Diagnostic accuracy and safety of percutaneous bone biopsy in histopathological diagnosis of metastatic bone lesions with known or unknown origin

Cennet Sahin, Fevziye Kabukcuoglu

The corresponding and the first author:
Name: Cennet Sahin, Expert in Radiology
Affiliation: University of Health Sciences, Istanbul Sisli Hamidiye Etfal Training and Research Hospital, Radiology Department
E-mail adress: cennetsahin2@hotmail.com
Telephone Number: +90 505 748 57 41; +90 212 3735000 (4645)
Orcid ID: https://orcid.org/0000-0002-8695-327X

The second author:
Name: Fevziye Kabukcuoglu, Prof. Dr., Expert in Pathology
Affiliation: University of Health Sciences, Istanbul Sisli Hamidiye Etfal Training and Research Hospital, Pathology Department
E-mail adress: fkabukcuoglu@hotmail.com
Telephone Number: +90 212 373 50 00 (5016); +90 505 5236523
Orcid ID: https://orcid.org/0000-0002-7705-7510

(Received: 2020. 11. 09.; Accepted: 2021. 04. 20.)

Copyright: The Author(s)

Open Access statement. This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 International License (https://creativecommons.org/licenses/by-nc/4.0/), which permits unrestricted use, distribution, and reproduction in any medium for non-commercial purposes, provided the original author and source are credited, a link to the CC License is provided, and changes – if any – are indicated.

Acknowledgements
There is no funding source for this manuscript.
Introduction

Metastasis of a primary cancer is an important determining factor in morbidity and mortality. A new lesion in the bone may be more likely a metastasis than a primary bone cancer [1-3]. On the other hand, although a new bone lesion may be a metastasis of an unknown primary cancer, a new lesion detected during follow up of a cancer may not be associated with the known primary tumor. Thus, to plan a personalised treatment, diagnosis of a newly detected bone lesion is crucial.

Bone metastasis may be present in most of the cancers; most frequently in lung, breast and prostate cancers [1-3]. Pain and pathological fractures are the main symptoms of bone metastasis. Needle core biopsy or surgical biopsy is recommended for histological evaluation. As a less invasive diagnostic tool, image-guided percutaneous biopsy may be preferred over surgical biopsy [4].

In this study, we aimed to share our results of image guided percutaneous bone biopsies and histopathological diagnosis of metastatic bone masses in patients with known and unknown primary cancers.

Patients and Methods

This retrospective study was approved by our institution’s ethical committee (Number 2506; Date: 03.09.2019). Between 2016 and 2019, the patients who were diagnosed with bone metastases of either a known or unknown primary cancer by image guided percutaneous bone biopsy were included in the study. For all the patients, the reason for the biopsy, locations of
the lesions, compatibility of the patients with the biopsy procedure (hemogram-coagulation profile, antiplatelet-anticoagulant drug use) were evaluated. Previous cross-sectional computed tomography (CT), Magnetic Resonance (MR) examinations and positron-emission-tomography (PET) images of patients were reviewed before biopsy. All the patients were informed about the biopsy procedure and biopsy related complications. Written informed-patient-consents were obtained from all the patients before biopsies.

