Surgical biopsy with intra-operative frozen section

AN ACCURATE AND COST-EFFECTIVE METHOD FOR DIAGNOSIS OF MUSCULOSKELETAL SARCOMAS

R. U. Ashford,
S. W. McCarthy,
R. A. Scolyer,
S. F. Bonar,
R. Z. Karim,
P. D. Stalley

From the Royal Prince Alfred Hospital, Camperdown, Australia

The most appropriate protocol for the biopsy of musculoskeletal tumours is controversial, with some authors advocating CT-guided core biopsy. At our hospital the initial biopsies of most musculoskeletal tumours has been by operative core biopsy with evaluation by frozen section which determines whether diagnostic tissue has been obtained and, if possible, gives the definitive diagnosis. In order to determine the accuracy and cost-effectiveness of this protocol we have undertaken a retrospective audit of biopsies of musculoskeletal tumours performed over a period of two years.

A total of 104 patients had biopsies according to this regime. All gave the diagnosis apart from one minor error which did not alter the management of the patient. There was no requirement for re-biopsy. This protocol was more labour-intensive and 38% more costly than CT-guided core biopsy (AUS\$1804 vs AUS\$1308). However, the accuracy and avoidance of the anxiety associated with repeat biopsy outweighed these disadvantages.

■ R. U. Ashford, FRCS(Trauma & Orth), Fellow in Orthopaedic Oncology

■ P. D. Stalley, FRACS, Consultant Orthopaedic Oncologist

Department of Orthopaedics

■ S. W. McCarthy, FRCPA, Anatomical Pathologist

■ R. A. Scolyer, FRCPA, Anatomical Pathologist

■ R. Z. Karim, FRCPA, Anatomical Pathologist

Department of Anatomical Pathology

New South Wales Bone & Soft Tissue Sarcoma Service, Royal Prince Alfred Hospital, Missenden Road, Camperdown, New South Wales 2050, Australia.

■ S. F. Bonar, FRCPA, Anatomical Pathologist
New South Wales Bone & Soft Tissue Sarcoma Service
Douglass Hanly Moir Pathology, 95 Epping Road, North Ryde, New South Wales 2133, Australia.

Correspondence should be sent to Mr R. U. Ashford; e-mail: robert.ashford@virgin.net

©2006 British Editorial Society of Bone and Joint Surgery
doi:10.1302/0301-620X.88B9.17680 \$2.00

J Bone Joint Surg [Br]
2006;88-B:1207-11.

Received 23 January 2006;
Accepted after revision 8 May 2006

Diagnosis, without compromising subsequent surgery, is a key step in the multidisciplinary care of patients with musculoskeletal sarcomas.¹⁻⁴ The initial biopsy should obtain an adequate volume of representative tissue for diagnosis without complications. To ensure that the procedure does not compromise any definitive operation it should be performed by a surgeon or radiologist familiar with the approach for definitive resection.⁵ An inadequate biopsy may adversely affect the rates of survival and amputation.¹ Initial CT-guided core biopsy has a reported accuracy of approximately 80%.⁶ At our hospital, biopsy by a surgeon with intra-operative frozen section is carried out on most patients with suspected sarcomas. This study was undertaken to evaluate the accuracy and cost-effectiveness of this protocol for musculoskeletal tumours.

Patients and Methods

We undertook a retrospective audit of all biopsies of musculoskeletal tumours performed at our hospital. All the specimens from patients under the care of the senior author (PDS), between July 2003 and June 2005 were identified from the database of the Department of Anatomical Pathology and the medical records were reviewed. Biopsies were defined as: 1) operative core; 2) inadequate operative core on frozen section, therefore proceed to open; 3) open; or 4) radiological core. They were cat-

egorised later as either diagnostic or non-diagnostic and the biopsy and resected specimens were then compared.

Data were stored in a Microsoft Excel (Microsoft Corporation, Redmond, Washington) spreadsheet. Errors were reported using the definitions of Altuntas et al⁶ of the biopsy and the final histology. In keeping with the Washington Cancer Institute,⁷ major diagnostic errors were defined as any error in histopathology, radiology or pre-operative planning which resulted in an adverse effect on planning of the treatment.

