RESEARCH ARTICLE

A Systematic Review of MRI, Scintigraphy, FDG-PET and PET/CT for Diagnosis of Multiple Myeloma Related Bone Disease - Which is Best?

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Abstract

Aim: The purpose of the current study was to conduct a systematic review of the published literature to evaluate the diagnostic accuracy of FDG-PET, PTE/CT, MRI and scintigraphy for multiple myeloma related bone disease. Methods: Through a search of PubMed, EMBASE, and the Cochrane Library, two reviewers independently assessed the methodological quality of each study. We estimated pooled sensitivity, specificity, positive and negative likelihood ratios (PLR and NLR), and two sample Z-tests were conducted to evaluate for differences in sensitivity, specificity, area under the curve (AUC), and the Q* index between any two diagnostic modalities. Results: A total of 17 studies were reviewed. The MRI had a pooled sensitivity of 0.88, specificity of 0.68, AUC of 0.897, and Q*index of 0.828, whereas for MIBI, the corresponding values were 0.98, 0.90, 0.991, and 0.962, respectively, and for bone scan, they were 066, 0.83, 0.805, and 0.740, respectively. The corresponding values of MIBI were 0.98, 0.90, 0.991, and 0.962, respectively. For PET and PET/CT, the values were 0.91, 0.69, 0.927 and 0.861, respectively. Statistically significant differences were not found in the sensitivity, specificity, AUC, and Q* index between MRI, scintigraphy, FDG-PET and PET/CT. Conclusions: On the condition that X ray is taken as a reference in our study, we suggested that FDG-PET, PTE/CT, MRI and scintigraphy are all associated with high detection rate of bone disease in patients with MM. Thus, in clinical practice, it is recommended that we could choose these tests according to the condition of the patient.

Keywords: Multiple myeloma - MRI - FDG PET - PET/CT - bone scan - systematic review - meta-analysis

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Introduction

Multiple myeloma (MM) is a neoplastic monoclonal proliferation of plasma cells within the bone marrow. This malignancy involves the skeleton in more than 80% of patients at the time of initial diagnosis. In the guidelines of the International Myeloma Working Group (IMWG), the presence of bone disease in conventional radiography is a criterion of symptomatic MM indicating the necessity of treatment (International Myeloma Working Group, 2003). Osseous lesions in MM have been traditionally detected by whole body radiographic survey. And with advanced technology, Multiple imaging modalities including computed tomography (CT), magnetic resonance imaging (MRI), 99mTc-methylene diphosphonate (MDP) bone scintigraphy (BS), sestamibi (MIBI) scintigraphy and positron emission tomography with 18F-fluorodeoxyglucose (18F-FDG PET) have been introduced to depict skeletal lesions.

Materials and Methods

Search strategy

A search of the bibliographic databases PubMed, Cochrane and EMBASEwas conducted up to July 2014. The search included combinations of the following terms: (1) multiple myeloma; (2)'MR' or 'MRI'or 'magneticresonance' or 'CT' or 'computed tomography' or 'positron emission tomography' or 'PET' or 'FDG' or 'fluorodeoxyglucose' or '18-fluoro-deoxyglucose' or '18F' or 'MIBI' or 'sestamibi' or 'MDP' or 'Tc99m' or 'bone scan' or 'scintigraphy' or 'bone survey'. Searches were limited to studies on human subjects. Case reports, editorials, letters, management guidelines, studies performed in animals, and ex-vivo studies were excluded. Although no language restrictions were used initially, the full-text review and final analysis were limited to articles published in English. The CNKI (China National Knowledge Infrastucture) databases were used for Chinese

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articles with the same keywords mentioned above in Chinese.

