Review Article

Meta-analysis:

Comparison of F-18 Fluorodeoxyglucose-Positron Emission Tomography and Bone Scintigraphy in the Detection of Bone Metastasis in Patients with Lung Cancer

Ming-Che Chang, MD, Jin-Hua Chen, PhD, Ji-An Liang, MD, Cheng-Chieh Lin, MD, PhD, Kuang-Tao Yang, MD, Kai-Yuan Cheng, PhD, Jun-Jun Yeh, MD, Chia-Hung Kao, MD

Rationale and Objectives: The aim of this review was to evaluate the diagnostic properties of ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) or PET/computed tomography (CT) and bone scintigraphy in the detection of osseous metastases in patients with lung cancer.

Materials and Methods: MEDLINE was searched for relevant original articles published between January 1995 and August 2010. Inclusion criteria were as follows: FDG-PET or PET/CT and bone scintigraphy was carried out to detect bone metastases in patients with lung cancer, sufficient data were presented to construct a 2 × 2 contingency table, and histopathologic analysis and/or close clinical and imaging follow-up and/or radiographic confirmation by multiple imaging modalities was used as the reference standard. Two reviewers independently extracted data related to research design, sample size, imaging techniques, technical characteristics, reference standards, methods of imaging interpretation, and totals of true-positives, false-positives, true-negatives, and false-negatives. Stata was used to obtain per patient and per lesion pooled estimates of sensitivity, specificity, and positive and negative likelihood ratios, and areas under summary receiver-operating characteristic curves (AUCs) were calculated.

Results: The pooled patient-based sensitivity of FDG-PET or PET/CT was 0.93 (95% confidence interval [CI], 0.88–0.96), specificity was 0.95 (95% CI, 0.91–0.98), and the AUC was 0.94. The pooled sensitivity of bone scans was 0.87 (95% CI, 0.79–0.93), specificity was 0.82 (95% CI, 0.62–0.92), and the AUC was 0.91. The pooled lesion-based sensitivity of FDG-PET or PET/CT was 0.93 (95% CI, 0.84–0.97), specificity was 0.91 (95% CI, 0.80–0.96), and the AUC was 0.97. The pooled sensitivity of bone scans was 0.92 (95% CI, 0.87–0.95), specificity was 0.57 (95% CI, 0.09–0.95), and the AUC was 0.92.

Conclusions: Although FDG-PET or PET/CT has higher sensitivity and specificity than bone scintigraphy, further research with a less biased design is needed to determine the most efficacious imaging modality for the detection of metastatic lung cancer.

Key Words: Lung cancer; bone scan; bone scintigraphy; FDG-PET; bone metastasis.

Lung cancer is the most commonly diagnosed form of cancer as well as the leading cause of cancer death in men. Among women, lung cancer is the fourth most commonly diagnosed cancer and the second leading cause of cancer death (1). A typical staging system includes the assessment of primary tumor characteristics, detection of lymph node metastasis, and detection of distant metastases to determine the treatment regimen for lung cancer. Historically, 30% to 40% of patients with advanced lung cancer have developed bone metastasis (2). Curative surgical resection is impossible in these late-stage patients. Alternatively, chemoradiotherapy, chemotherapy, targeted therapy, or best supportive care is considered advisable (3,4). Furthermore, with the development of newer, more sensitive screening and imaging technologies, the proportion of late-stage patients is expected to increase following initial implementation.

Osseous metastases in lung cancer are typically detectable via bone scintigraphy (BS), because of its high sensitivity and ability to survey the entire skeleton quickly at a relatively low cost. The uptake of skeletal-seeking radiotracers depicts osteoblastic activity and regional blood flow to bone. However, the specificity of BS is lowered by benign processes such as osteoarthritis, fractures, and inflammation. Suspicious

Acad Radiol 2012; 19:349–357

From the Nuclear Medicine Department, Changhua Christian Hospital, Changhua, Taiwan (M.-C.C., K.-T.Y.); the Institute of Radiological Science, Central Taiwan University of Science and Technology, Taichung, Taiwan (M.-C.C., K.-Y.C.); the Biostatistics Center and Graduate Institute of Biostatistics (J.-H.C.) and Institute of Clinical Medicine Science and School of Medicine (J.-A.L., C.-C.L., J.-J.Y., C.-H.K.), China Medical University, Taichung, Taiwan; the Department of Radiation Oncology (J.-A.L.), Department of Family Medicine (C.-C.L.), and Department of Nuclear Medicine and PET Center (C.-H.K.), China Medical University Hospital (J.-J.Y.), Taichung, Taiwan; the Department of Healthcare Administration (C.-C.L.), College of Health Science, Asia University, Taichung, Taiwan; and Pingtung Christian Hospital and Mei-ho University (J.-J.Y.), Pingtung, Taiwan. Received April 27, 2011; accepted October 13, 2011. This study was supported by grants DMR-98-050 and DMR-98-051 provided by the authors' hospital and by the Taiwan Department of Health Clinical Trial and Research Center for Excellence (grant DOH100-TD-B-111-004) and the Taiwan Department of Health Cancer Research Center for Excellence (grant DOH100-TD-C-111-005). Drs Chang and Chen contributed equally to this work. **Address correspondence to:** J.-J.Y. e-mail: d10040@mail.cmuh.org.tw

doi:10.1016/j.acra.2011.10.018

abnormalities identified on BS generally require further investigation using x-ray, computed tomography (CT), magnetic resonance imaging, or biopsy for confirmation.

In recent years, ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT has been used increasingly for staging and restaging of various malignancies, including lung cancer (5,6). FDG-PET has been shown to have high sensitivity and specificity in the detection of local and distant neoplastic processes, including osseous metastasis (7,8). However, differences in the efficacy between FDG-PET and BS in the detection of osseous metastasis in patients with lung cancer have not been clearly delineated. The aim of this meta-analysis was to compare the diagnostic accuracy of FDG-PET to that of BS for the detection of osseous metastasis in patients with lung cancer.

MATERIALS AND METHODS

Literature Search

A search of the biomedical literature was performed by two researchers (M.-C.C. and C.-H.K.), working independently and using the MEDLINE, EMBASE, and Cochrane search engines to identify studies involving human subjects. Each researcher covered the period from January 1995 to August 2010. They used the following search string: ("PET" OR "positron emission tomography" OR "FDG" OR "fluorodeoxyglucose" OR "bone scan" OR "bone scintigraphy") AND ("lung cancer" OR "lung neoplasm" OR "lung carcinoma" OR "carcinoma of lung") AND ("sensitivity" OR "specificity" OR "false negative" OR "false positive" OR "diagnosis" OR "detection" OR "accuracy") AND ("recurrence" OR "bone metastasis"). An additional manual search was performed using references from the retrieved articles. Study authors were not contacted to identify additional studies. A total of 138 potential studies were retrieved from this search.

