Diagnostic use of intramedullary reaming biopsy in metastatic long bone disease

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ABSTRACT

INTRODUCTION Bone is the third most common site of metastasis. A histological diagnosis is important in guiding therapy and prognosis. In up to 15% of cases of metastatic disease, the primary tumour remains unknown. This emphasises the importance of adequate, reliable and accurate sampling when performing any type of biopsy. Reaming biopsy is commonly performed during intramedullary nailing of metastatic long-bone disease but there is little published evidence on the diagnostic use and reliability of this technique.

AIMS AND METHODS We reviewed 49 cases of confirmed metastatic bone disease to determine adequacy for analysis, diagnostic accuracy and factors affecting reliability.

RESULTS Adequate tissue for histopathological analysis was obtained in 96% of cases but metastasis was confirmed in only 51% of cases. The presence of a pathological fracture had no effect on accuracy of the results but metastasis was more likely to be missed in the presence of tissue crushing and or necrosis ($P=0.015$).

DISCUSSION This study determines the use and accuracy of bone reaming biopsy in metastatic disease and, to the best of our knowledge, is the only study determining the effect of additional factors such as the presence of a pathological fracture and tissue necrosis or crushing on the diagnostic accuracy of this technique.

CONCLUSIONS In spite of adequate tissue sampling, the diagnostic accuracy and, hence, reliability of intramedullary reaming biopsy in metastatic bone disease is less than optimal. A reaming histopathology report suggesting no evident metastasis should always be taken in clinical context.

KEYWORDS

Bone Disease – Biopsy

Accepted 4 February 2017

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Introduction

Bone is the third most common site of cancer metastasis.^{1–3} Pathological fractures of long bones (commonly the femur followed by the humerus) are a major source of morbidity. Such fractures occur in up to 22% of patients and are associated with a higher mortality.^{1,4–6}

In the context of metastatic bone disease, a histological diagnosis is important, as histology may be needed to reveal whether a lesion is benign or from a different primary, or a recurrence of a known cancer, or a change in tumour phenotype, with implications on adjuvant therapy and prognosis. Reaming samples may be sent for histopathological analysis at the time of intramedullary nailing for long-bone metastatic disease.

There is little published evidence as to the reliability and diagnostic accuracy of reaming biopsy and this paper aims to explore this and related factors.

Aims and Methods

The aims of this study were to determine:

- > whether reaming sampling during intramedullary nailing yields sufficient tissue to allow comprehensive histopathological analysis
- > the diagnostic accuracy of reaming sampling
- > whether any other factors affect the reporting accuracy of metastatic disease in reaming sample histology.

All patients in our NHS trust with metastatic bone disease are reviewed and followed-up by an established bone metastasis multidisciplinary team (MDT) and entered into a database. All data were thus collected prospectively and retrieved from this database. The MDT constitutes consultants in orthopaedic surgery, clinical oncology, musculoskeletal radiology and an administrator.

Inclusion criteria were patients identified from this database as having: 1) undergone intramedullary nailing for known metastatic bone disease; and 2) tissue from reamings sent for histopathological analysis. There were no exclusion criteria.

Prophylactic intramedullary nailing was offered to patients deemed at significant risk of sustaining a pathological fracture, based on Mirels' scoring and disease prognosis. Therapeutic intramedullary nailing was carried out for pathological fractures.^{7,8}

Histopathology reports were reviewed for: 1) adequacy of bone reaming sample; 2) positive tumour tissue diagnosis; and 3) reports of tissue crushing or necrosis. Adequacy of samples was defined as containing sufficient bone and marrow derived tissue to allow complete histological analysis, including both microscopy and more specific tests such as immunohistochemistry and cytogenetics, as indicated. All histopathology reports were by a consultant histopathologist.

This non-experimental study did not require formal research ethics committee review. All data were generated through routine clinical practice only and were completely anonymised for use. Data were analysed in SPSS for Mac OSX, version 23. Descriptive statistics were provided as mean for continuous data and percentage for nominal data. The Chi square test was used to test for independence of two variables. Statistical significance was set at $P < 0.05$. Bonferroni correction was carried out where multiple comparisons were made.