Data Selection

Two investigators independently checked all of the retrieved articles to determine whether they satisfied the following selection criteria: (a) CT, MRI, FDG-PET, FDG-PET/CT and scintigraphy was used to identify and characterize suspected multiple myeloma patient without treated. If the study includ patients before and after treatment, should have valid results of pro-treatment patients; (b) Studies assessed the diagnostic accuracy of bone disease can use WBXR or/and CT as a reference standard; (c) Sufficient data were presented to calculate the true-positive (TP), false-positive (FP), falsenegative (FN), and true-negative (TN) values for the imaging techniques; (d) Patients with a secondary malignoma were excluded from the study. (e) Concerning to the quality of study design, only the article in which the number of the answer 'yes' for the 14 questions in QUADAS quality assessment tool was larger than 8 was included. if the number of the answer 'No' or 'unclear' was larger than 5, the article was excluded. Theoretically, the reference standard would be a local biopsy to confirm clonal plasmacytosis. The Durie and Salmon staging system introduced in 1975 relied on the radiographic skeletal survey as the sole imaging criterion. Given that it is both practically and ethically impossible to perform biopsies of all detected lesions, the use of this method as a reference standard in clinical studies was not achievable. The International Myeloma Working Group (IMWG) reported a consensus statement on the role of imaging techniques in multiple myeloma1 in which whole body X-ray (WBXR) was considered the gold standard in initial staging, and if available WBXR might be replaced by CT (Barlogie et al., 2004). So we used X-rayor/and CT and clinical follow-up as alternative reference standards.

Data extraction

Data were obtained for author, year of publication, country, patient characteristics, reference standard and diagnostic performance of imaging modalities. Data were extracted independently by 2 investigators. To resolve disagreement between reviewers, a third reviewer assessed all discrepant items, and the majority opinion was used for analysis.

Study design characteristics

The QUADAS quality assessment tool was used to extract relevant study design characteristics of each study. This tool and the definitions of the characteristics are fully described by Penny Whiting. It is the first systematically developed evidence based quality assessment tool to be used in systematic reviews of diagnostic accuracy studies. Two investigators independently assessed whether each item of QUADAS was fulfilled (yes, no or unclear).

Data analysis

Data were separately analyzed for MRI, scintigraphy, PET and PET/CT. We calculated pooled sensitivity, specificity and diagnostic odds ratio (DOR) for each modality Data were separately analyzed for PET, CT, and MRI, we calculated pooled sensitivity, specificity and diagnostic odds ratio (DOR) for each modality, and we also calculated summary receiver operating characteristic curves (SROC) and the Q* index.

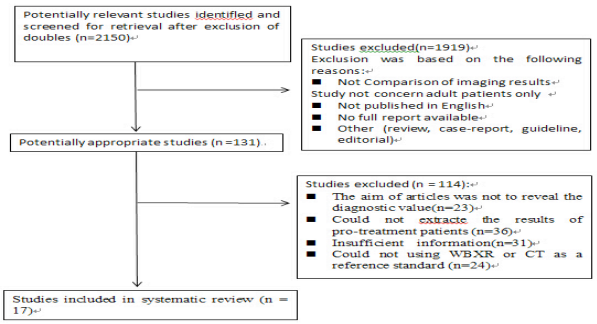

Figure 1. Flow of Studies through Selection Process

Results

Study selection

After the computerized search was performed and reference lists were extensively cross-checked, we extracted 2150 abstracts for analysis; however, 1919 articles were excluded on the basis of their titles, abstracts or full text. We screened the full text of 134 articles, 23 studies were excluded because the aim of the articles was not to reveal the diagnostic value of MRI, FDG-PET, PET/CT or scintigraphy for identification and characterization of multiple myeloma related bone disease; 36 studies were excluded because the study compared patients before and after treatment, but the valid results for pro-treatment patients could not be extracted; 31 studies were excluded owing to insufficient information construct or calculate true-positive, false-positive, true-negative, and/or false-negative results. 24 studies were excluded for the identification of bone disease could not using WBXR or CT as a reference standard.Finally, 17 articles fulfilled all inclusion criteria and were selected for data extraction and data analysis. The selection process and reasons for exclusion of the articles are summarized in Figure 1.

Study characteristics

There were total 575 patients in the selected studies and the age ranged from 20 to 93 years. 14 studies use one imaging techniques compared with the reference test when four studies use two imaging techniques compared with the reference. Twelve studies were performed prospectively. Six studies included patients with MM staged according to the diagnostic criteria of Durie-Salmon or Durie -Salmon Plus, one described patients with SPC only, and the remaining seven studies included patients with MM, SPC and/or MGUS. The number of patients included per study varied from 9 to 119. Scintigraphy was the index test in 8 (include four MIBI and four bone scan), MRI in 7, FDG-PET in 2 and FDG-PET-CT in 3 studies. Three papers included more than one index test. The characteristics of the included studies are presented in Table 1.