A total of 87.7% of the patients had CT (Toshiba, Alexion, Japan and Siemens, Somatom, Emotion, Germany) and the rest of 12.3% had ultrasound (US) (Mindray, China) guided biopsies under aseptic conditions. All the biopsies were performed by the same radiologists with 6 years of experience in interventional radiology. For each of the patients, the shortest path between the skin and the lesion was planned for the needle approach to avoid neurovascular damage. Also, a probable operation route is concerned to avoid possible tumor seeding during the biopsies. For each of the lesions, the most suspicious part on CT or Magnetic Resonance Images (MRI) or the most fluoro-deoxy-glucose (FDG) avid portion on PET-CT were concerned to obtain a qualified sample of tissue for diagnosis. For bone marrow biopsies, CT guided curettage biopsy of iliac bone marrow was performed on prone or supine position due to patient’s clinical pain condition. All the biopsies were performed under local-anesthesia paying special attention to infiltrate the periosteum. An 11 Gauge 10 cm bone biopsy needle or a 14 Gauge 10-15 cm semi-automatic core biopsy needle was used under CT or US-guidance. US guidance was preferred for the lesions which could be visualized under US and which had a prominent lytic component. A minimum of 1 cm specimen length was considered enough for an adequate biopsy (Fig. 1). All the obtained samples were sent for histopathological analysis in formaline solution. After fixation for 8 hours in 10% neutral formaline solution, the biopsy materials were decalcified in 10% formic acid 20 times their
volume for 12 hours. After the specimens were decalcified, they were rinsed thoroughly in tap water. Then routine paraffin embedding procedures were applied. Hematoxylin eosin dyed slides were evaluated and immunohistochemical study was performed when necessary. All the biopsy samples were evaluated by the same histopathologist who has been specialized on musculoskeletal pathology and has over twenty years of experience in histopathology. The histopathologist was familiar with the background history of the patient (whether they had a primary cancer or not) and assumed radiological diagnosis. After biopsy, patients were observed in hospital for about an hour for possible complications such as hemorrhage or pain. Complications were assessed on the basis of the classification of Society of Interventional Radiology [5]. Radiologic and histopathologic analyses, diagnostic yield rate and complications were reviewed retrospectively. Based on the histopathology results, patients were grouped as; had a bone metastasis of a primary known tumor (Group 1), had a bone metastasis of a primary unknown tumor (Group 2).

For statistical analysis, Statistical Package for the Social Sciences (SPSS) for Windows (Version 21.0, Chicago, SPSS Inc.) program was used. Descriptive statistics were given as number and percentage for categorical variables and as mean, standard deviation, minimum, maximum and median for numerical variables.

Results

A total of 57 patients (32 M, 25F; median age of 58.0; age range 28-89) who had diagnosis of solitary or multiple metastasis of a known or unknown primary cancer were included in the study. Eight patients had bone marrow biopsy, not a bone mass biopsy. So, they have been
excluded from evaluation of median diameter of lesion size. Median diameter of the 49 sampled masses in 49 patients was 37.7 mm (ranged between 4-80 mm).

From all patients, 54.4% had a known and 45.6% had unknown primary cancers in background history. One patient had two different (breast and lung) known primary cancer in background. Twenty-nine (59.2%) of the 49 bone masses were localized in pelvic bones (iliac, sacral, ischial, pubic bones). Ten (20.4%) of the 49 bone masses were localized in dorsolumbar vertebral bones.

Almost all the samples were adequate for diagnosis except for two patients (false negatives). One of them had history of primary larynx cancer. Histopathological analysis was not possible due to tumor necrosis in this patient (Fig. 2a). The biopsy was not repeated since the patient did not confirm re-biopsy. On his follow-up, although the relevant lesion responded to chemotherapy, new metastatic bone lesions developed and the lesion was secondarily diagnosed as metastasis of larynx cancer. In the second patient, who had a bone mass in pelvic bone and did not have a known cancer history, the biopsy sample was not adequate due to tumor fibrosis and necrosis. She had diagnosis of plasmacytoma with open surgical biopsy (Fig. 2b). Thus, the diagnostic yield rate was 97% in this study.

In 3 patients who had a primary known (tongue, larynx, lung) cancer, biopsy results were revealed benign degenerative findings which were consistent with radiological findings (true negatives). Among the patients who had a primary known cancer origin, the metastases were originated from primary cancer of breast (n=10), lung (n=9), renal-cell (n=2), prostate (n=1), larynx (n=1), tongue (n=1), malignant melanoma (n=1), rectum cancer (n=2), gastric (n=1), hepatocellular carcinoma (n=1). The patient who had breast and lung cancer in background
history, had diagnosis of lung cancer metastasis. Among the patients who did not have a primary known cancer origin, the metastases were originated from lung (n=8), plasmositoma (n=8), renal-cell (n=3), multiple myeloma (n=2), gastric (n=1), thyroid (n=1) and prostate cancer (n=1), lymphoma (n=1) in Goup 2 patients respectively. In 17 (31,5%) of 54 metastatic patients, metastases were originated from lung cancer mostly. Breast (18,5%) carcinoma was the second most frequent metastatic cancer. The informations about age and gender of the patients, locations of the lesions, existence of a primary known cancer and final diagnoses is shown in Table 1.

