Non-Spine Bone Metastasis as an Initial Manifestation of Cancer in Korea

Wanlim Kim,[1] Ilkyu Han,[1,2]
Seungcheol Kang,[1] Sang A Lee,[1]
and Han-Soo Kim[1,2]

[1]Department of Orthopaedic Surgery and
[2]Musculoskeletal Tumor Center, Seoul National
University Hospital, Seoul, Korea

Received: 12 October 2013
Accepted: 16 December 2013

Address for Correspondence:
Ilkyu Han, MD
Department of Orthopaedic Surgery, Seoul National University
Hospital, 101 Daehak-ro, Jongno-gu, Seoul 110-744, Korea
Tel: +82.2-2072-0682, Fax: +82.2-764-2718
E-mail: hik19@snu.ac.kr

Non-spine bone metastasis accounts for approximately 20% of all skeletal metastases, but little data have been published that focused on bone metastasis to the pelvis and extremities as an initial manifestation of cancer. We determined 1) clinicopathologic characteristics of patients who presented with non-spine bone metastasis of unknown primary malignancy, and 2) process by which the diagnosis of primary cancer was made. We retrospectively reviewed 84 patients with bone metastasis of unknown primary cancer site at the time of presentation. The study population consisted of 56 men and 28 women, with a mean age of 59.1 yr (17.5-85.6 yr). The average follow-up period was 20.8 months (1-120 mo). Primary cancer site was identified in 79 patients (94.0%), and was determined to be the lung (46.4%), kidney (13.1%), liver (9.5%), thyroid (8.3%), and prostate (4.8%). Five-year overall survival rate was 28.0%. Multiple bone metastases, distant organ metastasis, and multiple bone with organ metastases were the significant prognostic factors in univariate analysis. Multiple bone metastases remained significant after multivariate analysis ($P = 0.008$). Lung cancer is the most common site of primary cancer, and patients with multiple bone metastases have a poor prognosis, possibly due to disseminated cancer and a greater tumor burden.

Keywords: Neoplasm Metastasis; Neoplasms; Non-Spine; Diagnosis

INTRODUCTION

The most common sites for metastatic carcinoma are the lung, liver, and skeleton, respectively (1). Most patients presenting with metastasis of an unknown primary cancer have a poor prognosis and short life expectancy, possibly due to dissemination of the cancer and multi-organ failure. Metastasis is generally believed to occur late in the disease process, long after the primary disease has been identified (2); however, the reported incidence of metastasis as the initial manifestation of cancer is 3%-4%, with 10%-23% of these patients presenting with bone metastasis (1-4). While the primary cancer may be asymptomatic, the most common symptom of bone metastasis that causes the patient to seek treatment is localized bone pain. Plain radiography is somewhat limited in evaluating bone destruction, as 40%-50% of the trabecular bone must be destroyed before it becomes evident on imaging (5); accordingly, it usually takes some time to identify bone metastasis in an early stage and elicit a referral to an orthopedic oncologist. Hence, the search for the primary cancer often becomes the task of orthopedic surgeons, and a rational approach to this challenging clinical problem is needed (4).

Metastases to the pelvis and extremities occur less frequently than metastases to the spine, which accounts for up to 80% of skeletal metastases with unknown primary tumors at the time of presentation (1, 3). Most patients with metastasis to the spine are treated by a spine surgeon, while most patients with tumors of the pelvis or extremities are treated by orthopedic oncologists. Though the frequency is relatively low, patients with non-spine metastasis have similar difficulties with respect to normal work and sleeping problems (6). While there are many reports on bone metastases of unknown origin regardless of the site of metastases (3-5, 7-11), little data has been published focusing on non-spine bone metastasis as an initial presentation of cancer based on Korean population for reference by primary physicians and orthopedic surgeons.

Therefore, we determined 1) clinicopathologic characteristics and clinical importance of patients who presented with non-spine bone metastasis as an initial manifestation of cancer, and 2) process by which the diagnosis of primary cancer was made.