Methodological Quality Assessment

Methodological quality was assessed by 14 items

Table 1. Characteristics of Studies Included

Authors	Publication year	Study design	Country	Diagnosis	Whole-body/Part	Reference	No of patients
Alperet al.	2002	prospective	Turkey	MM	whole body	X-ray	20
Catalano et al.	2005	prospective	Italy	MM	whole body	X-ray	9
Svaldi et al.	2001	prospective	Italy	Normal/MGUS/MM	whole body	X-ray	44
Balleari et al.	2001	prospective	Italy	MM/MGUS	whole body	X-ray	27
Peng et al.	2003	retrospective	China	MM	whole body	X-ray	20
Shen et al.	2008	retrospective	China	MM	whole body	X-ray/CT	11
Ludwig et al.	1987	Prospective	Vienna	MM	part	X-ray	18
Baur-Melnyk et al.	2008	Prospective	Germany	MM	whole body	CT	41
Narquinet al.	2013	prospective	France	MM /MGUS/SPC	whole body	X-ray	27
Nanniet al.	2006	Prospective	Italy	MM	Whole body/Part	X-ray	28
Tertti et al.	1995	prospective	Finland	MM	Part	X-RAY	41
Sager et al.	2011	retrospective	Turkey	MM/SPC	whole body	CT/ MRI/follow up	42
Schirrmeister et al .	2003	Prospective	Germany	SPC	whole body	X-ray/CT/MRI follow up	11
Zamagniet al .	2006	prospective	Italia	SPC/MM	Part	X-ray/MRI	46
Zhu et al.	2001	prospective	China	MM	Part	X-ray	41
Wolf et al.	2014	retrospective	Germany	MGUS/MM/SPC	Part	X-ray	119
Durieet al.	2002	retrospective	USA	MGUS/MM	whole body	X-ray	30

MGUS, monoclonalgammopathy of undetermined significance; MM, multiple myeloma; SPC, solitaryplasmacytoma

Table 2. Reported PLR, NLR, and DOR of MRI, Scintigraphy, FDG-PET and PTE/CT on per-patient-basis in Patients with MM Related Bone Disease

Imaging modality	Authors	No. of patients	TP	FP	TN	FN	PLR (95% CI)	NLR (95% CI)	DOR (95% CI)
MRI									
	Ludwig et al.	18	2	10	6	0	1.349(0.719-2.531)	0.436(0.032-5.877)	3.095 (0.127-75.182)
	Baur-Melnyk et al	41	22	4	15	0	4.348(1.923-9.829)	0.028(0.002-0.440)	155.00 (7.775-3090.1)
	Narquin et al.	27	19	5	3	0	1.595(0.943-2.699)	0.064 (0.004-1.119)	24.818 (1.106-556.80)
	Nanni et al.	28	11	11	4	2	1.154(0.787-1.693)	0.577(0.125- 2.654)	2.000(0.302-13.265)
	Tertti et al.	41	15	13	13	0	1.938(1.315-2.854)	0.063 (0.004-0.982)	31.000 (1.680-572.18)
	Wolf et al.	119	24	19	76	0	4.825(3.234-7.199)	0.025 (0.002-0.391)	192.23 (11.189-3302.6)
	Zhu et al.	41	15	0	13	13	14.966 (0.963-232.46)	0.483 (0.323-0.722)	31.000 (1.680- 572.18)
Scintigraphy (MIBI)									
	Alper et al.	20	18	2	0	0	1.168 (0.701-1.949)	0.158 (0.004-6.555)	7.400 (0.118-463.09)
	Catalano et al.	9	9	0	0	0	1.900 (0.266-13.558)	0.100 (0.004-2.815)	19.000 (0.150-2409.8)
	Svaldi et al.	44	13	2	29	0	12.343 (3.738-40.753)	0.039 (0.003-0.590)	318.60 (14.296-7100.1)
	Balleari et al.	27	13	0	14	0	28.929 (1.892-442.27)	0.037 (0.002-0.563)	783.00 (14.494-4230.1)
Scintigraphy (bone scan)									
	Alper et al.	20	15	0	2	3	4.895 (0.386 -62.021)	0.221 (0.076-0.646)	22.143 (0.858-571.29)
	Ludwig et al	18	2	0	16	0	28.333 (1.763-455.45)	0.172 (0.014-2.159)	165.00 (2.629-10357.1)
	Peng et al.	20	9	0	0	11	0.905(0.121-6.791)	1.095(0.148-8.078)	0.826(0.015-45.694)
	Shen et al.	11	6	3	0	2	0.825(0.477-1.429)	2.222(0.135-36.494)	0.371(0.014-10.098)
PETCT									
	Nanni et al.	28	15	9	4	0	1.428(0.985-2.069)	0.097(0.006-1.651)	14.684(0.709-304.32)
	Sager et al.	42	30	0	8	4	15.686 (1.058-232.64)	0.136(0.057-0.327)	115.22(5.628-2358.8)
	Zamagni et al .	46	24	9	9	4	1.714(1.054-2.787)	0.286(0.103-0.791)	6.000(1.472-24.454)
PET									
	Schirrmeister et al .	11	2	1	7	1	5.333 (0.722-39.424)	0.381 (0.075-1.928)	14.000 (0.579-338.78)
	Durie et al.	30	16	0	14	0	29.118 (1.906-444.89)	0.030 (0.002-0.468)	957.0 (17.830-51365.7)

