Combined radiology and cytology in the diagnosis of bone lesions—a review of 399 cases

V. Söderlund

Dept of Radiology, Karolinska Hospital, Stockholm
veli.soderlund@ks.se

Most patients with symptoms from the locomotor system undergo radiological examination, among which a minority is found to have a lesion arousing the suspicion of neoplasia. The diagnosis of primary bone tumors is generally perceived as difficult. A main reason is the low incidence making it difficult to gain wide diagnostic experience. Basically, this can only be attained at referral centers. However, even for specialists the diagnosis of bone lesions may pose considerable difficulties because of highly variable macro- and microfeatures (Figure 1). Hence, it is important to collect data from different diagnostic modalities while considering also age, clinical history and clinical findings. Most importantly, the diagnostic approach should entail both a macro- and a microcharacterization.

Over the last years, core needle biopsy and fine needle aspiration have gradually gained acceptance as a diagnostic alternative to open biopsy to circumvent associated inconveniences and risks (Hajdu 1971, Tehranzadeh et al. 1983, El-Khoury et al. and Bhatia 1984, Mink 1986, Kreicbergs et al. 1996, Bommer et al. 1997, Åkerman et al. 1998, Wedin et al. 2000). The increasing number of cytological reports on bone lesions, consistently emphasize the importance of combining the cytologic findings with the radiologic (Kreicbergs et al. 1996, Bommer et al. 1997, Åkerman et al. 1998, Jorda et al. 2000, Maitra et al. 2000,Ward and Kilpatrik 2000 et al, Wedin et al. 2000, Kilpatrik et al. 2001, Jones et al. 2002). Nonetheless, there are only two studies (Söderlund et al. 2002, 2004) designed to assess the validity of such a combined approach. Notably, fine needle aspiration biopsy cannot be routinely employed in the diagnosis of bone lesions without the support of radiology, in which the radiologist has a dual role. One is to classify the lesion, another is to identify the target and insert the needle appropriately for subsequent aspiration by the cytologist (Figure 2).

Thus, fine needle aspiration cytology of bone lesions presupposes a “close to patient” co-operation between specialists from two different diag-

Figure 1. Examples of osteosarcomas in the distal femur.

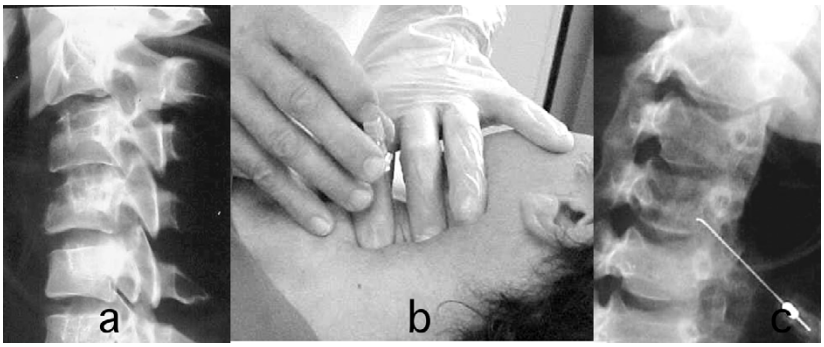

Figure 2. FNAB. Lateral radiography of the cervical spine with a lymphoma lesion of C3 and 4 (a) needle insertion (b) and oblique view of needle position.

nostic disciplines. This has been the routine at the Karolinska Hospital since 1986. In this presentation I summarize our experience.

Patients and methods

This summary includes 404 patients with a newly detected bone lesion, who were referred from 1986 through 1998 to Karolinska Hospital for radiologically guided fine needle aspiration cytology. It is based on two series of 374 (Söderlund et al. 2003) and 30 (Söderlund et al. 2002) consecutive cases, which were retrieved from the files from the Department of Diagnostic Radiology. 45 patients had a previous diagnosis of carcinoma (breast 14, gynecologic 7, colon 7, kidney 5, lung 5, prostate 4, larynx 3), 7 had myeloma, lymphoma or leukemia, 7 sarcoma and 4 benign bone lesions. Thus, 341 of 404 patients were referred for biopsy without a medical record of neoplasia. Radiographs of 4 patients could not be found and one biopsy failed because of pain, leaving 399 patients for the study. The analysis of the series was based on the original reports on 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 and 4) non-neoplastic lesion.