Assessing the complications, we had 2 (3.5%) minor complications. One patient had a superficial hematoma and one had severe pain that was relieved with medical treatment in one hour. No major complication was seen related to the biopsies.

Discussion

A newly detected bone lesion may be a metastasis as well as a primary benign or malignant bone tumor (Fig. 3). Bone is a common cite of metastasis that bone metastasis may be presented in almost all cancer types [1-3]. Almost 10-23% of patients with metastasis present with bone metastasis from unknown primary tumors at the time of admission [6]. Diagnosis of a newly detected bone lesion, especially when it is solitary and when there is no cancer in background history, is crucial for treatment.

Bone metastases are often presented with severe bone pain and they are uncommonly asymptomatic [3]. Asymptomatic lesions may be detected incidentally during check-up imagings of non-cancer patients or during follow-up examinations of cancer patients. We have an interesting case among our patients who represents as a notable example of this prospect (Fig. 4).
Image-guided percutaneous bone biopsy, as an efficient, safe, and cheap method, plays an important role in diagnosis of a newly detected bone lesion and planning an accurate treatment method. It provides minimally invasive and exact approach to the target lesion, accurate positioning of the needle in to the most suspicious area of the lesion and high diagnostic value of sampling compared to open surgical biopsies that may require wide excisions and bone grafting [7].

To identify potential contraindications and predict potential complications, pre-biopsy preparation and planning are important to have a qualified biopsy and to have greatest diagnostic yield. Review of pre-procedural cross-sectional images may provide a significant contribution in obtaining adequate and sufficient sample of tissue for diagnosis. We reviewed most cellular part (on MRI) or the most FDG-avid part of the lesions in corresponding CT-images. Usually, osteolytic part of the lesions was that corresponding area in CT. Another issue was the needle type that was used in biopsy. If the lesion was superficial and could be visualised under US, US guided biopsy was performed either by an 11 Gauge bone needle (as trocar or jam-shidi) or a 14 Gauge core biopsy needle. If the lesion was deep and CT-guidance was required, we used an 11 Gauge bone needle to obtain a thick sample under CT-guidance. Although fine needle aspiration (FNA) can distinguish a metastasis from a benign lesion, the core needle biopsy is recommended rather than FNA in histopathological evaluation which is required for the diagnosis of metastatic lesions [4]. As we agree with this recommendation, all the biopsies were obtained with thick needles as core biopsy. To our experience, a single long core (1-2 cm) of abnormal tissue by an 11-gauge needle has been enough for lytic-sclerotic bone lesions while a (1-2 cm) 14-Gauge core biopsy needle was enough for bone lesions had a prominent lytic component. Also, bloody sample could be aspirated from the lesion through
bone needle for cell block preparation using bone needle as a coaxial approach pathway. In our study, almost all the samples were adequate for diagnosis out of 2 (3%) patients (false negatives). As diagnostic yield rate was 97% in this study, the patients with or without a known primary tumor could be diagnosed and referred for appropriate treatment. It showed that primary tumor diagnosis can also be made indirectly by biopsy of a metastatic bone lesion.

Regarding the location of primary origin of the cancers, breast and lung cancer metastasis were seen as most frequent cancers in Group 1, while lung cancer was the most frequent cancer among the Group 2. Overall, lung cancer metastasis was the most frequent cancer in total patients. We think that bone metastases of unknown origin increase the likelihood of a primary lung or breast carcinoma.

According to CIRSE (Cardiovascular and Interventional Radiological Society of Europe) guidelines, which grades the adverse effects on the basis of the outcome, hospitalization duration and severity of a specific sequel in patient’s everyday life, percutaneous bone biopsy procedure is in the group of low risk category [5, 8, 9]. The potential complication rate for percutaneous bone biopsy is reported as less than 5% whereas open biopsy has a complication rate of up to 16% in many of the papers [4]. Consistent with the literature, we had two (3.5%) minor complications. No major complication was observed during or after biopsies in our study.

