Combined radiology and cytology in the diagnosis of bone lesions

A retrospective study of 370 cases

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Background **Some of the risks with open biopsy can be avoided by fine-needle aspiration biopsy. The diagnostic contribution of radiologic findings has not been systematically studied.**

Patients and methods **We retrospectively analyzed the validity of combined radiology and fine-needle aspiration cytology for the diagnosis of bone lesions in a consecutive series of 370 patients. The treatment diagnosis was based solely on radiology and cytology in 234 cases, whereas in 136 cases histopathology was also applied.**

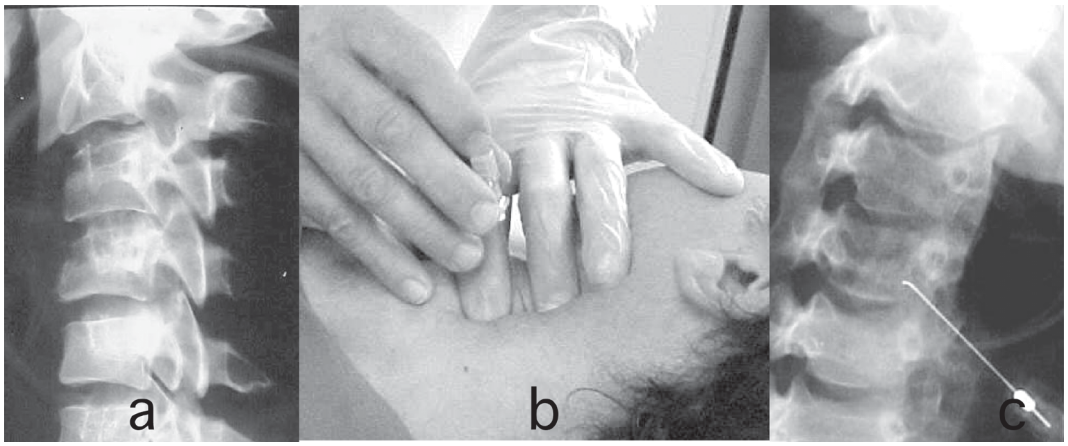
Results **Comparison of radiology and cytology showed diagnostic compliance in 256 cases (69%) and non-compliance in 101 (28%). 13 (3%) cases failed to yield diagnostic material for cytology. Among the 256 compliant cases, the diagnostic error rate was 1% (2 were falsely benign), whereas the corresponding rate was 17% among the 101 non-compliant cases. In the latter group, 36 cases yielded only normal cells at aspiration, out of which 20 proved to have a neoplastic lesion (8 metastases, 12 benign).**

The overall sensitivity of cytology alone in recognizing malignancy was 90%. The specificity was 95%. Given a malignant or benign diagnosis, the positive predictive value was 97% and the negative predictive value was 84%.

Interpretation **Our study suggests that a simple approach based on conventional radiography and fine-needle aspiration cytology offers a valid means of diagnosing bone lesions. Provided there is compliance between radiology and cytology, the risk of false diagnosis is around 1%.**

It is widely recognized that the diagnosis of bone lesions should entail a multimodal approach taking age, clinical history, radiology and cytology/histopathology into consideration. As for radiology, the sensitivity in detecting bone lesions has increased considerably using modern imaging techniques, yet the specificity remains low. In fact, conventional radiography is still generally believed to offer the highest specificity in the diagnosis of bone lesions. Nonetheless, most radiological assessments should be combined with microscopic analysis of tissue samples to reach a diagnosis. An approach based on histopathology of specimens from open biopsy or core biopsy is generally advocated. The latter procedure is now increasingly replacing open biopsy. Yet, it still requires local anesthesia and preferably CT guidance for deep-seated lesions to avoid neurovascular damage. For some vertebral locations, the procedure should be avoided. Notably, the most common malignant bone tumor is metastasis to the axial skeleton. In addition, tumor cell seeding has been described in several reports as being a potential hazard to needle and biopsy, especially in the diagnosis of thoracic and abdominal carcinoma. This problem can be avoided, however, by completely excising the needle track at definitive surgery of sarcoma (de Santos et al. 1979, Stoker et al. 1991, Davies et al. 1993).