Costs. Four consecutive operative core biopsies were audited at the end of the study. Each patient was admitted as a day-case. The mean duration of the operating time and the mean total time of anaesthesia from induction to leaving theatre were calculated. The cost of the surgeon, anaesthetist and theatre staff was calculated from the Commonwealth of Australia Medicare rebate rates.⁸ A similar audit of four CT core biopsies was undertaken. The duration of the scan and radiation exposure were identified from the records of the Department of Radiology. The same Medicare rebate rates⁸ were used for costing.

Biopsy protocol (Fig. 1). The biopsy was performed through a stab incision and multiple 14G Trucut (Allegiance Healthcare, McGaw Park, Illinois) specimens were taken. If the lesion was purely intra-osseous, a 3.5 mm drill

Fig. 1

The protocol for surgical core biopsy with evaluation of the frozen section of the New South Wales Sarcoma Service.

hole was made and core biopsies taken through this. Evaluation of a representative proportion of the tissue cores by frozen section was performed and reviewed by both a musculoskeletal pathologist (SWM, RAS, RZK or SFB) and the surgeon (PDS or RUA), and the pathological features were correlated with the clinical, radiological and operative findings. If a definitive diagnosis was made, or if the tissue was thought to be representative of a tumour but further investigations (e.g. paraffin sections, immunohistochemistry, electron microscopy, flow cytometry, cytogenetics) were required, the biopsy was considered complete. If the tissue did not enable diagnosis a repeat core or open biopsy was performed, again supplemented by evaluation by frozen section.

The use of this protocol made a subsequent biopsy unnecessary because evaluation by frozen section ensured that diagnostic tissue had been obtained. After fixation in formalin and embedding in paraffin, the tissue was assessed by histological examination of sections stained with haematoxylin and eosin, plus ancillary studies as necessary.

Image-guided biopsy (usually by CT) was reserved for sites where an operative biopsy was inappropriate either because of inherent risks (e.g. medical co-morbidity) or accessibility (e.g. vertebra or pelvis). There were also situations in which it was inappropriate to perform a limited biopsy, for example, the differential diagnosis between a

Table I. Types of biopsy procedure

Biopsy	Number	Percentage
Trucut operative core with frozen section	93	34.3
Operative core proceed to open	11	4.1
CT-guided core	24	8.9
Open (incisional, curetting)	76	28.0
Excisional	58	21.4
Reamings	9	3.3
Total	271	100.0

deep soft-tissue lipoma and a well-differentiated liposarcoma.

Results

A total of 271 patients was investigated for lesions of bone or soft-tissue. Of these, 104 had a core biopsy by a surgeon with evaluation by frozen section. The remaining 167 had a CT-guided core biopsy (24), open biopsy (76), excisional biopsy (58) or bone-reaming biopsy (9) (Table I).

In the 24 patients who had CT-guided biopsy, the site of the lesion, usually vertebral or pelvis, made it the most appropriate method.⁶ Their results were included for comparison in our analysis. All the core-needle biopsies were performed as day-cases. When it was necessary to proceed to open biopsy, this was also usually carried out

Table II. Results of biopsies using different protocols

	Number	Diagnostic tissue	Non-diagnostic	Major error	Minor error	Accuracy (%)
All tumours						
Core biopsy	93	93	0	0	0	100.0
Core proceed to open*	11	11	0	0	1	90.9
CT core biopsy	24	24	0	0	0	100.0
Malignant						
Core biopsy	72	72	0	0	0	100.0
Core proceed to open*	3	3	0	0	1	66.7
CT core biopsy	16	16	0	0	0	100.0
Benign						
Core biopsy	22	22	0	0	0	100.0
Core proceed to open*	8	8	0	0	0	100.0
CT core biopsy	7	7	0	0	0	100.0
Bone lesions						
Core biopsy	66	66	0	0	0	100.0
Core proceed to open*	3	3	0	0	0	100.0
CT core biopsy	21	21	0	0	0	100.0
Soft-tissue lesions						
Core biopsy	27	27	0	0	0	100.0
Core proceed to open*	8	8	0	0	1	87.5
CT core biopsy	3	3	0	0	0	100.0