Fine needle aspiration biopsy

The FNAB was done as an out-patient 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 needle with a diameter between 0.47 to 0.70 mm were used. The radiologist inserted the needle in each lesion and the needle position was checked by fluoroscopy or CT-scan before aspiration by the cytopathologist (Figure 2). In 5 patients the lesion was purely intra-osseous prompting the use of an eccentric drill device to penetrate the intact cortical bone (Ahlström and Åström 1993).

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 non-diagnostic. The aspirates were routinely stained with May-Grünwald-Giemsa (MGG). In some cases the aspirate was used for auxillary studies, e.g., immunocytochemistry, molecular genetics and karyotyping. 339 patients underwent aspirations at one occasion, whereas 28 had to be called back for a second and 3 for a third FNAB, because of non-conclusive cytology.

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

Histology

In 146 of the 399 patients, tissue samples for histopathological assessment were also obtained. This was based on specimens from open biopsy in 30 patients and definitive surgery in 116. 12 patients

Table 1. Test of radiological and cytological compliance in 385 cases

	Cytology				
Radiology	Sarcoma	Metastasis	Benign	Non-neoplastic/ normal	All
Sarcoma	**22**	6	2	3	33
Metastasis	11	**121**	5	42	179
Benign	3	1	**29**	21	54
Non-neoplastic	2	6	4	**107**	119
All	38	134	40	173	385

Bold denotes compliance.

provided tissue for histopathology from both open biopsy and definitive surgery. To allow comparison with the cytological assessment the histopathological findings were likewise categorised as 1) sarcoma, 2) metastasis or myeloma/ lymphoma, 3) benign bone tumors, 4) non-neoplastic lesions (infection, degenerative/reactive changes) and 5) normal tissue.

The comparison of radiology and cytology was based on four categories; the cytological category 'non-diagnostic' was for obvious reasons excluded (Table 1).

Results

Among the 399 cases, 172 were cytologically diagnosed as malignant and 213 as nonmalignant. The remaining 14 cases were cytologically non-diagnostic. The malignant group included 38 sarcomas, among which a specific diagnosis could be established in 25, i.e. 8 chondrosarcomas, 8 osteosarcomas, 5 Ewing's/PNET's and 3 chordomas and 1 MFH. Moreover, there were 100 metastases, and 34 myelomas/lymphomas. Among the 214 nonmalignant lesions, 40 were assessed as benign tumors, 66 as non-neoplastic changes and 102 as normal tissue.

In the 100 metastatic cases, cytology correctly suggested the tumor type in 51. Out of 173 non-neoplastic lesions, 71 were diagnosed as non-neoplastic changes. Aspirates from the remaining 102 cases only yielded normal cells. After exclusion of the 14 non-diagnostic cases, there remained 385 cases for the comparative analysis of radiology and cytology showing that 279 (72 %) were compliant and 106 non-compliant. The rate of compliance among the 4 categories varied from 0.58 (sarcoma) to 0.90 (metastasis).

Compliance

The distribution of the 279 compliant cases according to category was: sarcoma 22, metastasis 121, benign tumor 29 and non-neoplastic/normal 107. The management varied considerably between the diagnostic categories. Among the malignant lesions, all 22 sarcomas were surgically treated and the specimen assessed by histopathology; the corresponding rate for metastases was 39 of 121. As for the benign tumors, 25 of 29 were surgically treated and analyzed by histopathology, whereas 4 were discharged without further measures. In addition, all 107 cases assessed as non-neoplastic/ normal, were considered innocent and discharged. None of those discharged with a benign tumor or a non-neoplastic/normal lesion without surgery has returned to our centre until August 2002. In the remaining 82 cases managed without histopathologic confirmation, the combined radiological and cytological diagnosis was considered safe enough to permit decisions about therapy. These patients were followed for at least 3 years without clinical findings prompting a change of the diagnosis.