To circumvent the inconveniences and risks associated with open or core biopsy, a few centers have introduced fine-needle aspiration biopsy (FNAB) for the diagnosis of bone lesions. It is



FNAB. Lateral radiography (a) of the cervical spine with a lymphoma lesion of C3 and 4. Needle insertion (b) and oblique view of needle position (c).

more convenient for the patient, seldom requires anesthesia, can be done under fluoroscopic guidance, is applicable to the whole skeleton and has a negligible complication rate. The objection to FNAB pertains to sampling problems and difficulties in interpretation. Most importantly, tumor heterogeneity is claimed to entail a significant risk of diagnostic error (Hajdu et al. 1971, Tehrandez et al. 1983, Bhatia 1984). In the present study, we assessed the validity of combined radiology and cytology in the diagnosis of bone lesions in a consecutive series of 370 patients.

Patients and methods

Patients

Between 1993 and 1997, 374 consecutive patients with a newly detected bone lesion were referred to the Department of Radiology, Karolinska Hospital, for diagnostic work-up. 344 lesions had been identified by radiography, 21 by MRI and 5 by bone scan. 41 patients had a previous diagnosis of carcinoma (breast 12, gynecological 7, colon 6, kidney 5, prostate 4, lung 4, larynx 3), 6 had myeloma, lymphoma or leukemia, 5 had sarcoma and 4 had benign bone lesions. Thus, 318 of 374 patients were referred for biopsy without a medical record of neoplasia. The radiographs of 4 patients could not be found, leaving 370 patients for the study. The mean age among the 199 female and 171 male patients was 56 (2–89) years. The analysis was based on the original reports of clinical, radiological, cytological and histopathological findings.

Radiology

Based on the original radiographic diagnosis, the lesions were categorized into 4 groups: 1) sarcoma, 2) metastasis or myeloma/lymphoma, 3) benign tumor or 4) non-neoplastic lesion.

Fine-needle aspiration biopsy

The FNAB was done as an outpatient procedure. The lesions were identified by fluoroscopy or CT. The needle path was planned to avoid large nerves, vessels and pleura. All needles had a stylet, and needles with a diameter between 0.47 and 0.70 mm were used. The radiologist inserted the needle into the lesion and the needle position was checked by fluoroscopy or CT-scan before aspiration, which was done by the cytopathologist (Figure). In 5 patients the lesion was purely intraosseous, prompting the use of an eccentric drill device (Ahlström and Åström 1993) to penetrate the intact cortical bone.

The aspirates were placed onto glass slides, smeared and air-dried. The yield was immediately checked by quick-staining and wet-look (microscopy). A repeat biopsy was performed if the cellular yield was low or not diagnostic. The aspirates were routinely stained with May-Grünwald-Giemsa (MGG). In some cases the aspirate was used for supplementary studies, e.g. immunocytochemistry, molecular genetics and

Table 1. Anatomical distribution (370 cases)

Site		Total
Axial skeleton		240
Pelvis	75	
Lumbar vertebra	64	
Thorax [a]	31	
Sacrum	30	
Thoracic vertebra	26	
Cervical vertebra	8	
Skull	6	
Long bones		115
Femur	54	
Humerus	30	
Tibia and fibula	24	
Radius and ulna	7	
Small bones		15
Hand	3	
Foot	9	
Mandible	3	
All	370	370

[a] Sternum, rib, scapula and clavicle.

karyotyping. 339 patients underwent FNAB at a single session, whereas 28 had to be called back for a second FNAB and 3 for a third, because of inconclusive cytology and/or to obtain material for complementary analysis.

The diagnoses from the original cytological reports were categorized into 6 groups: 1) sarcoma, 2) metastasis or myeloma/lymphoma, 3) benign tumor, 4) non-neoplastic lesion (infection, degenerative/reactive change), 5) normal cells (e.g. blood, bone marrow), and 6) undiagnosed (inconclusive or insufficient cell material).