Selection of Studies

Disagreements were resolved by consensus. The inclusion criteria were as follows: (1) studies were reported in the English language; (2) they evaluated patients with lung cancer of all ages in any stage of disease, regardless of treatment status; (3) bone metastasis findings were confirmed with CT, magnetic resonance imaging, or bone biopsy with clinical follow-up > 6 months; and (4) the two imaging modalities (FDG-PET and BS) were performed within 3 months of each other. Studies were excluded on the basis of the following criteria: (1) only FDG-PET or bone scanning was performed; (2) the total numbers of true-positives, false-positives, true-negatives, and false-negatives were not provided; and (3) no data from subanalyses were provided. On the basis of these criteria, seven studies were eligible for this study.

Data Extraction

The reviewers independently assessed the methodologic quality of the selected studies. The reviewers used the criteria list recommended by the Cochrane Methods Working Group on Systematic Review of Screening and Diagnostic Tests. A number of items on the list were modified for this specific review (Table 1). Internal validity (IV) criteria were scored as "positive" (adequate methods), "negative" (inadequate methods, potential bias), or "unclear" if insufficient information has been provided on a specific item. External validity (EV) criteria evaluated generalizability. Standard performance of FDG-PET or PET/CT was scored positive when the type of PET or PET/CT camera, the dose of FDG, the time between injection and scanning, and the method of reconstruction were described. The criteria for EV were scored positive if sufficient information was provided to judge generalizability of findings. Following the consensus meeting, it was decided to mark unclear scores as negative. Agreement between both reviewers was quantified using Cohen's κ. Quality scores were expressed as percentages of the maximum score. Subtotals were calculated for IV (maximum, 6) and EV (maximum, 6) separately.

Statistical Analysis

Data on the sensitivity, specificity, positive predictive value, and negative predictive value of FDG-PET or PET/CT in the detection of bone metastasis were calculated from the original numbers provided in the publications. The data sets were pooled by adding the true-positive, false-positive, true-negative, and false-negative results from all relevant studies to determine the summary sensitivity and specificity of the combined data using the bivariate mixed-effect model regression approach, and the corresponding 95% confidence intervals were also established. When estimation of mean sensitivity and specificity for individual studies provided at least one zero cell, a correction of one half was added to every cell in that study to ensure the definition of the estimators. We showed the data as forest plot of sensitivity and specificity and constructed summary receiver-operating characteristic curves from the bivariate random-effects model for the logit transforms of sensitivity and specificity between studies. The area under the curve (AUC) could be used to determine the accuracy of screening tools.

Exploring heterogeneity other than the threshold effect was performed using I^2 statistics, measuring the degree of heterogeneity between studies. A higher value indicated a higher degree of heterogeneity. Heterogeneity due to the threshold effect was investigated using Spearman's correlation coefficient. In these studies, heterogeneity from the threshold effect was nonexistent except lesion based with FDG-PET or PET/CT. We attempted to detect the source of heterogeneity by meta–regression analysis. We performed Begg's test, Egger's test, and funnel plots to explore possible publication bias. In this study, .05 was the significance level. Statistical

TABLE 1. Criteria Used to Assess the Methodologic Quality of the Studies

Criteria of Validity	Positive Score
Internal validity	
1. Valid reference test	Additional radiography, CT, MRI, biopsy, or follow-up
2. Blind measurement of BS, FDG-PET, or PET/CT without knowledge of reference test results	
3. Blind measurement of reference test without knowledge of results of BS, FDG-PET, or PET/CT	
4. Avoidance of verification bias	Assessment by reference test independent of results of FDG-PET or PET/CT
5. BS, FDG-PET, or PET/CT interpreted independently of all clinical information	Mentioned in publication
6. Prospective study	Mentioned in publication
External validity	
1. Spectrum of disease	Primary stage of disease
2. Demographic information	Age and sex information given
3. Inclusion criteria	Mentioned in publication
4. Exclusion criteria	Mentioned in publication
5. Avoidance of selection bias	Consecutive series of patients
6. Standard execution of BS, FDG-PET, or PET/CT	Type of camera, dose of FDG, time interval, reconstruction

BS, bone scintigraphy; CT, computed tomography; FDG, ^{18}F-fluorodeoxyglucse; MRI, magnetic resonance imaging; PET, positron emission tomography.

analysis was performed with Stata version 11 (StataCorp LP, College Station, TX) using the "midas9" command (9).

RESULTS

Literature Search

Figure 1 shows the flow diagram of the literature search. A total of 138 studies were identified in the initial search. After reviewing titles and abstracts, 125 studies were excluded. The excluded studies included reviews, case reports, studies not related to lung cancer, studies analyzing multiple forms of cancer, or studies not using both FDG and BS tracers. Of the remaining 13 studies, the data of one study did not describe the time interval between FDG-PET and BS, three studies were not reported in English, and two were excluded because of insufficient information to construct a 2×2 table. Seven studies met the inclusion criteria and met none of the exclusion criteria (10–16).

The characteristics of the retrieved studies are presented in Table 2. Six studies were retrospective cohort studies (10–15), and one study was a prospective cohort study (16). The scans in four studies were only FDG-PET (10–13), whereas three recent studies used PET/CT, providing not only computed tomographic attenuation correction but also anatomic correlation (14–16). One study used single-photon emission CT (SPECT) in addition to planar imaging (16). One study used ^{99m}Tc diphosphono-propane-dicarbon acid as a bone scan tracer (15), another study used ^{99m}Tc hydroxymethane diphosphonate (16), and the other studies used ^{99m}Tc methylene diphosphonate. Sample sizes in these studies ranged between 48 and 1000 patients. Six of the studies provided results on a per patient basis, totaling 1746 patients (10–12,14–16), and three studies provided results on a per lesion basis (12,13,16), comprising a total of 1263 lesions.