Results

Data from 331 cases (306 patients) of metastatic bone disease were reviewed, over a 7-year period. Of these, 49 cases were identified that met both inclusion criteria. The mean age was 71 years (range 47–89 years) while 69% of patients were female ($n = 34$). The most common primaries in our cohort were breast and lung cancer and multiple myeloma (Table 1). Sixty-five per cent of patients ($n = 32$) underwent therapeutic intramedullary nailing of a pathological fracture versus 35% ($n = 17$) of patients who underwent prophylactic intramedullary nailing. The femur was the most frequently involved long bone, with 86% ($n = 42$) of all intramedullary nailings occurring here, while 14% ($n = 7$) of procedures carried out were of the humerus. No tibial intramedullary nailing was performed in this group of patients.

Analysis of histological reports showed that two samples (4%) were inadequate or insufficient to allow for a complete histological examination and report. In both cases, the samples sent consisted mostly of clotted blood. One of these was not suitable for microscopy while the second was studied on microscopy but was insufficient to allow further specific testing. Fifty-one per cent ($n = 25$) of bone reaming samples yielded a positive tissue diagnosis of metastatic bone disease. Thus, 45% ($n = 22$) of bone reaming samples provided a false negative result. All patients included in this study had confirmed metastatic bone disease which was not detected in this group (Fig 1).

Table 1 Frequency distribution by primary tumour type

Primary tumour	Frequency (n)	Percent (%)
Breast	14	29
Lung	12	25
Multiple myeloma	9	18
Prostate	3	6
Renal	3	6
Colon	2	4
Others ^a	6	12
Total	49	100

^a Haematological, squamous cell carcinoma, malignant melanoma

The presence of a pathological fracture (i.e. prophylactic versus therapeutic intramedullary nailing) had no effect on the adequacy of sample for analysis or the detection of metastatic disease ($P = 0.108$). Fifty-three per cent ($n = 26$) of tissue samples contained varying degrees of crushed and or necrotic tissue. Statistical analysis (chi square test) showed that the tissue diagnosis was more often reported as false negative for metastatic disease in the presence of crushing or necrosis ($P = 0.015$; Fig 1).

Discussion

Metastatic bone disease may be the first presentation of cancer. Tissue diagnosis is essential for the appropriate management of these patients, with implications for both adjuvant treatment and prognosis. In up to 15% of cases of metastatic disease, the primary tumour remains unknown.^{9,10} This emphasises the importance of adequate, reliable and accurate sampling when performing any type of biopsy.

We set out to study cases with a confirmed diagnosis of metastatic cancer, with a view to establishing the diagnostic accuracy of reaming biopsy. Furthermore, to the best of our knowledge, this is the only published study that determines the effect of additional factors, such as the presence of a pathological fracture and tissue necrosis or crushing on the diagnostic accuracy of this technique.

Of the 49 cases studied, we found that 4% ($n = 2$) of samples precluded comprehensive histopathological analysis. A similar figure was reported by Clarke *et al.* in their 1993 study on intramedullary nail reamings.¹¹ They reported that a tissue analysis was obtainable in all of the 17 cases studied. In contrast, Hassan *et al.*, in 2007, retrospectively studied intramedullary nail reaming histology reports over a 5-year period in 90 cases of suspected pathological fractures and found that the sample obtained was inadequate for histological analysis in 30 cases (35%).¹² Of the inadequate samples, 17 cases were known to have a history of a primary malignancy while 1 case was subsequently diagnosed. They concluded that a histological diagnosis was made in 55 of 85

cases (65%) where the sample was adequate for analysis. The authors did not, however, determine the diagnostic accuracy of their reaming biopsies. This is a significant difference from our study.