MATERIALS AND METHODS

The medical records of 378 patients who were referred to our institute between 1989 and 2012 for bone metastases with unknown primary cancer sites at the time of initial presentation were retrospectively analyzed. To construct a homogeneous study group, the following exclusion criteria were applied: 1)

patients who had a remote history of cancer with bone metastasis (n = 22), 2) patients who presented with spinal metastasis as their initial symptom (n = 226), 3) insufficient information from the medical record (n = 17), and 4) hematologic malignancies (n = 29). Eighty-four patients remained for analysis after the exclusion criteria were applied. The clinical information reviewed in our study included age, sex, initial presentation symptoms, the location of the primary cancer, the diagnostic modalities used to identify the primary cancer, the time to identification of the primary cancer, and the oncologic outcome at the last follow-up. We also evaluated radiographs of the bone metastases at the initial presentation.

We included 56 men and 28 women, with a mean age of 59.1 yr (range: 25.3-85.6 yr); 92.9% of patients were over 40 yr of age. The average follow-up period was 20.8 months (range: 1-120 months).

Although our institution did not have a standard protocol for identifying the primary cancer in patients with bone metastasis with an unknown primary site, a chest radiograph, basic laboratory studies, and computed tomography (CT) or magnetic resonance imaging of the metastatic lesion were obtained in all patients. Clinical tests were performed according to the clinical suspicion from the patient history, physical examination findings, and results from subsequent diagnostic evaluations.

A chi-square or Fisher's exact test was performed for comparisons of proportions, and a Student's t-test was performed for comparisons of continuous variables. Kaplan-Meier analysis was used to describe survival experience in this study population, and a log rank test was used to compare survival functions. We utilized a Cox proportional hazards model to determine factors associated with mortality. Analysis was performed using the SPSS for Windows statistical package (version 19.0; SPSS Inc., Chicago, IL, USA), and significance was set at a P value < 0.05.

Ethics statement

The study protocol was approved by the institutional review board of Seoul National University Hospital (IRB No. H-1307-059-503). Informed consent was waived by the board.

RESULTS

The most common initial symptom was pain at the affected site (94.0% of patients) (Table 1). The 3 most common sites of bone metastasis were the femur, pelvis, and humerus. These 3 sites accounted for approximately 92% of the total bone metastases when the primary cancer site was unknown. By radiographical imaging, 77.4% of bony lesions were osteolytic metastases, and pathologic fracture was present in 26.2% of patients. On average, it took 4.6 months (range: 0-84 months) from the onset of symptoms to referral to an orthopedic oncologist, and the presence of pathologic fracture did not significantly shorten the time interval (P = 0.320). Seven patients had a history of remote cancer, which showed no evidence of disease at the latest follow-up and was not the cause of the bone metastasis at the time of presentation (Table 2). We identified the primary cancer in 74 cases (94.0%) (Table 3), with an average time to identification of the primary cancer of 0.3 months (range 0.1-4.0 months). In 5 patients, no primary cancer was detected by the end of follow-

Table 1. Characteristics of patients at the initial presentation

Characteristics	No. (%) of patients
Sex	
Men	28 (33.3)
Women	56 (66.7)
Mean age (yr) (range)	59.1 (25.3-85.6)
Presentation symptom	
Pain	79 (94.0)
Mass	3 (3.6)
Incidental finding	2 (2.4)
Location	
Femur (n = 39)	39 (46.4)
Proximal	32 (38.1)
Shaft	5 (5.9)
Distal	2 (2.4)
Pelvis (n = 29)	29 (34.5)
Acetabulum	11 (13.1)
Pubic ramus	8 (9.5)
Ilium	4 (4.7)
Sacrum	2 (2.4)
Ischium	1 (1.2)
Sacroiliac joint	3 (3.6)
Humerus	9 (10.7)
Proximal	7 (8.3)
Shaft	1 (1.2)
Distal	1 (1.2)
Scapula	3 (3.6)
Proximal Tibia	2 (2.4)
Proximal Fibula	1 (1.2)
Clavicle	1 (1.2)
Radiologic appearance	
Osteolytic	65 (77.4)
Osteoblastic	7 (8.3)
No bony abnormality	6 (7.1)
Mixed	6 (7.1)
Unplanned procedure	
No	80 (95.2)
Yes	4 (4.8)
Total	84 (100)