As a shortcoming of this study, we had a limited number of cases. This can be overcome in future comprehensive studies involving a large number of cases.

To sum up with, image guided biopsy is a useful, reliable, micro invasive, effective and cheap method in diagnosis of metastatic bone lesions with low complication and high diagnostic
yield rates. Primary tumors may also be diagnosed indirectly by percutaneous biopsy of a metastatic bone lesion.

Authors’ contributions

CS and FK conceived of the study, participated in its design, and supervised the selection of cases and controls. CS performed the biopsies and FK evaluated the pathological samples. CS conducted the clinical part of the imaging, reviewed cases and carried the statistical analysis, and drafted and finalized the manuscript. Both of the authors read and approved the final manuscript and accepted the publication.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Competing interests

The authors declare that they have no competing interests.
References

1. D’Oronzo S, Coleman R, Brown J, Silvestris F. Metastatic bone disease: Pathogenesis and therapeutic options: Up-date on bone metastasis management. J Bone Oncol 2018;15:004–4. doi: 10.1016/j.jbo.2018.10.004.

2. Coleman RE. Metastatic bone disease: clinical features, pathophysiology and treatment strategies. Cancer Treat Rev 2001;27:165–76.

3. Macedo F, Ladeira K, Pinho F, Saraiva N, Bonito N, Pinto L. Bone metastases: an overview. Oncol. Rev 2017;11(321):43–49.

4. Taylor MB, Bromham NR, Arnold SE. Carcinoma of unknown primary: key radiological issues from the recent National Institute for Health and Clinical Excellence guidelines. Br J Radiol 2012; 85(1014):661–671. doi:10.1259/bjr/75018360.

5. Indravadan JP, Davidson JC, Nikolic B, Salazar GM, Schwartzberg MS, Walker G et al. Consensus Guidelines for Periprocedural Management of Coagulation Status and Hemostasis Risk in Percutaneous Image-guided Interventions. J Vasc Interv Radiol 2012;23:727–736. DOI: 10.1016/j.jvir.2012.02.012.

6. Kim W, Han I, Kang S, et al. Non-spine bone metastasis as an initial manifestation of cancer in Korea. J Korean Med Sci 2014;29:357–62.

7. Espinosa LA, Jamadar DA, Jacobson JA et al. CT-guided biopsy of bone: a radiologist's perspective. CT-Guided Biopsy of Bone: A Radiologist’s Perspective. AJR Am J Roentgenol 2008;190(5):283-9. Doi: 10.2214/AJR.07.3138.

8. Gupta, S.; Wallace, M.J.; Cardella, J.F.; Kundu, S.; Miller, D.L.; Rose, S.C. Quality improvement guidelines for percutaneous needle biopsy. J Vasc Interv Radiol 2010;21:969–975.

9. Veltri, A.; Bargellini, I.; Giorgi, L.; Almeida, P.A.M.S.; Akhan, O. CIRSE Guidelines on Percutaneous Needle Biopsy (PNB). Cardiovasc Interv Radiol 2017; 40:1501–1513.
Table 1. List of patients with information about age, gender, locations of the lesions, existence of a primary known cancer and final diagnoses.