Methodologic Quality Assessment

Methodologic quality was assessed using 12 items for each of the seven selected studies. There was disagreement in 36 of the 84 scores, with a Cohen's κ value of 0.70. Main disagreements were related to questions IV3, IV4, IV5, and IV6. Disagreements were caused by reading error and differences in interpretation. The scores for IV and EV of the seven selected studies are presented in Table 3. All studies had valid reference tests. However, the reference tests were based in part on a comparison of initial and follow-up images (IV3), and verification bias could not be avoided in every study, because patients had been selected for assessment by the reference test according to the results of BS or FDG-PET or PET/CT (IV4). The interpretation of BS and FDG-PET or PET/CT was not independent of clinical information in all studies (IV5). Six of the seven studies were retrospective, and only one was a prospective study (IV6). The primary stage of the disease was described in five studies. In three studies, patients entered the study consecutively. The total score for the combined IV and EV, expressed as a fraction of the maximum score, ranged between 42% and 67%, with a median of 58% (Table 3).

Diagnostic Accuracy of FDG-PET or PET/CT

Figures 2 to 5 illustrate sensitivity, specificity, and their 95% confidence intervals for each enrolled study. Among the studies with patient-based data, the sensitivity of FDG-PET or PET/CT ranged between 88.9% and 96.0% (heterogeneity

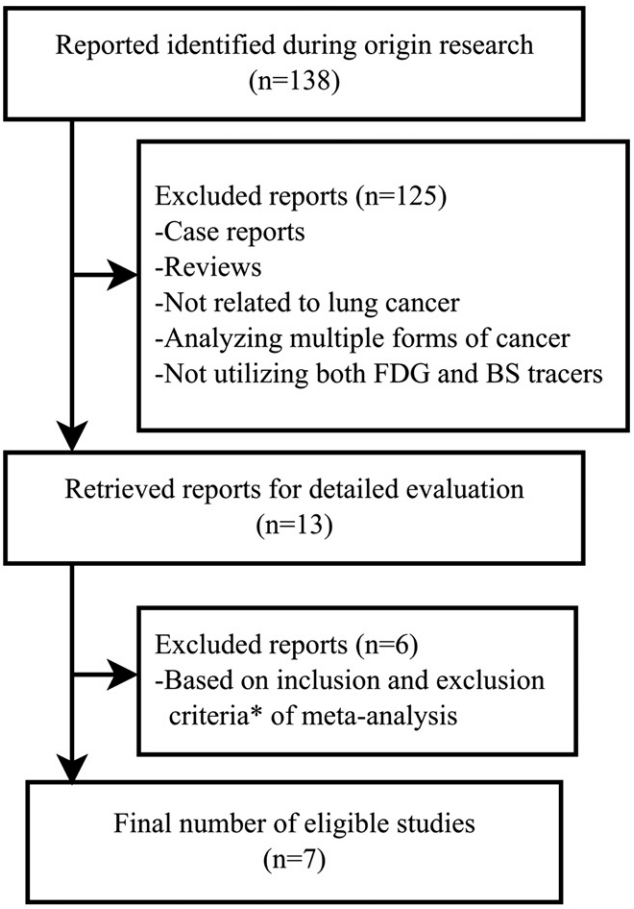

Figure 1. Selection of studies. *The inclusion criteria were as follows: (1) studies were reported in the English language; (2) they evaluated patients with lung cancer of all ages in any stage of disease, regardless of treatment status; (3) bone metastasis findings were confirmed with computed tomography, magnetic resonance imaging, or bone biopsy with clinical follow-up > 6 months; and (4) the two imaging modalities (^{18}F-fluorodeoxyglucose [FDG] positron emission tomography and bone scintigraphy [BS]) were performed within 3 months of each other. The exclusion criteria were as follows: (1) only FDG positron emission tomography or bone scanning was performed; (2) the total numbers of true-positives, false-positives, true-negatives, and false-negatives were not provided; and (3) no data from subanalyses were provided.

test P = .932). The homogeneity among studies was demonstrated by the I^2 value of 0%. Specificity ranged between 85.6% and 98.8% (heterogeneity test P < .001). There was a higher degree of heterogeneity among studies (I^2 = 91.5%). The pooled patient-based sensitivity for FDG-PET or PET/CT was 0.93, and specificity was 0.95. The AUC was 0.94. The high sensitivity and specificity translated into a positive summary likelihood ratio of 20 and a negative likelihood ratio of 0.07. The sensitivity of BS ranged between 75.4% and 96.0% (heterogeneity test P = .06). There was a moderate degree of heterogeneity among studies (I^2 = 52.56%). Specificity ranged between 44.1% and 97.1% (heterogeneity test P < .001). There was a higher degree of heterogeneity among studies (I^2 = 98.73%). The pooled sensitivity of BS was 0.87, and

TABLE 2. Characteristics of Studies Evaluating FDG-PET and BS for the Detection of Osseous Metastasis From Lung Cancer

Study	Year	Sample Size	Study Type	Data Type	PET Technique	BS Technique	Statistical Test	Notes
Buy et al (10)	1998	110	Retrospective cohort	Patient based	200–250 MBq FDG, uptake 60–90 min	20 mCi ^{99m}Tc diphosphonate, 4-h delay	—	
Hsia et al (13)	2002	48	Retrospective cohort	Lesion based	10 mCi (370 MBq) FDG, uptake 30–45 min	925 MBq ^{99m}Tc MDP, 2-h to 3-h delay	—	
Gayed et al (12)	2003	82	Retrospective cohort	Patient and lesion based	555 MBq FDG, uptake 60 min	1036–1110 MBq ^{99m}Tc MDP, 90-min to 120-min delay	Weighted average	
Cheran et al (11)	2004	257	Retrospective cohort	Patient-based	5.365 MBq/kg, maximum 20 mCi, uptake 30 min	430 μCi/kg (maximum 30.0 mCi) ^{99m}Tc MDP, 2-h to 3-h delay	McNemar	
Takenaka et al (16)	2009	115	Prospective cohort	Patient and lesion based	3.3 MBq/kg, uptake 60 min	555 MBq (15 mCi) ^{99m}Tc HMDP, 2-h delay	McNemar	PET/CT, whole-body SPECT performed
Song et al (15)	2009	1000	Retrospective cohort	Patient based	550 MBq, uptake 60 min	1110 MBq ^{99m}Tc DPD, 4-h to 6-h delay	McNemar	PET/CT
Min et al (14)	2009	182	Retrospective cohort	Patient based	0.14 mCi/kg FDG, uptake 60 min	35–40 mCi ^{99m}Tc MDP, 3-h delay	McNemar	PET/CT

BS, bone scintigraphy; CT, computed tomography; DPD, diphosphono-propane-dicarbon acid; FDG, ^{18}F-fluorodeoxyglucose; HMDP, hydroxymethane diphosphonate; MDP, methylene diphosphonate; PET, positron emission tomography; SPECT, single-photon emission computed tomography.