Table 2. Patients with previous history of cancer

	Sex	Age (yr)	Previous cancer			Current cancer
			Diagnosis	Treatment	Status	
1	M	60	Gastric cancer	Gastrectomy, 15 YA	NED	Lung
2	M	61	Gastric cancer	Gastrectomy, 10 YA	NED	Kidney
3	F	35	Meningioma	Tumorectomy, 10 YA	NED	Unknown
4	F	64	Thyroid cancer	Thyroidectomy, 1.5YA	NED	Lung
5	M	64	Gastric cancer	Gastrectomy, 2.5 YA	NED	Lung
6	F	60	Cervix cancer	Hysterectomy, 23YA	NED	Lung
7	F	60	Lung cancer	Pneumonectomy, 20YA	NED	Unknown

NED, no evidence of disease; YA, years ago; RT, radiation therapy; HT, hormonal therapy.

Table 3. Distribution of primary tumors

Organs	No. (%) of patients
Lung	39 (46.4)
Kidney	11 (13.1)
Liver	8 (9.5)
Thyroid	7 (8.3)
Unknown primary	5 (6.0)
Prostate	4 (4.8)
Breast	3 (3.6)
Colon	3 (3.6)
Esophagus	2 (2.4)
Cholangiocarcinoma	1 (1.2)
Endometrium	1 (1.2)
Total	84 (100)

Table 4. Diagnostic modalities to identify primary tumor

Diagnostic methods	No. performed
Lung	
Chest radiograph	21
Chest CT	16
Bronchoscopy	1
Bone biopsy	1
Kidney	
Abdomen CT	11
Liver	
Abdomen CT	7
Abdomen sonography	1
Thyroid	
Bone biopsy	6
Neck CT	1
Prostate	
PSA and TRUS	4

CT, computed tomography; PSA, prostate specific antigen; TRUS, trans-rectal ultrasound.

up. The lung was the most frequent primary cancer site, accounting for 46.4% of primary cancers.

Approximately 53.8% of lung cancers were identified by plain radiograph. A CT revealed a carcinoma of the lung that was not seen on the plain radiograph in an additional 41% of cases (Table 4). CT of the abdomen revealed 18 sites of primary cancers: 11 patients had a carcinoma of the kidney, and 7 had carcinoma of the liver. A bone scan was performed in 46 cases, and we observed hot uptake lesions or photon defect at bone metastasis sites. Whole body fluorodeoxyglucose (FDG) positron emission tomography (PET) was performed in 41 cases, and hypermetabolic lesions at the primary site were found in 87.8% of cases. However, PET could not determine any hypermetabolic lesions at the primary site in 2 cases with a thyroid carcinoma, 1 case with renal cell carcinoma, and 2 cases with unknown primary cancer. Pathological diagnosis was obtained in 97.6% of cases. Planned biopsy was performed in 71.4% of cases from the most eligible sites, and the rest of the tissue diagnosis was obtained through surgical biopsy at the time of operative treatment for bone metastases. Operative treatment was performed in 67.9% (n = 57) of cases for pathologic fracture (n = 20) or impending fracture (n = 37).

The overall 2- and 5-yr survival rates were 56.0% and 28.0%, respectively (Fig. 1A). Multiple bone metastases were observed in 65.5% of cases, and distant organ metastases in 51.2% of cases at the time of initial presentation (Table 5). Only 23.8% of patients had a solitary bone metastasis, and 76.2% of patients had multiple metastases. In univariate analysis, multiple bone metastases, distant organ metastasis, and multiple bone with organ metastases were the significant prognostic factors (Fig. 1B-D). In multivariate analysis, the presence of multiple bone metastases was significantly associated with low survival rate (hazard ratio: 2.80, 95% CI, 1.31-5.99, P = 0.008).