| Patient | Age | Gender | Known-Primary cancer | Lesion Localisation | Lesion Diameter | Diagnosis (Metastasis of primary cancer of) |
|---------|-----|--------|----------------------|--------------------|----------------|------------------------------------------|
| 1       | 61  | M      | No                   | Ischion            | 50 mm          | Lung                                     |
| 2       | 37  | F      | Breast               | Iliac bone         | 4 mm           | Breast                                   |
| 3       | 61  | F      | No                   | Acetabulum         | 40 mm          | Gastric                                  |
| 4       | 65  | M      | No                   | Iliac bone         | 80 mm          | Lung                                     |
| 5       | 43  | M      | No                   | Iliac bone         | 65 mm          | RCC                                     |
| 6       | 46  | M      | Lung                 | Sacral bone        | 20 mm          | Lung                                     |
| 7       | 82  | F      | Lung and Breast      | L2 vertebra        | 20 mm          | Lung                                     |
| 8       | 62  | M      | No                   | Costa              | 75 mm          | Lung                                     |
| 9       | 73  | M      | No                   | Costa              | 35 mm          | Lung                                     |
| 10      | 57  | M      | No                   | Scapula            | 30 mm          | RCC                                     |
| 11      | 74  | M      | No                   | Acetabulum         | 60 mm          | RCC                                     |
| 12      | 77  | M      | RCC                  | L4 vertebra        | 45 mm          | RCC                                     |
| 13      | 59  | M      | Lung                 | Scapula            | 60 mm          | Lung                                     |
| 14      | 57  | M      | Malignant melanoma   | Iliac bone         | 15 mm          | Malignant melanoma                       |
| 15      | 49  | F      | Rectum               | Iliac bone         | 50 mm          | Rectum                                  |
| 16      | 46  | F      | Breast               | Pubic bone         | 20 mm          | Breast                                  |
| 17      | 81  | M      | No                   | Femur diaphysis    | 70 mm          | Prostate                                |
| 18      | 58  | M      | Larynx               | Iliac bone         | 23 mm          | False negative (Larynx)                 |
| 19      | 58  | M      | No                   | Humeral bone       | 20 mm          | Lung                                    |
| 20      | 44  | M      | No                   | Iliac bone         | 46 mm          | Lung                                    |
| 21      | 58  | M      | No                   | Pubic bone         | 60 mm          | Lung                                    |
| 22      | 43  | F      | Tongue               | D7 vertebra        | 20 mm          | Tongue                                  |
| 23      | 65  | F      | Breast               | Mandibula          | 30 mm          | Breast                                  |
| 24      | 72  | M      | Lung                 | Iliac bone         | 20 mm          | Lung                                    |
| 25      | 49  | M      | Lung                 | Costa              | 65 mm          | Lung                                    |
| 26      | 60  | F      | Lung                 | Costa              | 50 mm          | Lung                                    |
| 27      | 54  | M      | RCC                  | Iliac              | 20 mm          | RCC                                     |
| 28      | 46  | F      | Breast               | D10 vertebra       | 5 mm           | Breast                                  |
| 29      | 68  | M      | Lung                 | Iliac bone         | 30 mm          | Lung                                    |
| 30      | 28  | F      | No                   | Costa              | 75 mm          | Thyroid                                 |
| 31      | 76  | M      | No                   | Costa              | 40 mm          | Lung                                    |
| No. | Age | Gender | Site 1       | Site 2       | Site 3       | Site 4       | Site 5       | Site 6       |
|-----|-----|--------|--------------|--------------|--------------|--------------|--------------|--------------|
| 32  | 46  | M      | Lung         | Sacrum       | 20 mm       | Lung         |
| 33  | 58  | F      | Breast       | Sacrum       | 80 mm       | Breast       |
| 34  | 68  | M      | Prostate     | Pubic        | 50 mm       | Prostate     |
| 35  | 59  | F      | Breast       | L4 vertebra  | 40 mm       | Breast       |
| 36  | 62  | F      | Breast       | L4 vertebra  | 20 mm       | Breast       |
| 37  | 46  | F      | Breast       | Calvarium    | 50 mm       | Breast       |
| 38  | 64  | M      | No           | L3 vertebra  | 35 mm       | Lung         |
| 39  | 40  | F      | Breast       | Iliac bone   | 35 mm       | Breast       |
| 40  | 64  | M      | Breast       | Scapula      | 20 mm       | Breast       |
| 41  | 64  | F      | HCC**        | Scapula      | 30 mm       | HCC          |
| 42  | 66  | F      | No           | Ischion      | 35 mm       | False negative (Plasmocytoma) |
| 43  | 55  | F      | No           | Orbita bone  | 28 mm       | Plasmocytoma |
| 44  | 73  | F      | No           | L4 vertebra  | 30 mm       | Multiple Myeloma |
| 45  | 62  | F      | No           | L5 vertebra  | 20 mm       | Plasmocytoma |
| 46  | 68  | M      | No           | Iliac bone   | 55 mm       | Plasmocytoma |
| 47  | 52  | M      | Tongue SCC***| Sacrum       | 20 mm       | True Negative |
| 48  | 56  | F      | Larynx SCC   | Clavicula    | 15 mm       | True Negative |
| 49  | 51  | M      | Lung         | L2 vertebra  | 20 mm       | True Negative |
| 50  | 33  | M      | Rectum       | Bone marrow-iliac | Rectum        |
| 51  | 38  | M      | Gastric      | Bone marrow-iliac | Gastric     |
| 52  | 89  | F      | No           | Bone Marrow-iliac | Multiple Myeloma |
| 53  | 71  | M      | No           | Bone Marrow-iliac | Plasmocytoma |
| 54  | 55  | F      | No           | Bone Marrow-iliac | Plasmocytoma |
| 55  | 50  | F      | No           | Bone Marrow-iliac | Plasmocytoma |
| 56  | 43  | M      | No           | Bone Marrow-iliac | Lymphoma     |
| 57  | 66  | F      | No           | Bone Marrow-iliac | Plasmocytoma |