TABLE 3. Quality Assessment of the Seven Diagnostic Studies Included in the Present Review

Study	Year	IV Criteria						EV Criteria						Total IV Score	Total EV Score	% of Maximum Score
		IV1	IV2	IV3	IV4	IV5	IV6	EV1	EV2	EV3	EV4	EV5	EV6			
Bury et al (10)	1998	+	+	–	–	–	–	+	+	+	+	+	+	2	6	67
Hsia et al (13)	2002	+	–	–	–	–	–	+	+	+	+	–	+	1	5	50
Gayed et al (12)	2003	+	–	–	–	–	–	–	+	+	+	–	+	1	4	42
Cheran et al (11)	2004	+	–	–	–	–	–	+	+	+	+	+	+	1	6	58
Takenaka et al (16)	2009	+	+	–	–	–	+	–	+	+	+	+	+	3	5	67
Song et al (15)	2009	+	+	–	–	–	–	+	+	+	+	–	+	2	5	58
Min et al (14)	2009	+	+	–	–	–	–	+	+	+	+	–	+	2	5	58

EV, external validity; IV, internal validity; +, score 1; –, score 0.
The full total score was 12, and the percentage of the maximum score was calculated as (total IV score + total EV score)/12 × 100%.

specificity was 0.82. The AUC was 0.91. The estimate of the positive likelihood ratio was 5, and the corresponding negative likelihood ratio was 0.15.

Among the studies with lesion-based data, the sensitivity of FDG-PET or PET/CT ranged between 84.6% and 97.0%, and specificity ranged between 78.4% and 95.4%. The pooled lesion-based sensitivity for FDG-PET or PET/CT was 93.5%, and specificity was 91%. The AUC was 0.97. The estimated positive and negative likelihood ratios were 10 and 0.08, respectively. The sensitivity of BS ranged between 81.5% and 95.5%, and the specificity ranged between 6.3% and 95.0%. The pooled sensitivity for bone scans was 0.92, and specificity was 0.57. The AUC was 0.92. The corresponding positive and negative likelihood ratios were estimated at 2 and 0.14, respectively.

Assessment of Publication Bias and Study Heterogeneity

To assess publication bias, we used sensitivity (or specificity) and its standard error by Begg's test, Egger's test, and funnel plots (Figs 6 and 7). For the sensitivity of patient-based results on FDG-PET or PET/CT, *P* values were .4694 for Begg's test and .2781 for Egger's test, indicating that there was no evidence of publication bias. For the specificity of patient-based results on FDG-PET or PET/CT, *P* values were .0028 for Begg's test and .0083 for Egger's test, suggesting that there was publication bias. The results were the same for the sensitivity (or specificity) of patient-based results on BS. The cause of publication bias for specificity was large variation among studies. We did not confirm the true negative in nondisease in clinical. Another, the papers were included too few. Because only three pooling papers of FDG-PET or PET/CT and BS were in lesion based, we cannot analyze if there was the publication bias.

The sources of heterogeneity among studies included study populations, patient selection, clinical setting, disease severity, retrospective collection of data, and the specificities of index and reference tests (17). To determine the potential sources of heterogeneity, we used meta–regression analysis for patient-based results with FDG-PET or PET/CT and with BS. The variables were publication year (baseline, 1998), modality (PET/CT vs PET), sample size ($n > 150$ vs $n \leq 150$), and study design (reference group, prospective data) in the patient-based FDG-PET or PET/CT group. For patient-based BS studies, the variables included publication year, sample size, and study design. The covariates in the regression were all nonsignificant for both patient-based FDG-PET or PET/CT and BS (Table 4).

DISCUSSION

Bone metastasis is a poor prognostic factor for patients with lung cancer. Skeletal complications, such as bone pain, impaired mobility, hypercalcemia, pathologic fracture, spinal cord or nerve root compression, and bone marrow involvement result in a decline in the quality of life and eventual death. The treatment of bone metastasis in lung cancer remains a great challenge. The median survival is <6 months, and the 5-year survival rate is <5% (18). However, bone metastasis often goes undiagnosed because up to 40% of patients with proven bone metastases are asymptomatic, particularly in the early stage (19,20). The initiation of bone-targeting therapies may be delayed to prevent skeletal complications. Therefore, performing a routine survey of the entire skeletal system in patients with lung cancer would likely be helpful.

Before the development of FDG-PET, metastatic bone involvement was usually assessed by scintigraphy with bone-seeking ^{99m}Tc-labeled diphosphonates. Although FDG-PET or PET/CT has shown a high diagnostic yield in mediastinal staging of lung cancer and in the detection of metastasis (7,8), it remains unclear whether FDG-PET or PET/CT should supersede conventional BS as the primary diagnostic modality in patients with suspected osseous metastatic lung cancer.

The results of this meta-analysis indicate that FDG-PET or PET/CT has a high degree of diagnostic accuracy for the evaluation of bone metastasis in patients with lung cancer. Our patient-based studies demonstrated notably greater pooled sensitivity and specificity of FDG-PET or PET/CT than of BS. FDG-PET or PET/CT detects increases in the metabolic activity of tumor cells and is capable of detecting osseous metastatic disease at an earlier stage, even if it is limited