Histology

Tissue samples for histopathological assessment were also obtained from 136 of the 370 patients. This was based on specimens from open biopsy in 31 patients and definitive surgery in 116, as 11 patients provided tissue for histopathology from both open biopsy and definitive surgery. To allow comparison with the cytological assessment, the histopathological findings were categorized likewise as 1) sarcoma, 2) metastasis or myeloma/lymphoma, 3) benign bone tumors, 4) non-neoplastic lesions (infection, degenerative/reactive changes), and 5) normal tissue.

Results

Radiology

240 lesions were located in the axial skeleton, 115 in long bones and 15 in small bones (Table 1). 190 of the 370 lesions were classified radiologically as being aggressive, 54 as active and 25 as latent. 101 lesions could not be classified.

The radiological diagnostic accuracy as compared to the final treatment diagnosis was 74%. However, it varied for the different categories, i.e. 86% in non-neoplastic lesions, 64% in metastasis, 58% in sarcoma and 44% in benign lesions. Comparison of radiology and cytology according to diagnostic category showed compliance in 256 cases (69%). Among the remaining 114, there was non-compliance in 101 (27%), while 13 (4%) cases with a radiological diagnosis could not be diagnosed cytologically because of insufficient cell material (Table 2).

Cytology

Among the 370 cases, 156 were assessed cytologically as being malignant and 201 as non-malignant. The remaining 13 cases were not cytologically diagnostic. The malignant group included 32

Table 2. Comparison of radiological and cytological categorization (370 cases). Compliance is denoted by shading

	Cytology						
	Sarcoma	Metastasis	Benign	Non-neoplastic	Normal	Undiagnosed	All
Radiology							
Sarcoma	17	5	2	0	3	2	29
Metastasis	10	113	5	8	33	10	179
Benign	3	1	24	13	7	1	49
Non-neoplastic	2	5	4	45	57	0	113
All	32	124	35	66	100	13	370

Table 3. Comparison of results from cytology and histopathology (n = 125)

	Cytology	
	Malignant	Benign
Histopathology		
Malignant	74	8
Benign	2	41

sarcomas, among which a specific diagnosis could be established in 19, i.e. 7 chondrosarcomas, 5 osteosarcomas, 5 Ewing/PNET and 2 chordomas. Of the remaining 13, 8 were diagnosed as sarcoma with a suggestion of histotype (chondrosarcoma 1, angiosarcoma 1, osteosarcoma 2, Ewing/PNET 2, chordoma 2) and 5 as unspecified high-grade sarcoma. Moreover, there were 124 metastases (96 metastases, 28 myelomas/lymphomas). Among the 201 non-malignant lesions, 35 were assessed as being benign tumors, 66 as non-neoplastic changes, and 100 as normal tissue.

The cytomorphological diagnosis was corroborated by immunocytochemistry in 29 of 96 carcinomas, 16 of 18 myelomas and all 10 lymphomas. In the 124 cases of metastasis, cytology provided information on the primary tumor in 46 (kidney 14, breast 12, lung 4, prostate 4, squamous epithelium 4, melanoma 3, urothelium 2, testicle 1, colon 1 and liver 1). The remaining 50 cases were diagnosed as metastases from adenocarcinomas without specification of the primary site.

Among 35 cases cytologically assessed as benign bone "tumors", a specific diagnosis could be established in 32. These were 8 giant cell tumors, 7 eosinophilic granulomas, 7 enchondromas, 5 fibrous dysplasias, 2 aneurysmal bone cysts, 2 chondroblastomas, 1 fibromyxoma, and 1 synovial chondromatosis. The remaining 3 were diagnosed as benign bone tumors NOS. Out of 166 non-neoplastic lesions, 66 were diagnosed as being non-neoplastic changes. Aspirates from the remaining 100 cases only yielded normal cells.

