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The diagnostic performance of ^{18}F-fluoride PET/CT in bone metastases detection: a meta-analysis

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AIM: To assess the diagnostic performance of combined ^{18}F-fluoride positron-emission tomography (PET)/computed tomography (CT) in bone metastases (BM) and explore whether there is an added value when compared with ^{99m}Tc- methylene diphosphonate (MDP) planar bone scintigraphy (BS).

MATERIALS AND METHODS: PubMed, EMBASE, Web of Science, and the Cochrane Library were searched to December 2017. Studies evaluating the performance of ^{18}F-fluoride PET/CT in BM detection and using histopathology or clinical/imaging follow-up for ≥6 months as the reference standard were included. All analyses were performed on Stata/SE 12.0 and MetaDisc 1.4.

RESULTS: Twenty articles comprising 1,349 patients were included. On the patient basis, the pooled sensitivity and specificity of ^{18}F-fluoride PET/CT were 93% (95% confidence interval [CI], 91–96%) and 95% (95% CI, 93–96%) when equivocal results were considered as negative for BM; and 96% (95% CI, 93–97%) and 93% (95% CI, 91–95%) when equivocal results were considered as positive. On the lesion basis, the pooled sensitivity and specificity were 93% (95% CI, 92–94%) and 96% (95% CI, 95–97%) when equivocal results were considered as negative; and 94% (95% CI, 92–95%) and 95% (95% CI, 94–96%) when equivocal results were considered as positive. Seven articles reported the comparison between ^{18}F-fluoride PET/CT and ^{99m}Tc-MDP BS. ^{18}F-fluoride PET/CT showed both higher sensitivity ($p<0.005$) and specificity ($p<0.05$) when equivocal results were considered as positive. When the equivocal results were considered as negative, ^{18}F-fluoride PET/CT showed higher sensitivity ($p<0.005$), but no significant difference in specificity ($p=0.08$).

CONCLUSIONS: ^{18}F-fluoride PET/CT showed superior diagnostic performance in BM detection and had higher accuracy when compared with ^{99m}Tc-MDP BS.

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Introduction

Bone metastases (BM), which is one of the most common forms of distant metastases, is a vital prognostic factor for cancer patients. It is reported that approximately 350,000 cancer patients died with BM each year, most of them arise from prostate, breast, lung, thyroid, and kidney cancer.[1,2] Early detection of BM is crucial for tumour staging, treatment decision, and therapy efficacy monitoring. At present, there are a variety of imaging methods available to detect BM, including computed tomography (CT), magnetic resonance imaging (MRI), planar bone scintigraphy (BS), combined single-photon-emission CT (SPECT)/CT, and combined positron-emission tomography (PET)/CT, but there is no conclusion as to which method is the best as each of them has its own advantages and shortcomings. ^{99m}Tc-methylene diphosphonate (MDP) BS has now been widely used and has gradually become the standard for diagnosing, staging, and monitoring therapy of BM; however, many studies have highlighted its limited sensitivity and specificity.[3–5] Traditional imaging methods such as radiography, CT, and MRI can only provide anatomical information and depend on the size of the lesions when detecting BM.[6–8] PET/CT with the radiolabelled fluoride analogue ^{18}F-fluoride combines the functional information and high sensitivity of PET with the anatomical localisation and morphological features of CT, has been proved to be an excellent method of detection of BM.[9] Several clinical trials have been conducted to evaluate the diagnostic accuracy of ^{18}F-fluoride PET/CT in detecting BM. A previous meta-analysis published in February 2015[10] compared ^{18}F-fluoride PET or PET/CT with ^{99m}Tc-MDP BS, and confirmed that ^{18}F-fluoride PET or PET/CT is a convincing method for detecting BM and has higher diagnostic accuracy than ^{99m}Tc-MDP BS; however, the findings of that study should be viewed within the context of its limitations. The diagnostic values of ^{18}F-fluoride PET or PET/CT are not exactly the same, but they combined these two methods when evaluating the diagnostic accuracy. Similarly, the diagnostic value of ^{99m}Tc-MDP planar BS, SPECT, and SPECT/CT for BM varies widely, but this previous study did not distinguish them well. Besides, when compared with BS, there was no time interval limit for patients to undergo ^{18}F-fluoride and BS examinations, which may affect the reliability of the comparison. Importantly, the studies that were included were just updated to August 2013, and there has been a rapid development in this field over the past few years. Thus, a new update and a more rigorous comparison between ^{18}F-fluoride PET/CT and ^{99m}Tc-MDP BS are needed.

The aim of the present meta-analysis was to evaluate the diagnostic properties of ^{18}F-fluoride PET/CT in detecting BM. We also conducted a comparison to determine if there is any added value for ^{18}F-fluoride PET/CT when compared with traditional ^{99m}Tc-MDP BS.

Materials and methods

This meta-analysis was conducted in accordance with the recommendations by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses: the PRISMA Statement (see Electronic Supplementary Material Table S1).[11,12]

Literature search

Two reviewers independently searched PubMed, EMBASE, Web of Science, and the Cochrane Library updated to December 2017 without any language restriction. The combination of (NaF or fluoride) and (metastatic or metastasis or metastases or recurrence) and (bone or bony or skeletal or osseous) were used as search terms. The reference lists of all retrieved articles were assessed additionally and disagreement was solved by discussion until consensus was reached.