* core biopsy inadequate on frozen section therefore open biopsy performed

Table III. Histological diagnoses of the 128 patients having operative core, CT-guided core or operative core/open biopsies

Malignant	Number	Benign	Number
Bone			
Osteosarcoma	24	Giant cell tumour	7
Chondrosarcoma	9	Infection/inflammation	4
Malignant fibrous histiocytoma	7	Aneurysmal bone cyst	3
Lymphoma	8	Haemangioma	3
Ewing's sarcoma	7	Eosinophilic granuloma	2
Myeloma	2	Ganglion cyst	2
Chordoma	1	Chondromyxoid fibroma	1
Synovial sarcoma	1	Paget's disease	1
Non-Hodgkin's lymphoma	1	Osteoid osteoma	1
Metastasis	11		
Subtotal	71	Subtotal	24
Soft tissue			
Malignant fibrous histiocytoma	8	Desmoid/deep fibromatosis	3
Leiomyosarcoma	4	Fibroma variant	3
Synovial sarcoma	3	Schwannoma	2
Liposarcoma	1	Myxoma	2
Fibromyxoid sarcoma	1	Synovial chondromatosis	1
Fibrosarcoma	1	Morton's neuroma	1
Myofibrosarcoma	1	Haemangiopericytoma	1
Rhabdomyosarcoma	1		
Subtotal	20	Subtotal	13
Total	91	Total	37

as a day-case but an overnight stay was occasionally necessary.

Of the 271 patients, 76 underwent an initial open biopsy. In 43 of 54 benign lesions (79.6%) and 15 of 22 malignant lesions (68.2%) in which the imaging was interpreted as diagnostic, the biopsies had a confirmatory intra-operative frozen section as part of the definitive operation, be it resection, amputation or curettage. There was one diagnostic error in this group. A lesion considered radiologically to have been an aneurysmal bone cyst, confirmed histologi-

cally as such after curettage, recurred twice. At the second recurrence, 32 months after the initial operation, myofibro-sarcoma, not hitherto identified, was diagnosed.

In 58 patients, excision biopsy was appropriate (e.g. recurrent tumour, metastasis, or lipoma *versus* low-grade liposarcoma). All the biopsies in this group were diagnostic.

The final nine patients had reamings sent for histology while undergoing intramedullary nailing. In one case the reamings failed to demonstrate malignancy although the radiological features suggested a metastasis.

Table IV. Approximate costings (AUS) for surgical core biopsies with evaluation of the frozen section and CT-guided core biopsies

Service	Core biopsy	CT core
Multidisciplinary team assessment*	517	517
Pre-operative assessment (bloods, doctor and nurse)	180	0
Anaesthesia ^{††}	188	100
Surgeon/radiologist fee [‡]	160	100
Operating room charge [§]	235	0
CT scan charge [¶]	0	250
CT staffing charge (1 radiographer, 1 nurse)	0	90
Consumables (drapes, gowns, biopsy, needles)	60	100
In-patient bed	212	0
Pathology cost		
Frozen section	101	0
Definitive sections	151	151
Total	1804	1308

* based on consultation fee, radiological examination and MRI of limb (Medicare rebate rates)

† consumables for local anaesthetic/sedation for CT biopsy

‡ based on Medicare rebate

§ based on one hour procedure and recovery time, includes scrub nurse, scout nurse, recovery nurse, anaesthetic technician and operating department orderly

¶ based on one hour scan time

Surgeon-led operative core biopsy with evaluation by frozen section was performed on 104 patients. The non-diagnostic and error rates and the pathological diagnoses of the tumours are presented in Tables II and III. There was one minor diagnostic error attributable to misinterpretation of the frozen section. This case involved a 62-year-old woman with a mass in the thigh which was not diagnosed on clinical or radiological examination or by core biopsy. Frozen section diagnosis favoured Hodgkin's lymphoma. An open biopsy enabled identification of a B-cell lymphoma. This did not affect the surgical management.

There were no surgical complications related to the biopsies.

Costs. For operative biopsies, the mean duration of the operating time, including frozen section, was 34 minutes (25 to 45). The mean total time of anaesthesia was 54 minutes (45 to 60).