FDG-PET, 18F-fluorodeoxyglucose-positron emission tomography; TP, true-positive; FP, false-positive; FN, false-negative; TN, true-negative; PLR, positive likelihood ratios; NLR, negative likelihood; DOR, diagnostic odds ratio

for each of the 17 selected studies. Eight studies (47%) included are presentative patient cohort, meaning that suspected multiple myeloma patients (not only MM but also MGUSor SPC) were included, when the remain 9 studies had diagnosed MM. All studies had a clearly selection criteria described and a valid reference test (WBXR and/or CT) independently of the index test. 9 studies (53%) had the reference standard and index test between 2 weeks and 90 days. In 6 studies (35%), the clinicians were blinded from the results of the reference and index test. The mean QUADAS score, expressed as a percentage of the maximum score, was 77% (range, 64%-100%).

Heterogeneity assessment of studies and performance for diagnosis of MM related bone disease

MRI on per-patient basis: For the seven MRI studies (Department et al., 1987; Tertti et al., 1995; Zhu et al.,

Table 3. AUC, and Q* Index between MRI, Scintigraphy, FDG-PET and PET/CT

Pairwise comparisons		AUC		Q*		SEN		SPE	
		Z value	*P* value	*Z* value	P value	*Z* value	*P* value	*Z* value	*P* value
MRI	MIBI	-1.29	0.20	-1.10	0.27	-0.59	0.56	-0.46	0.64
MRI	bone scan	0.73	0.47	1.11	0.27	0.75	0.45	-0.29	0.77
MRI	PETCT+PET	-0.34	0.73	0.12	0.90	1.02	0.31	-0.03	0.98
MIBI	bone scan	1.79	0.07	0.00	1.00	1.39	0.16	0.12	0.90
MIBI	PETCT+PET	1.32	0.19	0.00	1.00	0.55	0.58	0.41	0.68
bone scan	PETCT+PET	-1.07	0.28	-1.13	0.26	-0.92	0.36	0.26	0.80
PETCT	bone scan	-0.89	0.37	-0.89	0.37	-0.97	1.67	0.52	0.60
MIBI	PETCT	0.97	0.33	1.24	0.22	1.07	0.28	0.68	0.50
MRI	PETCT	0.21	0.83	-0.21	0.83	-0.09	1.07	0.25	0.80
PETCT	bone scan	-0.89	0.37	-0.89	0.37	-0.97	1.67	0.52	0.60
MIBI	PETCT	0.97	0.33	1.24	0.22	1.07	0.28	0.68	0.50
MRI	PETCT	0.21	0.83	-0.21	0.83	-0.09	1.07	0.25	0.80

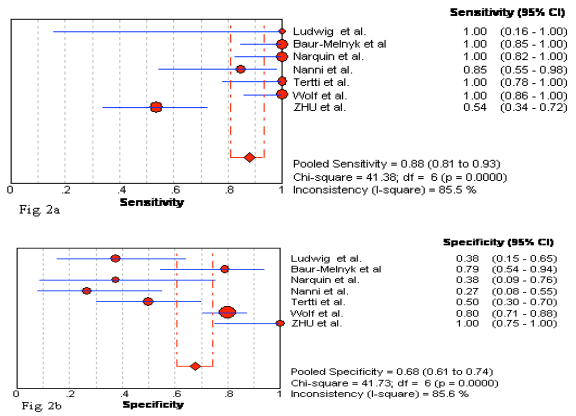

Figure 2. Sensitivities, Specificities, and 95% Confidence Intervals (CI) for Studies Assessing the Diagnostic Accuracy of MRI on Per-patient Basis in Patients with MM Related Bone Disease