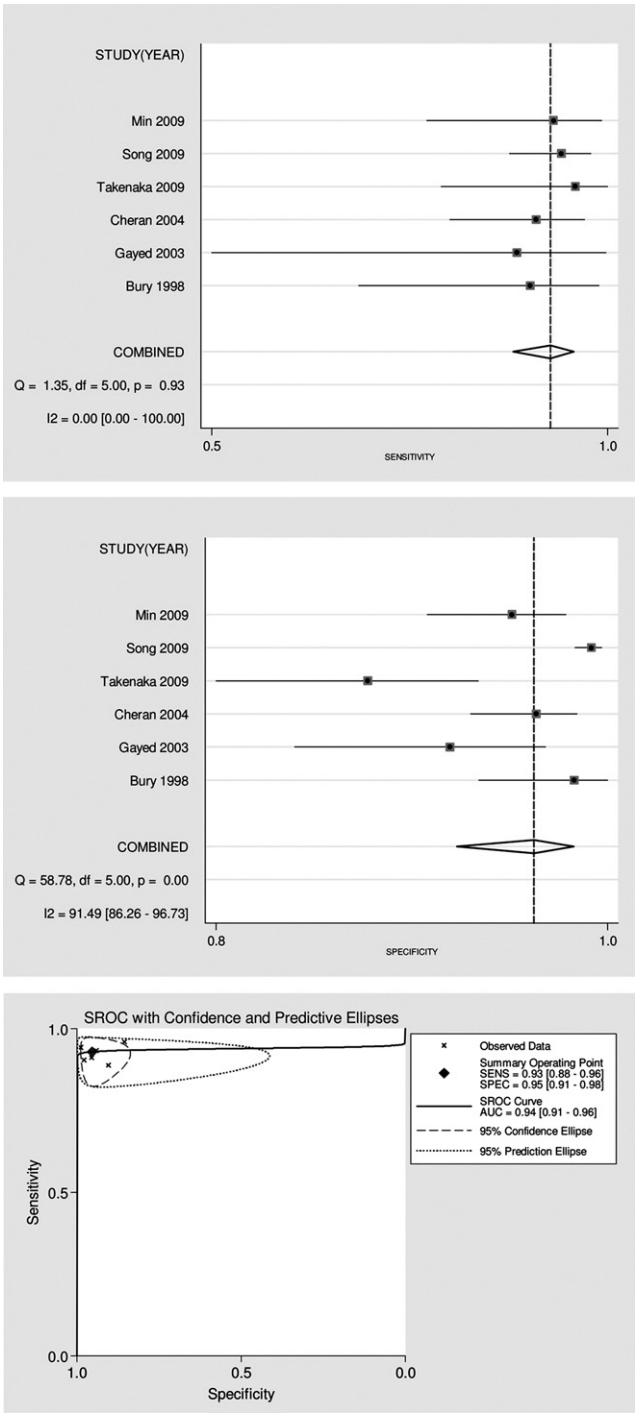

Figure 2. Individual study estimates of patient-based sensitivity and specificity of ^{18}F-fluorodeoxyglucose positron emission tomography (PET) or PET/computed tomography for the detection of bone metastasis in patients with lung cancer. AUC, area under the curve; SENS, sensitivity; SPEC, specificity; SROC, summed receiver-operating characteristic.

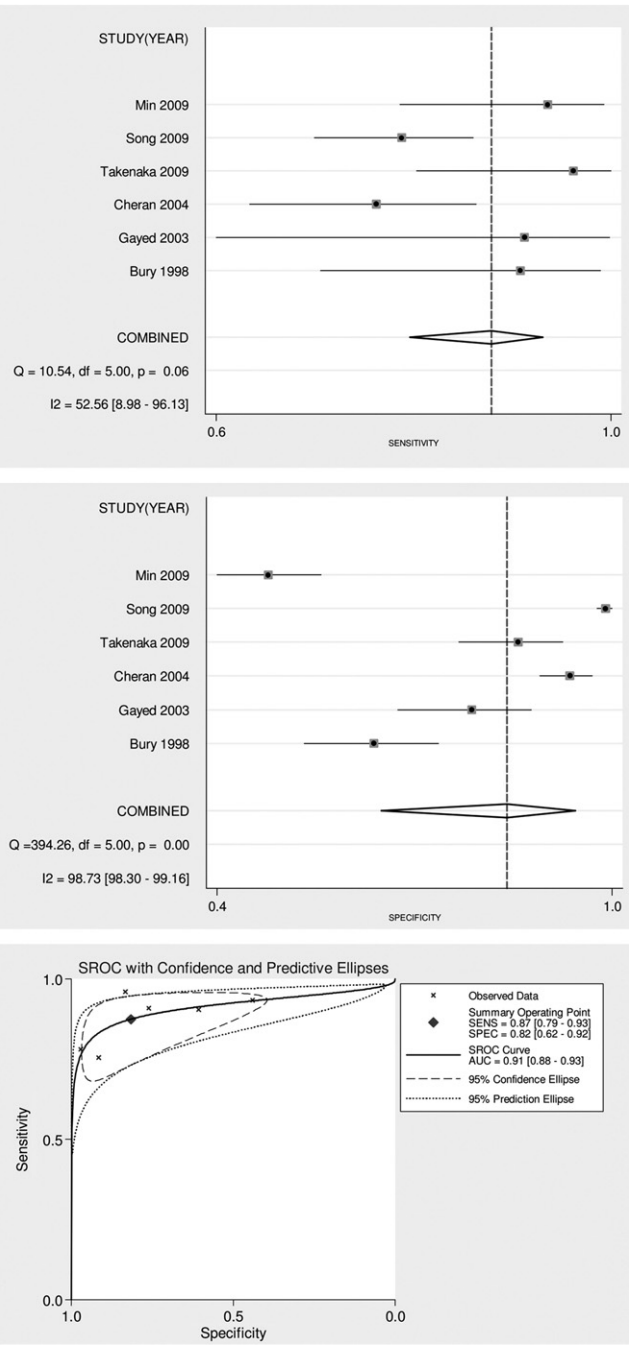

Figure 3. Individual study estimates of patient-based sensitivity and specificity of bone scintigraphy for the detection of bone metastasis in patients with lung cancer. AUC, area under the curve; SENS, sensitivity; SPEC, specificity; SROC, summed receiver-operating characteristic.

to the bone marrow, resulting in high pooled sensitivity and specificity (21,22). In addition, FDG-PET or PET/CT has better sensitivity and resolution and lower background than BS, which could also contribute to the diagnostic performance of FDG-PET or PET/CT. The mechanism behind the uptake of BS radiotracers depends primarily on blood flow and osteoblastic bone reaction to cancer cells. The higher prevalence of osteolytic lesions with no reactive osteoblastic reaction may demonstrate little or no uptake, lowering the sensitivity of BS (23,24). In a study by Song et al (15), 78.3% of the false-negatives on BS had osteolytic metastases on CT. In addition, the uptake mechanisms were not specific for metastases. Benign diseases may also increase bone