It is probable that sampling error as a consequence of the non-targeted nature of the technique plays a role in obtaining adequate tissue from reamings. Another factor affecting sampling may be the fact that reaming is in itself a destructive process, thus rendering tissue less suitable for subsequent histological analysis. Intramedullary reaming results in mechanical and thermal damage to tissue and rises in temperature exceeding 50 degrees celsius with thermal necrosis of bone have been studied.^{15–16}

In our study, 51% ($n = 25$) of reaming samples yielded a positive histology diagnosis of metastatic bone disease, correlating with the known clinical diagnosis of metastatic cancer. However, 45% ($n = 22$) of bone reaming histology from samples deemed adequate to allow for complete histopathological analysis provided a false negative result. Multiple factors may be responsible for this. As mentioned earlier, reaming does not target a specific lesion within the bone but samples the entirety of the medullary canal and endosteal bone. In addition, the process is accompanied by extensive endosteal bleeding from arterial vessel damage while, simultaneously, intramedullary contents may be forced into the metaphyseal venous vascular system, which could

further reduce the proportion of tumour cells within a sample.^{15,17,18} Also, in the presence of a pathological fracture, reaming may result in the process of autografting, where intramedullary debris collects at the fracture site and thereby possibly further reducing the proportion of tumour tissue available for sampling.¹⁹

Various techniques, some of which are lesion specific, have been suggested as potentially providing a good diagnostic yield during sampling. These include the use of intramedullary flexible, large-bore plastic catheters, core or open biopsy, long bronchial-type biopsy forceps, aspiration by paediatric chest tube, Charnley spoon, Paterson or Lloyd Davis biopsy forceps and laparoscopic graspers.^{11,12,20–25} However, studies are lacking as to how these techniques compare with 'conventional' intramedullary reaming sampling. Also, reaming results in both mechanical and thermal damage, which may make it more difficult to detect histological evidence of metastatic disease within a given sample.^{15–16} Lastly, there is the possibility of an alternate diagnosis; for example, patients having had a fracture unrelated to their cancer (e.g. osteoporosis or post-radiotherapy insufficiency), although this is highly unlikely in our patients, all of whom had clinical and radiological evidence of metastasis. No other lesion to explain the fracture was found in any of the histology reports.

Fifty-three per cent ($n = 26$) of tissue samples contained varying degrees of crushed and/or necrotic bone but were still adequate to allow complete histological analysis. We sought to determine whether the presence of crushed or necrotic bone reported in the histology had any effect on the detection of metastatic disease. Statistical analysis (chi square test) showed that the tissue diagnosis was more often reported as negative for metastatic disease in the presence of non-viable bone or crushing ($P = 0.015$). This further supports the hypothesis that the reaming sample may undergo significant mechanical and thermal stress and damage, which may adversely affect the ability to detect metastatic disease on subsequent histological analysis in spite of adequate sampling.

There was, however, no relationship between the reporting of metastatic disease and the nature of procedure performed – that is, prophylactic versus therapeutic intramedullary nailing ($P = 0.108$) – which may suggest that reaming-associated autografting that we had hypothesised as possibly contributing to loss of tumour sample at the fracture site may play a less important role. However, suitably designed, powered and preferentially multicentre experimental studies would be required to investigate these hypotheses further.

Conclusion

Our study goes some way to demonstrate that in spite of adequate tissue sampling, the diagnostic accuracy and, hence, the reliability of intramedullary reaming biopsy in metastatic bone disease is less than optimal, correlating clinically in only about 50% of the cases. A reaming histopathology report suggesting no evident metastasis should always be taken in clinical context.

Where no pre-existing cancer diagnosis is available, we recommend considering referral to a regional bone tumour unit for formal biopsy, mandatory in the solitary lesion, as accidental intramedullary nailing of a primary bone tumour has catastrophic consequences.^{1,8}

While we cannot endorse any specific intraoperative sampling method to improve accuracy during intramedullary nailing for metastatic bone disease, these may merit further study.