DISCUSSION

Most skeletal malignancies are metastatic lesions rather than

primary bone tumors, and the ratio between primary bone tumors and visceral metastases to the skeleton varies between 1:17 and 1:25 (8, 9). The skeleton is the third most common site of metastasis in terms of frequency and clinical effects, and as many as 60% of cancer patients are found to have bone metastases during autopsy (12). The type and site of the primary tumor is unknown in 3%-15% of all patients with metastatic carcinomas, and approximately 5%-20% of these patients present with skeletal metastases as the first detectable lesion (3, 7-9, 11). More than 90% of patients visit the hospital with skeletal pain at an affected site, and a difficult clinical scenario arises when an occasional patient with no prior cancer history presents to an orthopedic surgeon with a fracture that seems to be pathologic (4). If there is no fracture and the patient does not have a history of cancer, it may be difficult to identify bone metastasis. This is a challenge for primary physicians or orthopedic surgeons, because it is difficult to associate the pain with metastasis or the presence of cancer in patients with no known cancer, and bone metastases cannot be detected until they become evident on plain radiographs. This study is meaningful for investigating the clinicopathologic characteristics of these patients and process by which the diagnosis of primary cancer was made, especially in Korean.

Our study has several limitations. First, it was a retrospective study involving review of medical records. Due to the rarity of bone metastasis as the initial manifestation of cancer, it is not feasible to conduct prospective study with a large study population. Second, the patients included were treated over a long period of time; hence, the diagnostic modalities were not uniform. Finally, we excluded patients who initially presented with spine metastases which account for up to 80% of bone metastases (1). Therefore, our study may not describe the characteristics of whole patients who present with bone metastasis. However, we focused on non-spine bone metastases in order to provide rele-
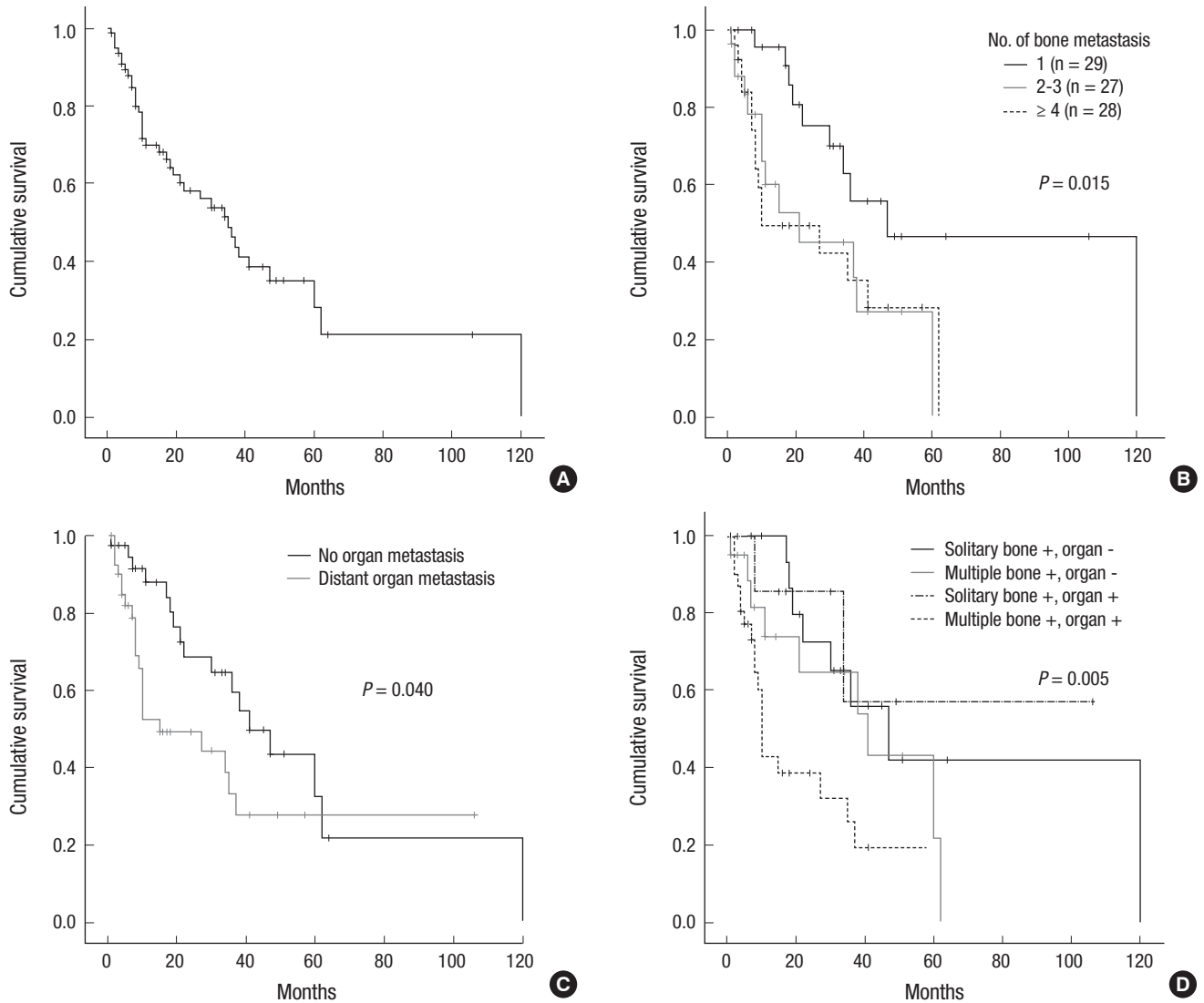
Fig. 1. Survival curves. (**A**) Overall survival of the 101 patients with bone metastasis from an unknown primary site is shown. (**B**-**D**) Survival by the metastatic status at the time of presentation are shown. In Fig. 1D, patients with multiple bone and organ metastases had a poorer prognosis than those with solitary bone metastasis ($P = 0.005$, log rank test).