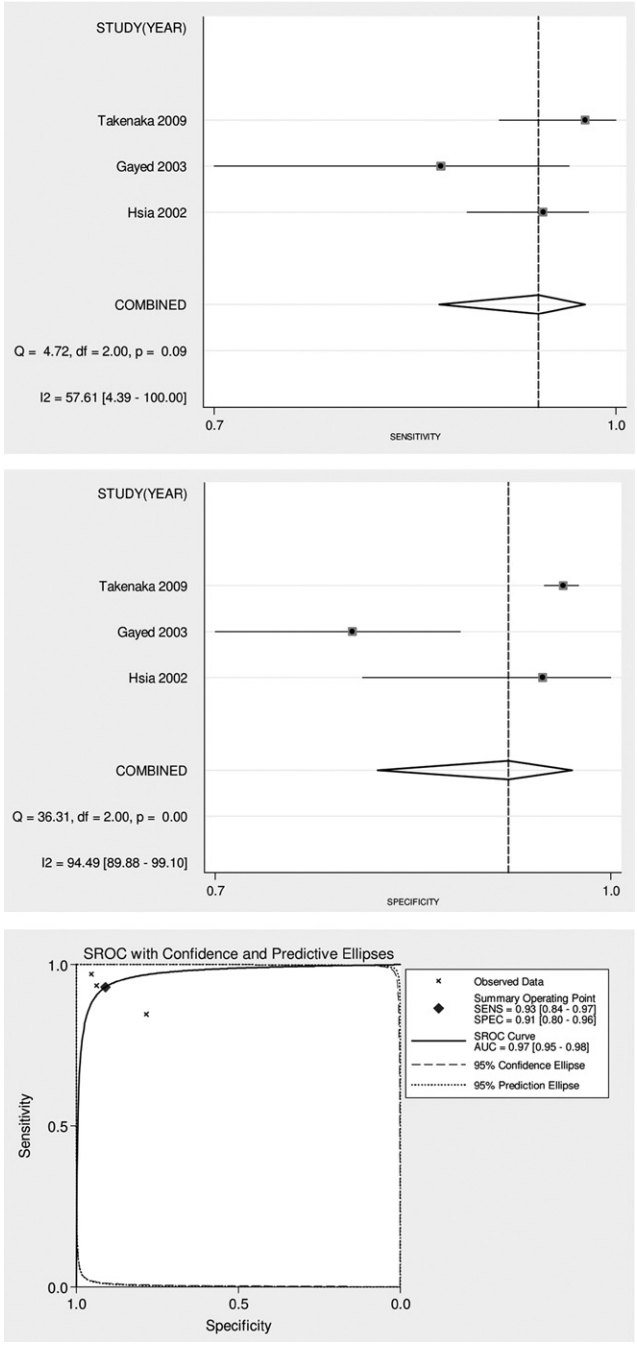

Figure 4. Individual study estimates of lesion-based sensitivity and specificity of ^{18}F-fluorodeoxyglucose positron emission tomography (PET) or PET/computed tomography for the detection of bone metastasis in patients with lung cancer. AUC, area under the curve; SENS, sensitivity; SPEC, specificity; SROC, summed receiver-operating characteristic.

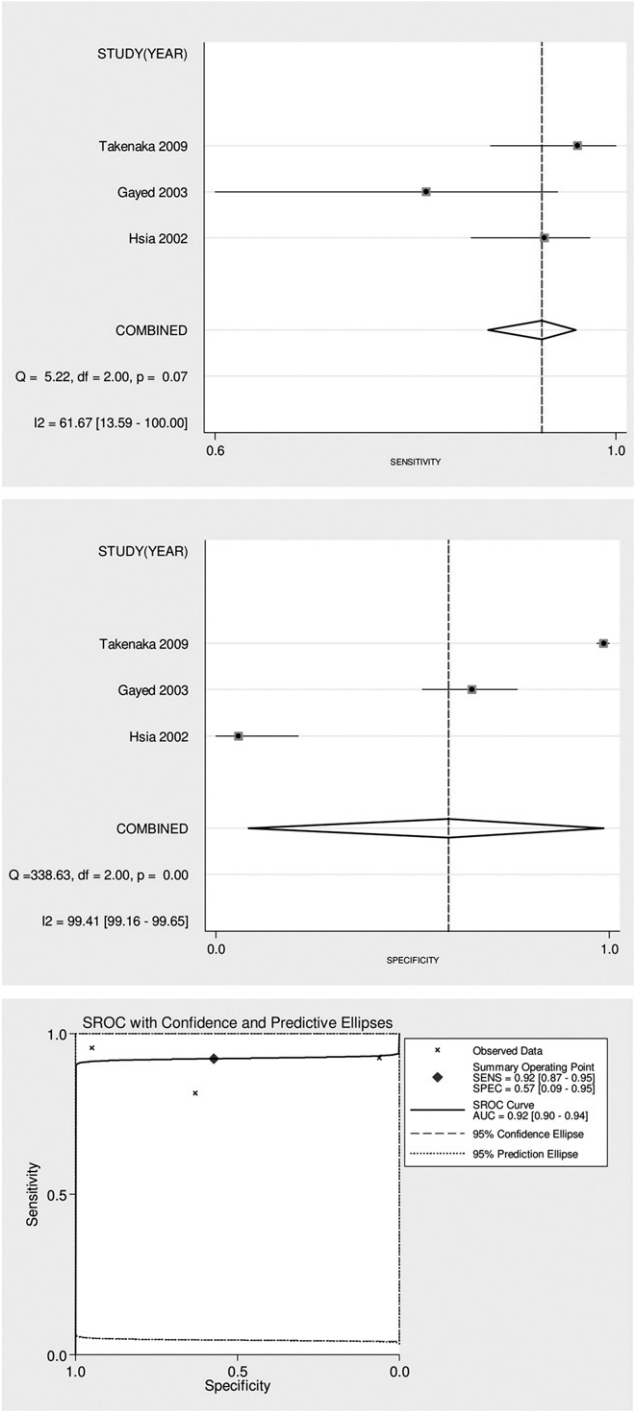

Figure 5. Individual study estimates of lesion-based sensitivity and specificity of bone scintigraphy for the detection of bone metastasis in patients with lung cancer. AUC, area under the curve; SENS, sensitivity; SPEC, specificity; SROC, summed receiver-operating characteristic.

turnover (degenerative change, inflammatory processes, and mechanical stress), causing false-positive findings on BS.