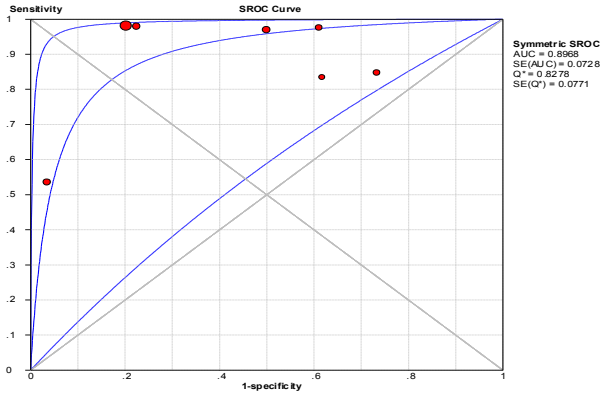

Figure 3. MRI on Per-patient Basis Sroc Curve

2001; Maya et al., 2004; Cristina et al., 2006; Andrea et al., 2008; Narquin et al., 2013) that we evaluated, the test of homogeneity indicated the presence of statistical heterogeneity (Q value for sensitivity [QSE] = 41.38, *P* = 0, I^2 = 85.5%; Q value for specificity [QSP] = 41.73, *P* = 0, I^2 = 85.6). The pooled sensitivity and specificity were 0.88 (95% CI, 0.81- 0.93) and 0.68 (95% CI, 0.61- 0.74) (Fiure 2). The overall PLR, NLR, and DOR were 2.263 (95%CI, 1.315 - 3.892), 0.139 (95% CI, 0.025 - 0.766), and 21.029 (95% CI, 4.809 - 91.965), respectively. The PLR, NLR, and DOR for each of the MRI studies are also presented in Table 2.

MIBI on per-patient basis: For the four MIBI studies (E.ALPER et al., 2003; LUCIO CATALANO et al., 2005; M. Svaldi et al., 2001; ENRICO et al., 2001) that we evaluated, the test of homogeneity indicated the presence of statistical heterogeneity (Q value for sensitivity [QSE] = 1.40, *P* = 0.7051, I^2 = 0%; Q value for specificity [QSP] =13.37, *P* = 0.0039, I^2 = 77.6%). The pooled sensitivity and specificity were 0.982 (95% CI, 0.903 - 1.000) and 0.898 (95% CI, 0.778 - 0.966). The overall PLR, NLR, and DOR were 4.824 (95%CI, 0.443 - 52.477), 0.059 (95% CI, 0.013- 0.269), and 103.81 (95% CI, 12.272 - 878.08), respectively. The PLR, NLR, and DOR for each of the MIBI studies are also presented in Table 2.

Bone scanon per-patient basis: Four studies evaluated 69 patients by bone scan (Department et al., 1987; Alper et al., 2003). The pooled sensitivity, specificity, PLR, NLR, and DOR were 0.66 (95% CI, 0.51 - 0.79), 0.83 (95% CI, 0.61- 0.95), 2.548 (95% CI, 0.352 -18.412), 0.412 (95% CI, 0.139 -1.227), and 5.342 (95% CI, 0.348 - 82.067), respectively. Q value for sensitivity [QSE] = 8.33, *P* = 0.-397, I^2 = 64.0%; Q value for specificity [QSP] = 16.85, *P* = 0.0008, I^2 = 82.2%

PETand PETCT on per-patient basis

There were 2 studies (Brian et al., 2002; Holger et al., 2003) evaluated 41 patients by PET and three studies (Cristina et al., 2006; Elena et al., 2007; Sait et al., 2011) evaluated 116 patients by PET/CT. The pooled sensitivity, specificity, PLR, NLR, and DOR of PET were 0.947 (95% CI, 0.740 - 0.999), 0.955 (95% CI, 0.772 - 0.999), 10.450 (95% CI, 1.429 - 76.388), 0.129 (95% CI, 0.007 - 2.306), and 97.229 (95% CI, 1.541- 6135.7), respectively. And 0.896 (95% CI, 0.806 - 0.954), 0.538 (95% CI, 0.372 - 0.699), 1.793 (95% CI, 0.887 - 3.622), 0.180 (95% CI, 0.094 -0.345), and 14.662 (95% CI, 2.650 - 81.129) for PET/CT. The heterogeneity test of pooled PET and PET/CT revealed [QSE] = 8.32, *P* = 0.0805, I^2 = 51.9%; [QSP] = 28.64, *P* = 0.00, I^2 = 86.0%. And the sensitivity, specificity, PLR, NLR, and DOR of pooled PET and PET/CT were 0.906 (95% CI, 0.829 - 0.956), 0.689 (95% CI, 0.557 - 0.801), 3.105 (95% CI, 1.149 - 8.397), 0.183 (95% CI, 0.099 - 0.340), and 27.090 (95% CI, 4.883 - 150.28) respectively.