The cytological diagnosis could be compared to the histopathological diagnosis in 125 cases. Table 3 summarizes the data in terms of truly and falsely malignant and truly and falsely benign lesions. The overall sensitivity of cytology alone in recognizing malignancy was 90%. The specificity was 95%. Given a malignant or benign diagnosis, the positive predictive value was 97% and the negative predictive value 84%.

Radiological and cytological compliance

The distribution of all 370 lesions according to category is shown in Table 2. The radiological assessment was based on 4 categories, whereas the cytological assessment included 6 categories. Thus, the latter treated normal findings and undiagnosed lesions as two separate categories. To permit analysis of the compliance between radiology and cytology, the cytological category "normal findings" was merged with the category "non-neoplastic lesions".

Among the 256 compliant cases, 126 were assessed as being non-malignant and 130 as malignant.

Benign

Of the 126 non-malignant cases, 102 were considered not to require surgical treatment. These cases, which included both neoplastic and non-neoplastic lesions such as non-ossifying fibroma and reactive changes, were discharged without further investigation (Table 2). Another 24 benign lesions requiring surgical treatment, such as giant cell tumors, were also analyzed by histopathology of the postoperative specimens. 2 of these cases proved to be malignant. One was assessed as being enchondroma according to radiology and cytology, but as low-grade chondrosarcoma according to histopathology. The other was assessed by radiology as being an aneurysmal bone cyst and by cytology as a giant cell tumor. Histopathology after curettage posed considerable diagnostic difficulties. Aneurysmal bone cyst was suggested initially. Second opinion from 4 external experts offered 4 diagnostic alternatives ranging from ABC to high-grade sarcoma. Finally, high-grade osteosarcoma was established and the patient was treated by chemotherapy and amputation.

Malignant

Of the 130 malignant cases, 17 were assessed as being sarcomas and 113 as metastases. Histopathology of the surgical specimens confirmed the sarcoma diagnosis in all 17, i.e. 5 osteosarcomas, 5 chondrosarcomas, 5 Ewing sarcomas and 2

Table 4. Cytological and histopathological categorization in 45 non-compliant cases

Cytology	Histology
15 sarcoma	14 sarcoma 1 metastasis
5 metastasis	3 metastasis 2 osteomyelitis
8 non-neoplastic	8 non-neoplastic
17 normal tissue	6 metastasis 6 benign 5 normal tissue

Table 5. 36 non-compliant cases lacking confirmation by histopathology

Radiology	Cytology
5 sarcoma	2 benign 3 normal
21 metastasis	5 benign, not requiring surgical treatment 16 normal [a]
1 benign	1 metastasis
9 non-neoplastic lesions	5 metastasis 4 benign

[a] 2 metastasis at follow-up

chordomas. Among the 113 cases of metastasis, 39 underwent surgery and histopathological analysis. In all 39, the latter confirmed the radiological and cytological diagnosis.

In summary, the series of 256 compliant cases entailed 2 diagnostic errors, i.e. 2 falsely benign cases (1%). Considering only the subset of 80 cases confirmed by histopathology, the rate increased to 3%.

Radiological and cytological non-compliance

A discrepancy between radiology and cytology was noted in 101 cases. In 20 of these cases the discrepancy pertained to lesions assessed as being benign by radiology, but as non-neoplastic by cytology; all were discharged without further investigation. Among the remaining 81, tissue material for histopathological analysis was obtained from 45 (Table 4). In 30 of these 45 cases, histopathology confirmed the cytological diagnosis (14 sarcomas, 3 metastases, 8 non-neoplastic lesions, and 5 normal cases). Thus, in 15 cases, there was a discrepancy also between cytology and histology.

In the remaining 36 non-compliant cases (Table 5) that were not checked by histopathology, the cytological diagnosis was considered to be safe enough to permit decision about therapy. These 36 patients were followed clinically and radiologically for 3 years. In 2 cases, the cytological diagnosis later proved to be erroneous. Both of these patients had a history of kidney cancer and a vertebral metastasis according to radiology, but the cytological aspirate from the vertebral lesion merely showed normal blood cells.

In summary, the series of 101 non-compliant cases entailed 17 diagnostic errors by cytology or radiology. The corresponding rate for the subset of 45 cases confirmed by histopathology was 33% .