Based on these data, the number of correct diagnoses among the 279 compliant cases was 277 (99 %). In the 2 misdiagnosed cases the errors pertained to the distinction between benign and malignant lesions, which had serious clinical consequences in one case. Thus, a distal metaphyseal lesion of femur in a 7-year-old boy was diagnosed by radiology as ABC and by cytology as GCT, but was assessed as high-grade osteosarcoma on

Table 2. Management of the 106 non-compliant cases

		Histopathology		No histopathology	
		agreement	discrepancy	treatment/ follow up	discharge
n	Cytology				
16	Sarcoma	14	1	1	
13	Metastasis	3	2	8	
11	Benign			11	
21	Non-neoplastic	16			5
45	Normal		12	17 (2)	16
		33	15	37 (2)	21
106		15 / 48		2 / 58	

Bold figure denotes misdiagnosis

histopathology of the curetted specimen. Notably, the histological assessment posed considerable diagnostic difficulties prompting external review. The patient was initially treated by curettage, but had subsequently to undergo above knee amputation and chemotherapy. The boy is alive without evidence of disease 9 years after treatment. The other case, classified as an enchondroma by both radiology and cytology was treated by curettage. Histopathology of the specimen disclosed grade I chondrosarcoma, which, however, did not require additional treatment (Bauer et al. 1995).

Non-compliance

A discrepancy between radiology and cytology was found in 106 of 385 (28 %) cases (Table 2). Among the 106 non-compliant cases, 85 underwent treatment, whereas 21 were discharged without further measures. None of the latter cases categorized radiologically as benign tumors, but cytologically as non-neoplastic/normal lesions returned to our center during the study period or thereafter till August 2002. As for the 85 cases treated, histopathology was done on 48 confirming the cytological diagnosis in 33, i.e. sarcoma 14, metastasis 3, non-neoplastic/normal lesions 16. Thus, in 15, there was a discrepancy also between cytology and histopathology (Table 2). The remaining 37 cases treated, all with malignancy previously diagnosed, were managed without histopathologic confirmation. These 37 patients were followed for a minimum of 3 years showing that 2 had been misdiagnosed by cytology. Thus, two with a known kidney cancer proved to have metastasis of the spine, despite normal findings on cytology.

Table 3. Incorrect diagnosis according to histopathology (n=15) or follow up (n=2) among 106 non-compliant cases

n	Histopathology/ follow up	Radiology	Cytology
1	Adenocarcinoma	Metastasis	Chordoma
8[a]	Adenocarcinoma	Metastasis	Normal
2	Benign tumor	Metastasis	Normal
4	Benign tumor	Benign tumor	Normal
2	Osteomyelitis	Osteomyelitis	Metastasis

[a] 2 by follow up

Based on these data the number of incorrect cytological diagnoses among the 106 non-compliant cases was 17 (16%). As can be seen in Table 3, the cytologic failure of distinguishing malignant from benign lesions pertained to 8 cases (shaded grey) as compared to histopathology and follow up. Surprisingly, the corresponding number for radiology was only 2 (shaded dark).

Discussion

For the whole series of 385 cases, the over all rate of cytologically correct diagnosis was 95 %. The corresponding rate for the compliant cases was 99 % and for the non-compliant cases 84%. The cytologic diagnostic error rate among the compliant and non-compliant cases, considering also the histopathologic assessment, is given below (Figure 3).