References

1. Stalley RU, Benjamin L, Pendlebury S, *et al*. The modern surgical and non-surgical management of appendicular skeletal metastases. *Orthop Trauma* 2012; **26**(3): 184–199.
2. Damron TA, Sim FH. Surgical treatment for metastatic disease of the pelvis and the proximal end of the femur. *Instr Course Lect* 2000; **49**: 461–470.
3. Choong PF. Reconstructive surgery following resection of primary and secondary tumours of the hip. *J Orthop Surg (Hong Kong)* 2000; **8**(2): 83–94.
4. Saad F, Lipton A, Cook R, *et al*. Pathologic fractures correlate with reduced survival in patients with malignant bone disease. *Cancer* 2007; **110**(8): 1,860–1,867.
5. Böhm P, Huber J. The surgical treatment of bony metastases of the spine and limbs. *J Bone Joint Surg Br* 2002; **84**(4): 521–529.
6. Galasko CS. Principles of management of metastatic disease. *Curr Orthop* 1988; **2**: 158–167.
7. Mirels H. Metastatic disease in long bones: a proposed scoring system for diagnosing impending pathologic fractures. *Clin Orthop Relat Res* 1989; **(249)**: 256–264.
8. Tillman RM, Ashford RU. *Metastatic Bone Disease: A Guide to Good Practice*. London: British Orthopaedic Association; 2013.
9. Takagi T, Katagiri H, Kim Y *et al*. Skeletal metastasis of unknown primary origin at the initial visit: a retrospective analysis of 286 cases. *PLoS ONE* 2015; **10**(6): e0129428.
10. Rougraff BT, Kneisl JS, Simon MA. Skeletal metastases of unknown origin: a prospective study of a diagnostic strategy. *J Bone Joint Surg Am* 1993; **75**(9): 1,276–1,281.
11. Clarke AM, Rogers S, Douglas DL. Closed intramedullary biopsy for metastatic disease. *J R Coll Surg Edinb* 1993; **38**(6): 368–369.
12. Hassan K, Kalra S, Moran C. Intramedullary reamings for the histological diagnosis of suspected pathological fractures. *Surgeon* 2007; **5**(4): 202–204.
13. Pape H-C, Giannoudis P. The biological and physiological effects of intramedullary reaming. *J Bone Joint Surg Br* 2007; **89**(11): 1,421–1,426.
14. Baumgart F, Kohler G, Ochsner PE. The physics of heat generation during reaming of the medullary cavity. *Injury* 1998; **29**(Suppl 2): B11–B125.
15. Giannoudis PV, Snowden S, Matthews SJ *et al*. Temperature rise during reamed tibial nailing. *Clin Orthop Relat Res* 2002; **(395)**: 255–261.
16. Müller C, McIlff T, Rahn BA *et al*. Intramedullary pressure, strain on the diaphysis and increase in cortical temperature when reaming the femoral medullary cavity: a comparison of blunt and sharp reamers. *Injury* 1993; **24**(Suppl 3): S22–S30.
17. Cuthbertson EM, Siris E, Gilfillan RS. The femoral diaphyseal medullary venous system as a venous collateral channel in the dog. *J Bone Joint Surg Am* 1965; **47**: 965–974.
18. Klein MP, Rahn BA, Frigg R *et al*. Reaming versus non-reaming in medullary nailing: interference with cortical circulation of the canine tibia. *Arch Orthop Trauma Surg* 1990; **109**(6): 314–316.
19. Frölke JP, Bakker FC, Patka P *et al*. Reaming debris in osteotomized sheep tibiae. *J Trauma* 2001; **50**(1): 65–70.
20. Jacobsson H. Percutaneous bone biopsy with a simple punch instrument. Indications, results and complications. *Acta Radiol Diagn (Stockh)* 1982; **23**(4): 415–422.
21. Heeten den GJ, Oldhoff J, Oosterhuis JW *et al*. Biopsy of bone tumours. *J Surg Oncol* 1985; **28**(4): 247–251.
22. Smith DG, Behr JT, Hall RF *et al*. Closed flexible intramedullary biopsy of metastatic carcinoma. *Clin Orthop Relat Res* 1988; **(229)**: 162–164.
23. Xia Z, Takano AM, Sittampalam K *et al*. Laparoscopic grasper for intramedullary biopsy: a technique to improve tissue sampling. *Singapore Med J* 2014; **55**(8): e116–e118.
24. Johnson JC, Kneisl JS. Bone marrow sampling in pathologic fractures: intramedullary pediatric chest tube technique. *J Orthop Trauma* 2004; **18**(5): 306–309.
25. Heaver C, Marsh A. Femoral intramedullary biopsy: improving tissue sampling. *Ann R Coll Surg Engl* 2011; **93**(5): 419–420.