Cases not diagnosed cytologically

Altogether, 13 cases were considered to be undiagnosed cytologically. Of these, 11 underwent open biopsy. Histopathology disclosed sarcoma in 3 cases, metastasis in 1, benign lesion in 2 (hemangioma) and a non-neoplastic lesion in 5. The remaining 2 cases, in which there was known bone metastatic carcinoma but where diagnostic material for cytology was not available, were not investigated further.

Discussion

Our study suggests that a simple approach based on conventional radiography and fine-needle aspiration cytology is reliable for discrimination of malign and benign bone lesions. Provided there is agreement between radiology and cytology, the risk of false diagnosis is low (< 1%). However, when the results of radiology and cytology fail to correlate with each other, open or core biopsy should be considered.

It must be emphasized that the patients in this study represented an unselected, consecutive series of patients, all of whom were referred because of uncertainty about the nature of the lesion as assessed by radiology. At our center, virtually all patients with a bone lesion undergo both radiologi-

cal and cytological assessment, which explains the high number of non-neoplastic lesions. Obviously, the simplicity of the approach leads to a liberal indication for biopsy. This practice can be expected to increase the overall diagnostic accuracy in unselected cases as compared to radiology alone, and also to reduce the need for surgical biopsies to aid decisions about therapy (Åkerman and Domanski 1998, Söderlund et al. 2003).

By using the diagnostic categorization described, the accuracy of radiology was around 70%, but varied from 44% to 86% for the different categories. Although the diagnostic categorization employed was mainly prompted by the feasibility of assessing the compliance between radiology and cytology, it also seems to be useful for making decisions about further diagnostic work-up and/or therapy. Notably, the categorization did not preclude a specific diagnosis. As for cytology, a specific diagnosis was suggested in as many as 357 of 370 lesions, even though 19 were misdiagnosed.

Compliance was recorded in 256 of 370 lesions (69%). Among these there were 2 misdiagnoses, both of which were falsely assessed as benign. In one of the 2 cases, the misdiagnosis had serious consequences for therapy, but it must be noted that even the histological assessment posed diagnostic difficulties in distinguishing between aneurysmal bone cyst and high-grade osteosarcoma. Overall, it seems that the diagnostic accuracy of radiology and cytology combined, if there is agreement, is comparable to that of radiology and histopathology.

As for the 101 non-compliant cases, the rate of false diagnosis increased markedly. This, however, had no clinical consequences. In 20 cases, the discrepancy prompted open biopsy, which provided the correct diagnosis. Another 25 cases underwent surgery without previous open biopsy; histological analysis of the surgical specimens confirmed the cytological diagnosis in 13, whereas 12 cases with normal cytological findings proved to have metastasis or benign tumors. Among 36 cases with known malignancy, 2 with benign aspirates (blood) from a bone lesion proved to have metastasis at later follow-up. It is notable that both had metastasis of kidney cancer, which is known to be highly vascular and therefore prone to yield aspirates consisting mainly of blood. Thus, this tumor entity appears to be associated with an increased risk of obtaining non-representative cell material. Finally, there were 20 non-malignant cases, where the discrepancy between radiology and cytology concerned assessment of benign neoplasia versus non-neoplasia. All 20 were discharged without further investigation and have never returned to our center, which strongly suggests that they had innocent lesions.

The reported overall accuracy of cytology in the diagnosis of bone lesions varies between 70% and 95% (El-Khoury et al. 1983, Tehranzadeh et al. 1983, Mink 1986, Kreicbergs et al. 1996, Wedin et al. 1996, Jorda et al. 2000, Welker et al. 2000, Kilpatrik et al. 2001, Ward and Kilpatrik 2001, Hau et al. 2002, Jones et al. 2002). Several of the authors emphasize multidisciplinary co-operation, but have not evaluated the diagnostic contribution of radiology. Our results show that the diagnostic accuracy of cytology is improved by confirmatory radiological information, i.e. in cases where cytology and radiology agree. Cytological assessment must correlate with radiological findings for optimal results.