Interestingly, the lesion-based studies showed similar pooled sensitivity between FDG-PET or PET/CT and BS. This may be because routine planar BS examines complete whole-body bone metastasis, while the routine imaging field of FDG-PET or PET/CT extends from just above the orbits to the midthighs. Therefore, lesions beyond the imaging field lead to false-negative results in lesion-based analysis and possibly decrease the sensitivity of FDG-PET or PET/CT. However, we could not determine how many metastatic lesions were beyond the imaging field of view of PET in the seven studies. Nevertheless, once inoperable osseous

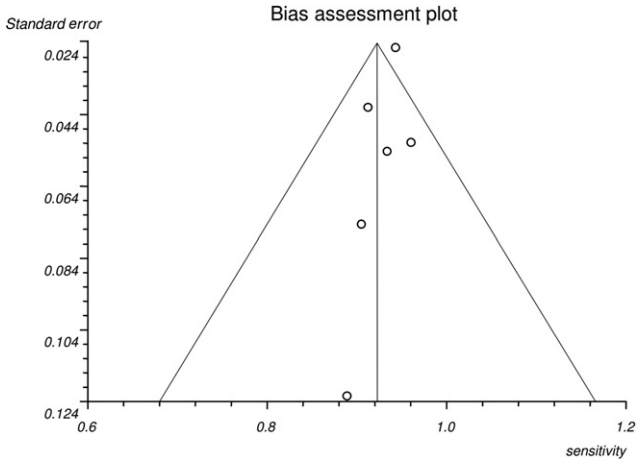

Figure 6. Funnel plot of sensitivity and standard error of patient-based positron emission tomography.

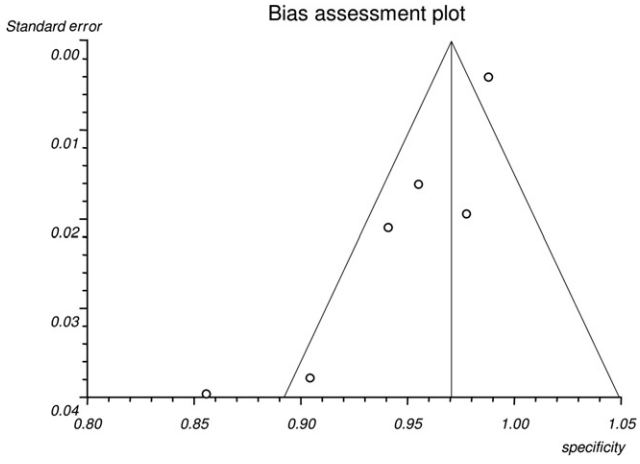

Figure 7. Funnel plot of specificity and standard error of patient-based positron emission tomography.

TABLE 4. Covariates of Metaregression Assessing Heterogeneity in Patient-based PET/CT or PET and BS

	Univariate	
Possible Confounder	Coefficient (Standard Error)	*P*
FDG-PET/CT or PET		
Year of publication	0.139 (0.0870)	.2082
PET/CT performance	1.073 (0.6131)	.1783
Sample size	0.406 (0.9030)	.6831
Study design	−2.343 (1.6923)	.2602
BS		
Year of publication	0.109 (0.0687)	.2106
Sample size	−0.721 (0.8697)	.4682
Study design	−1.958 (1.1954)	.2000

BS, bone scintigraphy; CT, computed tomography; FDG, ^{18}F-fluorodeoxyglucse; PET, positron emission tomography.

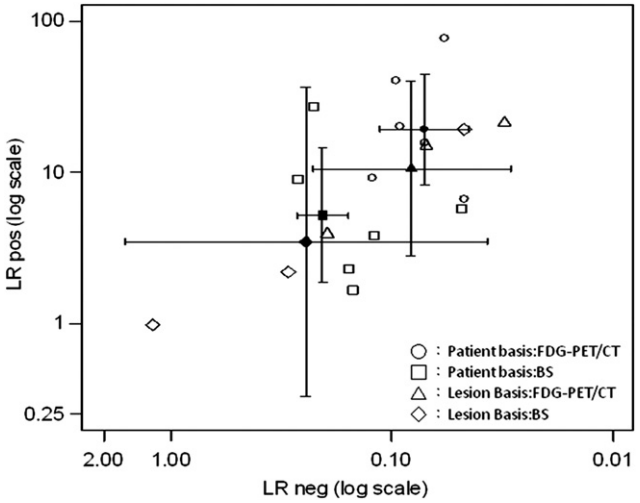

Figure 8. Likelihood ratio (LR) scatterplot of patient-based and lesion-based meta-analysis of ^{18}F-fluorodeoxyglucose positron emission tomography (PET) or PET/computed tomography (CT) and bone scintigraphy (BS). *Open symbols* represent individual studies. *Solid symbols* are summary likelihood ratios with related 95% confidence intervals. Both patient-based and lesion-based FDG-PET or PET/CT showed high sensitivity and high specificity. Patient-based and lesion-based BS had lower sensitivity and lower specificity.

metastatic disease is found, the absolute number of lesions seldom changes treatment plans. In this respect, FDG-PET or PET/CT had higher pooled sensitivity than BS in the patient-based subset. The supplement likelihood ratio scatterplot of the meta-analyses (Fig 8) shows that FDG-PET or PET/CT provides a reasonable shift in prior probability for both positive and negative findings in patient-based or lesion-based analyses. Bone scanning, however, has only weak power to confirm or exclude bone metastasis in patients with lung cancer.

There are several potential limitations to conducting a meta-analysis of diagnostic tests. First, the final metastatic status of a given site could not be pathologically diagnosed for every patient, because of patient discomfort, and in many cases, the results of the test would not change clinical management. Ethically, histopathologic correlation also could not be obtained for every lesion in every patient. On the other hand, even the absence of bone lesions on follow-up radiographic studies does not conclusively prove the absence of osseous metastases at the time of initial staging. These are common barriers to all studies assessing imaging procedures for diagnostic accuracy in the detection of distant metastases.

Second, meta-analysis often fails to account for verification or workup differences among studies. The presence of clinical heterogeneity (heterogeneity caused by the inclusion of patients at different stages of disease and other clinical characteristics, different imaging methodologies, and the methods of reference testing) influences the generalizability of the results. Verification bias originating through investigation was more likely in patients with initial positive results than negative results, and selection bias by retrospective study design in the majority of studies may also be present in the primary studies.

Third, only one study used SPECT in addition to planar BS. SPECT has been reported to greatly enhance anatomic localization and sensitivity in the detection of foci of tracer uptake (25). The sensitivity of SPECT in the diagnosis of bone metastasis is 90.5% to 100%, and its specificity is 92.8% to 95.3% (26). Using SPECT may improve diagnostic accuracy over that of planar BS. In a prospective study analyzing the clinical value of BS with or without SPECT and FDG-PET in 43 patients with small-cell lung cancer or locally advanced non-small-cell lung cancer, FDG-PET was the most accurate whole-body imaging modality for screening of bone metastasis. The investigators also concluded that routinely performed SPECT improves the accuracy of BS (27). Because FDG is the most common commercially available positron emission tomographic tracer, further investigation comparing planar and single-photon emission computed tomographic BS and 18F-FDG PET or PET/CT would be valuable.