**RCC**: Renal Cell Cancer
**HCC**: Hepatocellular Carcinoma
**SCC**: Squamous cell carcinoma
Figure Legends

Figure 1 a and b

All the interventions performed under aseptic conditions by the same interventional radiologist in the same center (a). A minimum of 1 cm specimen length was considered enough for an adequate biopsy (b).

Figure 2 a and b
The patients with false negative biopsies. A 58 years old man who had history of primary larynx cancer. Histopathological analysis was not possible due to tumor necrosis in this patient (Fig 2a). Re-biopsy was not performed since the patient did not accept. On his follow-up, since new metastatic bone lesions developed, the lesion was secondarily diagnosed as metastasis of larynx cancer. The second patient was a 66 years old female who did not have a primary known cancer history (Fig 2b). The biopsy sample was not adequate due to tumor fibrosis and necrosis. She had diagnosis of plasmocytoma with open surgical biopsy.

Figure 3 (a-d)
A 44-year-old male patient without malignancy in background history. The patient had pelvic MR examination for further evaluation of a disturbing new pain in his left hip. Concerning the patient’s age and no cancer history in background history, radiological findings were found suspicious for fibrous dysplasia according to MRI and CT findings (a). CT guided percutaneous biopsy was performed for diagnosis (a). As, the histopathological analysis revealed metastasis from lung adenocarcinoma, thorax CT was performed for further evaluation. A spiculated solitary mass lesion was shown in the upper lobe of the left lung which supported the diagnosis (b). Demonstration of epithelial feature of lung carcinoma metastasis by immunohistochemical pancytokeratin study (x200) (c). Malignant tumor cells that form adenoid structures in the cell block prepared in aspiration material (HEx200) (d).

Figure 4 (a, b)

A 28 years old woman who had a mass density on left hemithorax that was incidentally detected on chest radiograph (a). She had neither cancer history nor complaint of pain, swelling, cough or weakness. In background history, she had thyroid operation 15 years ago with no cancer diagnosis. She had thoracic CT and PET-CT for further investigation in our
hospital. The mass was a solitary destructive bone lesion without any other suspicious focus on PET-CT. Thyroid ultrasound examination had no abnormality with bilateral normal thyroid glandular tissue. Ultrasound guided core needle biopsy was performed and histopathological analysis revealed metastasis of thyroid cancer. The histopathological samples of previous thyroid operation were analyzed retrospectively and the cells of follicular neoplasm, which were overlooked 15 years ago, were detected. The patient had surgical operation for both rib metastasis and thyroid gland excision. Recurrence of thyroid follicular neoplasm was detected in thyroid gland although there was no obvious nodular lesion on US examination. Thyroid carcinoma metastasis that creates follicular structures adjacent to bone lamellae (HE X 200) (b).