 years of age at low risk of having a metastasis, the more likely diagnoses include benign or malignant bone tumours or infection and these patients do not need CT of the abdomen before diagnosis. We advise that such patients require focal imaging of the lesion, such as plain radiography, MRI or CT. Whether these are undertaken at the referring hospital or at a tertiary centre will depend on local resources, practices and expertise. Only simple systemic investigations are required (blood tests and radiography of the chest). The key to diagnosing these patients is a biopsy which should be performed in a tertiary centre. Reduction of the time to biopsy can be achieved by avoiding an unnecessary hunt for a primary tumour as a means of ruling out metastatic disease. Patients over the age of 35 years should be investigated further by systemic imaging as metastatic disease remains an important differential diagnosis in this group.

References