CONCLUSIONS

The result of this meta-analysis is that FDG-PET or PET/CT has higher sensitivity and specificity than BS. Although further research in this area should be performed in a well-designed clinical trial to minimize bias, meta-analytic techniques are still very useful for demonstrating the significant role of FDG-PET or PET/CT in the detection of bone metastasis in patients with lung cancer.

REFERENCES

1. Jemal A, Bray F, Center MM, et al. Global cancer statistics. CA Cancer J Clin 2011; 61:69–90.
2. Coleman RE. Metastatic bone disease: clinical features, pathophysiology and treatment strategies. Cancer Treat Rev 2001; 27:165–176.
3. Leonard CT, Whyte RI, Lillington GA. Primary non-small-cell lung cancer: determining the suitability of the patient and tumor for resection. Curr Opin Pulm Med 2000; 6:391–395.
4. Park BJ, Louie O, Altorki N. Staging and the surgical management of lung cancer. Radiol Clin North Am 2000; 38:545–561.
5. Mittra E, Quon A. Positron emission tomography/computed tomography: the current technology and applications. Radiol Clin North Am 2009; 47: 147–160.
6. Poeppel TD, Krause BJ, Heusner TA, et al. PET/CT for the staging and follow-up of patients with malignancies. Eur J Radiol 2009; 70: 382–392.
7. MacManus M, Hicks RJ. The use of positron emission tomography (PET) in the staging/evaluation, treatment, and follow-up of patients with lung cancer: a critical review. Int J Radiat Oncol Biol Phys 2008; 72: 1298–1306.
8. Miele E, Spinelli GP, Tomao F, et al. Positron emission tomography (PET) radiotracers in oncology—utility of 18F-fluoro-deoxy-glucose (FDG)-PET in the management of patients with non-small-cell lung cancer (NSCLC). J Exp Clin Cancer Res 2008; 27:52.
9. Boston RC, Sumner AE. Stata: a statistical analysis system for examining biomedical data. Adv Exp Med Biol 2003; 537:353–369.
10. Bury T, Barreto A, Daenen F, et al. Fluorine-18 deoxyglucose positron emission tomography for the detection of bone metastases in patients with non-small cell lung cancer. Eur J Nucl Med 1998; 25:1244–1247.
11. Cheran SK, Herndon JE II, Patz EF Jr. Comparison of whole-body FDG-PET to bone scan for detection of bone metastases in patients with a new diagnosis of lung cancer. Lung Cancer 2004; 44:317–325.
12. Gayed I, Vu T, Johnson M, et al. Comparison of bone and 2-deoxy-2-[18F] fluoro-D-glucose positron emission tomography in the evaluation of bony metastases in lung cancer. Mol Imaging Biol 2003; 5:26–31.
13. Hsia TC, Shen YY, Yen RF, et al. Comparing whole body 18F-2-deoxyglucose positron emission tomography and technetium-99m methylene diophosphate bone scan to detect bone metastases in patients with non-small cell lung cancer. Neoplasma 2002; 49:267–271.
14. Min JW, Um SW, Yim JJ, et al. The role of whole-body FDG PET/CT, Tc 99m MDP bone scintigraphy, and serum alkaline phosphatase in detecting bone metastasis in patients with newly diagnosed lung cancer. J Korean Med Sci 2009; 24:275–280.
15. Song JW, Oh YM, Shim TS, et al. Efficacy comparison between (18)F-FDG PET/CT and bone scintigraphy in detecting bony metastases of non-small-cell lung cancer. Lung Cancer 2009; 65:333–338.
16. Takenaka D, Ohno Y, Matsumoto K, et al. Detection of bone metastases in non-small cell lung cancer patients: comparison of whole-body diffusion-weighted imaging (DWI), whole-body MR imaging without and with DWI, whole-body FDG-PET/CT, and bone scintigraphy. J Magn Reson Imaging 2009; 30:298–308.
17. Harbord RM, Deeks JJ, Egger M, et al. A unification of models for meta-analysis of diagnostic accuracy studies. Biostatistics 2007; 8: 239–251.
18. Coleman RE. Skeletal complications of malignancy. Cancer 1997; 80: 1588–1594.
19. Cowan RJ, Young KA. Evaluation of serum alkaline phosphatase determination in patients with positive bone scans. Cancer 1973; 32: 887–889.
20. Hirsh V. Skeletal disease contributes substantially to morbidity and mortality in patients with lung cancer. Clin Lung Cancer 2009; 10: 223–229.
21. Ak I, Sivrikoz MC, Entok E, et al. Discordant findings in patients with non-small-cell lung cancer: absolutely normal bone scans versus disseminated bone metastases on positron-emission tomography/computed tomography. Eur J Cardiothorac Surg 2010; 37:792–796.
22. Chen YW, Huang MY, Hsieh JS, et al. Discordant findings of skeletal metastasis between Tc 99m MDP bone scans and F18 FDG PET/CT imaging for advanced breast and lung cancers—two case reports and literature review. Kaohsiung J Med Sci 2007; 23:639–646.
23. Donato AT, Ammerman EG, Sullesta O. Bone scanning in the evaluation of patients with lung cancer. Ann Thorac Surg 1979; 27:300–304.
24. Kato H, Miyazaki T, Nakajima M, et al. Comparison between whole-body positron emission tomography and bone scintigraphy in evaluating bony metastases of esophageal carcinomas. Anticancer Res 2005; 25: 4439–4444.
25. Chua S, Gnanasegaran G, Cook GJ. Miscellaneous cancers (lung, thyroid, renal cancer, myeloma, and neuroendocrine tumors): role of SPECT and PET in imaging bone metastases. Semin Nucl Med 2009; 39:416–430.
26. Savelli G, Maffioli L, Maccauro M, et al. Bone scintigraphy and the added value of SPECT (single photon emission tomography) in detecting skeletal lesions. Q J Nucl Med 2001; 45:27–37.
27. Schirrmeister H, Glatting G, Hetzel J, et al. Prospective evaluation of the clinical value of planar bone scans, SPECT, and (18)F-labeled NaF PET in newly diagnosed lung cancer. J Nucl Med 2001; 42:1800–1804.