The mean duration of CT-guided biopsies was 64 minutes (59 to 72). The mean active scanning time was 164 seconds (84 to 268) and the mean radiation exposure was 537.3 mGy/cm² (232.6 to 810.7). The CT biopsies were performed under local anaesthesia with sedation.

None of the eight patients in either of the audited groups required overnight admission.

Table IV outlines the approximate costs for the two types of procedure, namely AU\$1804 (£770; €131) for surgeon-led protocol and AU\$1308 (£558; €820) for a CT-guided biopsy.

Discussion

The time awaiting the result of a biopsy is difficult for a patient. It is therefore desirable to make a definitive diagnosis from the initial biopsy as quickly as possible and to avoid a repeat procedure if the first is not diagnostic. Whereas open biopsy is historically the technique of

choice,² core needle biopsy in tertiary cancer centres is reported as having an accuracy of up to 93%⁹ for soft-tissue sarcomas and up to 97% for bone tumours.¹⁰ Failure to determine the diagnosis on 5% to 20% has been reported with image- or CT-guided core biopsies of musculoskeletal tumours,^{6,11-15} more commonly in bone lesions.¹² All biopsies in our protocol were diagnostic. Whilst it may be technically relatively easy to repeat a CT-guided biopsy or do an open biopsy after non-diagnostic CT-guided biopsy, these further procedures may delay diagnosis and have a negative psychological impact on the patient. Similarly, rates of incorrect diagnosis of 6% to 12% have been reported from tertiary cancer centres for image-guided core needle biopsies.^{11,16} When the referring centre is included, this figure rises to 23%.¹⁴ In 1982, Mankin et al¹ demonstrated a rate of inaccuracy of 20% when the biopsy was performed in the referring centre. Ten years later this figure had decreased to 14%.¹⁴ Our protocol ensures a rapid diagnosis without the need to repeat the procedure.

Although our regime is labour-intensive, in our study approximately 4% of malignant and 27% of benign tumours had to undergo an open biopsy after the core procedure to obtain diagnostic tissue (Table II). It was more common for this further procedure to be needed for a soft-tissue lesion (23%) than for a bone tumour (4%) (Table II). Evaluation by frozen section is vital to ensure that diagnostic tissue has been obtained, thus avoiding repeat biopsy. Although it has been suggested that it is not possible to perform a frozen section on an outpatient basis⁴ this is not our experience.

Our patients can be admitted for biopsy within seven days of assessment as an outpatient. With the greater accuracy of our protocol, we do not use outpatient core biopsies under local anaesthesia, even if the mass is of soft tissue and palpable. In institutions which do not have the infrastruc-

ture for rapid admission, outpatient core biopsy under local anaesthesia may be a reasonable option, particularly for soft-tissue masses. Assessment by frozen section can be applied to an outpatient biopsy to ensure that diagnostic tissue is obtained. This would be less expensive than a CT-guided biopsy by AU\$300 and a surgical biopsy by AU\$800 (Table IV).

In cases in which the radiological diagnosis is clear (e.g. chondroblastoma and aneurysmal bone cyst), definitive surgery is undertaken at the outset and a frozen section used for confirmation before definitive curettage. Similarly, for well-differentiated adipocytic tumours, in which the radiological and clinical diagnosis is between a lipoma and a well-differentiated liposarcoma, marginal excision biopsy is our preferred initial treatment.

Although the duration of the biopsy procedure using our protocol was similar to that of CT-guided core biopsies, patients required a day stay and general anaesthesia. A similar degree of skill is required for both procedures and requirements of nursing-staff are similar, but radiation exposure is avoided with our protocol. The added cost of re-biopsy in up to 20% of cases must also be considered. Although our protocol is approximately 38% more costly, we feel that this is outweighed by the fact that all biopsies are diagnostic, the adverse psychological effect of re-biopsy is avoided and greater accuracy means that the potential costs of delayed or misdiagnosis are avoided.

The increased exposure to radiation from CT-guided biopsies should be considered when evaluating techniques of biopsy,^{17,18} but any additional exposure from CT-guided core biopsy of musculoskeletal tumours is probably insignificant.