Table 5. Profiles of metastasis

Status of metastasis	No. (%)	2-YSR
Bone metastasis		
Solitary	29 (34.5)	75.4%
Multiple	55 (65.5)	
2-3	27 (32.1)	45.1%
≥ 4	28 (33.3)	42.3%
Distant organ metastasis		
Absent	41 (48.8)	68.6%
Present	43 (51.2)	44.3%
Lung	11 (13.1)	
Liver	8 (9.5)	
Adrenal	5 (5.9)	
Spleen	4 (4.7)	
Lymph node	32 (38.1)	
Multiple metastasis*		
No	20 (23.8)	72.7%
Yes	64 (76.2)	32.3%

*Bone and distant organ metastasis were included. 2 YSR, 2 yr survival rate.

vant information to orthopedic surgeons, because non-spine bone metastases have not been the center of attention due to the relative rarity.

The age of the patients, the patterns of radiologic findings, and the distribution of the bone metastases within the non-axial skeleton were similar to those of other published reports (1, 2). We detected the primary cancer site in 94.0% of patients, which is higher than previous reports of 30%-90% (1, 4, 11). This is most likely due to improvements in various diagnostic modalities that enable surgeons to find small primary cancers. If present, breast and prostate cancers should be considered the most common cause of bone metastasis; however, if not present, the lung and kidney should be considered as the primary cancer site (3-5, 7-11). Our results confirm this pattern. Breast and kidney cancer metastasize easily to the bone and, when present, are common causes of bone metastasis. When no pre-