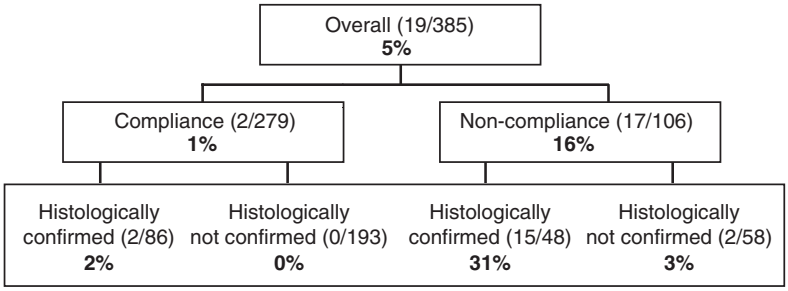

Figure 3. Cytologic diagnostic error rate in 385 unselected cases

Among the 279 compliant cases, there were 2 misdiagnoses (1 %), whereas among the 106 non-compliance cases there were 17 (16 %). Although, the diagnostic error rate was 20-fold higher among the non-compliant cases, not one single patient received inadequate therapy. Either they underwent open biopsy providing the correct diagnosis or histopathology of the surgical specimen confirmed the cytological diagnosis. Moreover, there were 37 cases under treatment for a malignancy, among which 2 at follow up proved to have vertebral metastasis, despite negative cytology. Finally, there were 21 nonmalignant cases, where the discrepancy pertained to the assessment of benign neoplasia versus non-neoplasia. All 21 were discharged without further investigation and never returned.

It may be concluded that the management of the non-compliant cases, which entailed radiology, FNAB and for some also open biopsy, definitive surgery or follow up, did not put the patients at risk. Closer analysis disclosed that the 17 misdiagnoses could be explained by misinterpretation of the aspirates in 3 cases, whereas in 14 they were due to sampling errors. The latter comprised 8 metastases and 6 benign tumors according to histopathology, which, however, only yielded normal cells at aspiration.

Altogether, there were 251 cases were the diagnosis was not confirmed by histopathology. This circumstance may imply a lower over all diagnostic success rate. However, this subset included many cases (n=132) with innocent lesions discharged without further investigation, and who never returned after diagnosis. The group included many patients, who traditionally would be managed by radiology only. Moreover, there was several cases (82 compliant, 37 non-compliant), in which the radiologic and/or cytologic information was considered safe enough to permit decision about therapy. These comprised 82 compliant cases with metastasis, myeloma or lymphoma, and another 37 with known malignant disease. In metastatic conditions an abundant yield of tumor cells at aspiration is mostly diagnostically conclusive. As for the myeloma and lymphoma cases, the cytological diagnosis was corroborated by immunocytochemistry in the vast majority (69/82). For the reasons given, it may be assumed that the rate of misdiagnosis influencing patient safety among the 251 cases not confirmed by histopathology is close to nil.

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 (including auxiliary analysis) suggests sarcoma or metastasis (including lymphoma, myeloma) this can be relied upon, despite non-compliant radiology. Conversely, whenever radiology suggests sarcoma or metastasis in contradiction to cytology, further diagnostic work up is recommended. This is best illustrated by cases in which cytology does not explain the nature of a lytic destruction.

The reported diagnostic accuracy using cytology in the diagnosis of bone lesions varies between 70 and 95 % (Tehranzadeh et al. 1983, El-Khoury et al. 1984, Mink 1986, Kreicbergs et al. 1996, Bommer et al. 1997, Jorda et al., Maitra et al., Wedin et al., Welker 2000, Kilpatrik et al. 2001, Hau et al. 2002). The results of the present summary indicate that the diagnostic accuracy is improved by confirmatory radiological information, i.e. in cases where cytology and radiology comply.

It may be concluded that a simple approach based on conventional radiography and cytology at a musculoskeletal tumor center offers a reliable means of discriminating benign from malignant bone lesions. Provided there is compliance between radiology and cytology, the risk of false diagnosis is low. However, when radiology and cytology fails to articulate, further measures like open or core biopsy should be considered. In the future, it may be assumed that new imaging techniques like MRI can be exploited to reduce the number of sampling failures by fine needle aspiration biopsy. Moreover, the feasibility of using fine needle aspirates not only for immunocytochemistry, karyotyping, DNA cytometry etc, but also for new techniques of molecular genetics will presumably increase the diagnostic accuracy of cytology in the management of patients with bone lesions.

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