Mankin et al¹ first demonstrated a higher rate of complications associated with the undertaking of biopsies for musculoskeletal tumours by surgeons who are not trained in the surgery of tumours and this has also been our experience.⁴ Therefore, it appears likely that diagnostic accuracy reflects the skills of the surgeon and pathologist.

We have described a cost-effective protocol for the biopsy of musculoskeletal tumours which achieves a diagnostic accuracy of 100%, without significant complications.

Supplementary Material

A further opinion by Mr Rob Grimer is available with the electronic version of this article on our website at www.jbjs.org.uk

We wish to thank Sue Camara for her help in the collection of data and Dr Richard Waugh for the information regarding CT-guided biopsies.

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

References

1. Mankin HJ, Lange TA, Spanier SS. The hazards of biopsy in patients with malignant primary bone and soft-tissue tumours. *J Bone Joint Surg [Am]* 1982;64-A:1121-7.
2. Simon MA. Biopsy of musculoskeletal tumors. *J Bone Joint Surg [Am]* 1982;64-A:1253-7.
3. Bickels J, Jelinek JS, Shmookler BM, Neff RS, Malawer MM. Biopsy of musculoskeletal tumors: current concepts. *Clin Orthop* 1999;368:212-19.
4. Pollock RC, Stalley PD. Biopsy of musculoskeletal tumours: beware. *ANZ J Surg* 2004;74:516-19.
5. Skrzynski MC, Biermann S, Montag A, Simon MA. Diagnostic accuracy and charge-savings of outpatient core needle biopsy compared with open biopsy of musculoskeletal tumors. *J Bone Joint Surg [Am]* 1996;78-A:644-9.
6. Altuntas AO, Slavin J, Smith PJ, et al. Accuracy of computed tomography guided core needle biopsy of musculoskeletal tumours. *ANZ J Surg* 2005;75:187-91.
7. Welker JA, Henshaw RM, Jelinek J, Shmookler BM, Malawer MM. The percutaneous needle biopsy is safe and recommended in the diagnosis of musculoskeletal masses. *Cancer* 2000;89:2677-86.
8. Medicare Benefits Schedule Book. Commonwealth of Australia (2004) at http://www.7.health.gov.au/pubs/mbs/mbs/css/mbs_book_november_2002_123.htm (accessed on 29th November 2005).
9. Heslin MJ, Lewis JJ, Woodruff JM, Brennan MF. Core needle biopsy for diagnosis of extremity soft tissue sarcoma. *Ann Surg Oncol* 1997;4:425-31.
10. Stoker DJ, Cobb JP, Pringle JA. Needle biopsy of musculoskeletal lesions: a review of 208 procedures. *J Bone Joint Surg [Br]* 1991;73-B:498-500.
11. Jelinek JS, Murphey MD, Welker JA, et al. Diagnosis of primary bone tumours with image-guided percutaneous biopsy: experience with 110 tumors. *Radial* 2002;223:731-7.
12. Kruyt RH, Oudkerk M, van Sluis D. CT-guided bone biopsy in a cancer center: experience with a new apple corer-shaped device. *J Comput Assist Tomogr* 1998;22:276-81.
13. Issakov J, Flusser G, Kollender Y, et al. Computer tomography-guided core needle biopsy for bone and soft tissue tumors. *Isr Med Assoc J* 2003;5:28-30.
14. Saifuddin A, Mitchell R, Burnett SJ, Sandison A, Pringle JA. Ultrasound-guided needle biopsy of primary bone tumours. *J Bone Joint Surg [Br]* 2000;82-B:50-4.
15. Dupuy DE, Rosenberg AE, Punyatabandhu T, Tan MH, Mankin HJ. Accuracy of CT-guided needle biopsy of musculoskeletal neoplasms. *Am J Roentgenol* 1998;171:759-62.
16. Mankin HJ, Mankin CJ, Simon MA. The hazards of the biopsy, revisited: members of the Musculoskeletal Tumor Society. *J Bone Joint Surg [Am]* 1996;78-A:656-63.
17. Barron D. Basic science: computerised tomography. *Curr Orthop* 2005;19:20-6.
18. Orchard JW, Read JW, Anderson IJ. The use of diagnostic imaging in sports medicine. *Med J Aust* 2005;183:482-6.