It may be concluded that the management of the 101 non-compliant cases, which entailed radiology and FNAB and, for some, also open biopsy, definitive surgery or follow-up, did not put the patients at risk. Thus, no patient among the non-compliant cases received inadequate treatment. The strategy described illustrates that different options are valid and should be considered for non-compliant cases. To a large extent, the choice depends on the relative strength of the different diagnostic modalities in different types of lesions. Whenever cytology suggests sarcoma or metastasis (including lymphoma and myeloma), this can be relied upon despite non-compliant radiology. Conversely, whenever radiology suggests sarcoma or metastasis and this contradicts cytology, further diagnostic work is recommended. This is best illustrated by cases in which cytology does not explain the nature of a lytic destruction. In summary, non-compliance prompts re-evaluation of the findings before decision about further diagnostic work or treatment.

In 125 cases, the cytological categories employed could be compared to the histopathological diagnosis. Considering only the subset of 80 compliant cases which were assessed also by histopathology,

the comparison disclosed a 3% rate of false diagnosis. For the whole series of 256 compliant cases, the corresponding rate was 1%.

Admittedly, the 232 cases not checked by histopathology may have included some false diagnoses not recognized in this study. This subset included 176 compliant and 56 non-compliant cases. The compliant group consisted of 102 cases with non-malignant lesions who were discharged without further diagnostic work-up, and 74 with metastases who were treated accordingly. The non-compliant group included 36 metastatic cases who were followed for 3 years, and 20 who were assessed as non-malignant and discharged. Presumably, the risk of false diagnosis in these 232 cases not confirmed by histopathology is low. Disregarding the 36 cases with known outcome, the remaining 196 represent lesions which are quite easily diagnosed by radiology and cytology, i.e. metastasis, myeloma, lymphoma and innocent lesions (Kreicbergs et al. 1996, Wedin et al. 1996, Bommer et al. 1997, Åkerman and Domanski 1998, Jorda et al. 2000, Maitra et al. 2000, Ward and Kilpatrik 2000, Kilpatrik et al. 2001, Jones et al. 2002). Among the latter, there were 20 non-compliant cases, all of whom were discharged, where the cytological findings of non-neoplastic or normal cells outweighed the radiological suggestion of benign tumor.

The results from this study of unselected bone lesions suggest that the risk of misinterpreting the cytological findings is low, whereas representative sampling by fine-needle aspiration may be a problem. Among 100 cases only yielding normal cells at aspiration, 8 proved to have a metastatic lesion and 12 had a benign tumor as assessed by histopathology or follow-up. It is notable that 31 cases had to be called back for additional FNABs, out of which 13 remained undiagnosed, prompting open biopsy. Although most bone lesions exhibit a thin or totally destroyed cortex and are, therefore, easily reached with a fine needle, there is sometimes a problem in obtaining representative material. This is somewhat surprising, since in most cases the needle can be easily moved and redirected to permit aspiration from different sites of the same lesion. Bony obstruction of rapid advance and withdrawal of the needle in the lesion during aspiration may be one explanation for inadequate cellular yield. However, we were unable to identify a specific anatomical location or diagnosis that was associated with sampling problems. The only feature of technical importance was the thickness of the cortex, sometimes requiring the use of a penetration drill (5 cases).

In multidisciplinary tumor centers, 70% of all patients with a bone lesion can be reliably diagnosed by combining information from radiography and FNAB. The remaining 30% who require further diagnostic work-up are easily identified. The strategy described entails a low risk of false diagnosis, which is comparable to that obtained by consistently resorting to histopathology.

This study was based on patients diagnosed and treated at the Orthopedic Oncology Service, Karolinska Hospital. In addition to the authors, the team members Edneia Tani Ph.D. of the Department of Pathology and Cytology, Hildur Einarsdottir M.D. of the Department of Radiology, Otte Brosjö Ph.D. and Professor Henrik Bauer of the Department of Orthopedics were engaged in the clinical management of the patients and made this study possible.

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