vious history of cancer was evident, the lung was the most common site of primary cancer, as reported previously (3-5, 7-11). Accessibility to clinical examinations, the efficacy of mammography or ultrasound, and the late dissemination of breast carcinoma are potential reasons why these 2 tumor types are detected before skeletal metastasis occurs. In contrast, lung and kidney cancers are deep-seated, lung cancer has the propensity to metastasize to the skeleton irrespective of tumor size, and delayed medical attention may explain the frequency of our result (1, 3, 7, 8, 10). About 17% of the primary cancers were in the gastrointestinal (GI) tract. This is relatively higher than the previous reports (4, 8, 11). Especially, the proportion of primary cancer in the liver was 9.5%, which is notable. Provided, our study population was based on only Asian, therefore, locations of primary cancers may be different. We found 7 patients with a history of remote cancer that was unrelated to the bone metastasis of interest. We suggest that these patients need to be examined with caution, as Destombe et al. (11) reported, because the assumption of a link between a bone metastasis and a primary cancer in the remote past can lead to serious mistakes in patient management, especially when there has been a long time interval or no evidence of the previous cancer during the latest follow-up.

Similar to previous studies, we did not have a standard protocol in place to identify the primary cancer in patients with bone metastasis from occult primary tumors (2-4, 7-11). While there have been many attempts to provide useful diagnostic strategies, there is currently no single, reliable diagnostic evaluation to detect primary cancer that can be applied to every clinical situation. Detailed history taking, physical examination, basic laboratory tests (complete blood cell count and serum chemistry), radiologic tests, and biopsy of the most accessible bone metastasis are recommended when determining the primary cancer site (5, 7, 8, 13). We found that CT of the chest and abdomen was also very useful and were able to detect the 3 most common solid tumors: lung, kidney, and liver cancer, respectively.

Because lung cancer was the most common primary cancer, when patients do not have a recent cancer history, we suggest that plain radiograph and CT of the chest should be included as an initial evaluation. CT of the abdomen should not be done routinely, but is recommended to determine kidney or liver cancers when the evaluation of the chest reveals no primary cancer (4). Endoscopic examination of the gastrointestinal tract, CT of the pelvis, and gynecologic examination are not routinely recommended but may be necessary according to the presence of abnormal symptoms or physical findings as cancers from these sites were a rare cause of unknown primary cancer in our study. Other organ metastases can also be determined from CT of the chest and abdomen. A whole body PET scan was helpful in the detection of the primary cancer site, multiple bone metastases, and other organ metastasis in our study; however, we believe

that PET has a somewhat limited role because PET alone is not sufficient to differentiate primary cancer from a metastatic lesion. Hence, the routine use of PET is still controversial and more investigation is required (14-16). In our study, planned biopsy was performed in 71.4% of cases to identify the site of the primary cancer. Biopsies were not taken directly from the skeletal metastasis but from the most eligible site with the most accessible measures, such as bronchoscopy and percutaneous needle biopsy of the lung. Skeletal biopsy should be performed with caution because ill planned biopsy may jeopardize future skeletal reconstruction or limb salvage.

The impact of the identification of the primary tumor after skeletal metastasis on the patient's prognosis is debatable as the cancer has already reached stage IV. Previous reports claimed that diagnosis of an occult primary tumor rarely resulted in an improved prognosis or life expectancy for the patient (9, 11). However, we believe that identification of the primary cancer can have a positive impact on the quality of life and prognosis as life expectancy can be predicted and proper surgical options chosen (4, 10). In accordance with previous reports, patients with primary tumors of the lung typically had a very poor prognosis, whereas patients with kidney and thyroid carcinomas had a very long survival, especially if they have isolated skeletal metastasis at the time of presentation (2). Skeletal reconstruction is suggested for patients with a longer life expectancy, as it is durable and long lasting.

In summary, the lung is the most frequent primary cancer site when patients present with bone metastasis as the initial manifestation of cancer in our study. Many of them have multiple metastases, which is a poor prognostic factor, potentially due to disseminated cancer, greater tumor burden, and multiorgan failure.