Statistically significant differences were not found in the sensitivity, specificity, AUC, and Q* index between MRI, scintigraphy, FDG-PET and PET/CT (Table 3)

Discussion

Multiple myeloma (MM) is not a rare disease, and is a research focus in China (Chen et al., 2012; Liu et al., 2012; Lin et al., 2013; Zhang et al., 2014). It is reported that patients with MM could have symptoms, e.g., fractures, bone pain, and elevated blood calcium etc, caused by bone abnormalities (Lecouvet et al., 1999; Umeda et al., 2002; Terpos et al., 2003; Kitano et al., 2005; Harousseau et al., 2004). The consequence is a decreasing of quality of life. Guideline based diagnosis and treatment includes imaging examinations of head, chest, extremities, vertebra, and the pelvis. Regarding imaging techniques for bone lesions, X ray, MRI, scintigraphy, FDG-PET and PET/CT are usually considered. In clinical practice, the value of these imaging techniques could be different when different patients with MM are encountered, and the characteristics of each imaging techniques are compared. The sensitivity of these imaging techniques in detecting myeloma related bone lesions is different. X ray is reported to have a low sensitivity in diagnosing MM related bone disease, when >50% bone mineral content has been lost. It was demonstrated that MRI is associated with a very good sensitivity in particular at the early stage of the disease. The main limitation of MRI is caused by partial field, usually, only spine and pelvis could be viewed. Another point should be mentioned regarding MRI is its poor performance when metallic prosthesis or claustrophobia is presented.

Scintigraphy was also employed to diagnose MM related bone disease. However, it is considered that both 99mTc-diphosphonate and MIBI were associated with low sensitivity due to low tracer uptake by MM related bone disease and to high physiological uptake by liver that could mislead vertebral or right rib disease.

Within these years, PET/CT was frequently performed in the diagnosed of MM related bone disease. 18F-FDG PET is associated with higher sensitivity due to its characteristic that the whole body could be imaged and both medullary and extra-medullary lesions could be detected.

However, the sensitivity and specificity of PET/CT are depended on the uptake of tracer, and the hot spot could be equivocal when disease is in early stage or is disseminated.

Our results showed that MRI had a pooled sensitivity of 0.88, specificity of 0.68, AUC of 0.897, and Q*index of 0.828; whereas for MIBI, the corresponding values were 0.98, 0.90, 0.991, and 0.962; and for bone scan, the values were 066, 0.83, 0.805, and 0.740; and for PET and PET/CT, the value were 0.91, 0.69, 0.927 and 0.861, respectively. Statistically significant differences were not found in the sensitivity, specificity, AUC, and Q* index between MRI, scintigraphy, FDG-PET and PET/CT. Several confounding factors should be mentioned before we draw the conclusion. First, we are not sure whether the diagnostic consensus of PET/CT is reached in each institute. The technological skill of staff members in each institute could be greatly different, and the diagnostic standard adopted by each institute could not be standardized. Second, there could be difference between ethnic groups in our selected studies, Oriental and Caucasian were both included into current study. We hypothesize that the sensitivity and specificity of imaging test could be different between ethnic groups. And third, imaging techniques and quality for one device in different study group could be greatly differed. For CT and MRI machines, we are not sure these machines are produced during the same period of time. And we suppose machine manufactured in recent years could have higher sensitivity and specificity than those come into use before 20 years. Fourth, the stage of patients in each study group was not standardized. We know patients with more advanced disease should be diagnosed with MM related bone lesions more frequently than those with early disease. In conclusions: on the condition that X ray is taken as a reference in our study, we suggested that FDG-PET, PTE/CT, MRI and scintigraphy are all associated with high detection rate of bone disease in patients with MM. Thus, in clinical practice, it is recommended that we could choose these tests according to the condition of patient.

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