DISCLOSURE

Each author certifies that he or she has no commercial associations (e.g., consultancies, stock ownership, equity interest, patent licensing arrangements, etc.) that might pose a conflict of interest with the article.

ORCID

Wanlim Kim *http://orcid.org/0000-0003-1544-7211*
Ilkyu Han *http://orcid.org/0000-0001-9841-3775*
Seungcheol Kang *http://orcid.org/0000-0002-0172-2721*
Sang A Lee *http://orcid.org/0000-0001-9006-4152*
Han-Soo Kim *http://orcid.org/0000-0002-6543-2598*

REFERENCES

1. Nottebaert M, Exner GU, von Hochstetter AR, Schreiber A. *Metastatic*

bone disease from occult carcinoma: a profile. *Int Orthop* 1989; 13: 119-23.

2. Rougraff BT. *Evaluation of the patient with carcinoma of unknown origin metastatic to bone. Clin Orthop Relat Res* 2003; 415 Suppl: S105-9.

3. Barón MG, de la Gándara I, Espinosa E, de Paredes ML, Zamora P, Mondéjar JL. *Bone metastases as the first manifestation of a tumour. Int Orthop* 1991; 15: 373-6.

4. 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: 1276-81.

5. Riccio AI, Wodajo FM, Malawer M. *Metastatic carcinoma of the long bones. Am Fam Physician* 2007; 76: 1489-94.

6. Zeng L, Chow E, Zhang L, Culleton S, Holden L, Jon F, Khan L, Tsao M, Barnes E, Danjoux C, et al. *Comparison of pain response and functional interference outcomes between spinal and non-spinal bone metastases treated with palliative radiotherapy. Support Care Cancer* 2012; 20: 633-9.

7. Simon MA, Karluk MB. *Skeletal metastases of unknown origin: diagnostic strategy for orthopedic surgeons. Clin Orthop Relat Res* 1982; 166: 96-103.

8. Simon MA, Bartucci EJ. *The search for the primary tumor in patients with skeletal metastases of unknown origin. Cancer* 1986; 58: 1088-95.

9. Jacobsen S, Stephensen SL, Paaske BP, Lie PG, Lausten GS. *Skeletal metastases of unknown origin: a retrospective analysis of 29 cases. Acta Orthop Belg* 1997; 63: 15-22.

10. Katagiri H, Takahashi M, Inagaki J, Sugiura H, Ito S, Iwata H. *Determining the site of the primary cancer in patients with skeletal metastasis of unknown origin: a retrospective study. Cancer* 1999; 86: 533-7.

11. Destombe C, Botton E, Le Gal G, Roudaut A, Jousse-Joulin S, Devauchelle-Pensec V, Saraux A. *Investigations for bone metastasis from an unknown primary. Joint Bone Spine* 2007; 74: 85-9.

12. Berrettoni BA, Carter JR. *Mechanisms of cancer metastasis to bone. J Bone Joint Surg Am* 1986; 68: 308-12.

13. Tsukushi S, Katagiri H, Kataoka T, Nishida Y, Ishiguro N. *Serum tumor markers in skeletal metastasis. Jpn J Clin Oncol* 2006; 36: 439-44.

14. Hoshi M, Taguchi S, Hayakawa K, Ieguchi M, Nakamura H. *Evaluation of clinical problems associated with bone metastases from carcinoma from unknown primary sites. Arch Orthop Trauma Surg* 2011; 131: 59-64.

15. Kole AC, Nieweg OE, Pruim J, Hoekstra HJ, Koops HS, Roodenburg JL, Vaalburg W, Vermey A. *Detection of unknown occult primary tumors using positron emission tomography. Cancer* 1998; 82: 1160-6.

16. Sève P, Billotey C, Broussolle C, Dumontet C, Mackey JR. *The role of 2-deoxy-2-[F-18]fluoro-D-glucose positron emission tomography in disseminated carcinoma of unknown primary site. Cancer* 2007; 109: 292-9.