Study selection

Two reviewers independently evaluated all studies that were retrieved. First, the titles and abstracts of all studies were read and studies that were appropriate were selected. Then, the full-text of those potential eligible articles was obtained and studies that satisfied the inclusion criteria after thorough discussion were included. The articles had to satisfy the following inclusion criteria: (1) the diagnostic value of ^{18}F-fluoride PET/CT in cancer patients with BM was evaluated; (2) histopathological examination or/and clinical/imaging follow-up for at least 6 months was used as the reference standard; (3) the studies were conducted on the patient basis or lesion basis, and sufficient data were available to calculate true-positive (TP), false-positive (FP), false-negative (FN), and true-negative (TN) results of ^{18}F-fluoride PET/CT compared to the reference standard; (4) the studies contained 10 or more patients; (5) if the data were presented in more than one study, the study with the most details or the most recent publication would be included.

The exclusion criteria were as follows: (1) studies not published in English; (2) reviews, letters, comments, editorial, case report, meeting abstract, animal and *in vitro* experiments, and original research without raw data; (3) all patients in the study were diagnosed with BM; (4) the study involved multiple imaging methods, and the diagnostic results were presented in combination, from which the results of ^{18}F-fluoride PET/CT could not be extracted separately.

Data extraction

The available data of all finally included studies were extracted by the same two reviewers independently. Data obtained could be simply divided into four categories: (1) study design characteristics; (2) basic information; (3)

imaging technique parameters; and (4) examination results. If the two reviewers still could not reach an agreement after discussion, the disagreement would be resolved by a third reviewer after carefully assessing the controversial data who then put forward an opinion acceptable to all reviewers.

The study design characteristic was extracted for the assessment of the quality of the included studies using the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2). The methodology of QUADAS-2 has been fully described in previous studies.[13,14] Briefly, the four domains of QUADAS-2: patient selection, index test, reference standard, and flow and timing would be classified based on the risk of bias and concerns. Studies with a low risk of bias would be classified as "L", whereas those unclear risks would be classified as "U" and high risks as "H".

The following basic information of studies was extracted: first author; year of publication; author's country; type of primary tumour; study design; sample size, including the number of patients and lesions; description of the study sample, including the distribution of patients' age and gender; and type of imaging methods.

The following technique parameters of ^{18}F-fluoride PET/CT were recorded: scanner; injection dose; time from injection to scan; bed position; acquisition time per bed position; reconstruction method; and attenuation correction.

In order to describe the examination results, the numbers of TP, FP, FN, and TN of ^{18}F-fluoride PET/CT compared with reference standard were recorded on both patient basis and lesion basis if available. For those studies that conducted a comparison between ^{18}F-fluoride PET/CT and BS, the examination results of BS were also recorded. It should be noted that ^{99m}Tc-MDP BS was limited to planar BS, and BS data was considered valid only if the interval between these two imaging methods did not exceed 1 month, and the study sample of them must be the same.

Statistical analysis

For each study, the pooled sensitivity (Sen), specificity (Spe), positive likelihood ratio (+LR), negative likelihood ratio (−LR), and diagnostic odds ratio (DOR) with their 95% confidence intervals (CIs) were calculated with original data using a random-effects model. The sensitivity and specificity are defined as TP/(TP + FN) and TN/(TN + FP) respectively. The +LR and −LR are defined as Sen/(1 − Spe) and (1 − Sen)/Spe respectively, while the DOR is defined as the ratio of +LR over −LR. Summary receiver operating characteristic (SROC) curves were drawn and the area under the curve (AUC) and Q* index were calculated. The AUC is a number that comprehensively summarises the diagnostic performance. It is generally considered that the AUC ranged from 0.7 to 0.9, indicating that the method had high diagnostic accuracy, while AUC = 0.5 indicates that this method has no diagnostic value. For those studies that evaluated ^{99m}Tc-MDP BS in the same sample as ^{18}F-fluoride PET/CT, Student's *t*-test was used to compare the efficacy between these two different imaging methods. Besides, a subgroup analysis of ^{18}F-fluoride PET/CT based on the sites of primary tumours on both patient basis and lesion basis was carried out. All statistical analyses were performed using Stata/SE 12.0 and MetaDisc 1.4.

Results

Literature search and study selection

A total of 1,151 articles were retrieved initially, and 243 were then excluded when duplicates were removed. The remaining 908 articles were screened, and 828 articles were excluded while the remaining 80 articles were further assessed using the full text of the article. After reading the full text carefully, another 60 articles were excluded for the following reasons: case report, meeting abstract, and review (n=43); non-English (n=4); the number of valid subjects was <10 (n=3); data were included in other more detailed studies (n=2); the reference standard did not satisfy the inclusion criteria (n=8). A PRISMA flow diagram of the study selection method is shown in Fig 1.[11,12] After exclusions, a total of 20 articles[15–34] were included in the present meta-analysis.

Data extraction and quality assessment

The basic information and examination results of the included studies and the technical parameters of ^{18}F-fluoride PET/CT are shown in Electronic Supplementary Material Tables S2 and S3. In brief, 18 studies[15,16,18–23,25–34] comprising 1,290 patients reported the outcome of the patient-based analysis, and 11 studies[15–20, 22, 24, 27, 29, 30] comprising 3,644 lesions reported the outcome of the lesion-based analysis. Among them, the earliest article was published in 2004, while the latest was published in 2017. The primary tumours of these patients were various, including prostate, breast, lung, and head and neck cancer, as well as meningioma, urinary bladder carcinoma, and so on. Seven studies [16, 20, 23, 25, 29, 31, 32] conducted a comparison between ^{18}F-fluoride PET/CT and ^{99m}Tc-MDP BS and their BS data were considered valid under the criteria. In these 20 studies, only one performed a histopathological examination on every patient, the remaining studies all had a follow-up for at least 6 months.

The results of the quality assessment are shown in Figs 2 and 3. The risk of bias was unclear for the index test in nine studies,[21, 25, 27–32, 34] for the reference standard in seven studies,[18, 21, 22, 24, 29, 30, 33] and for flow and timing in 12 studies.[15, 17, 18, 20, 21, 23–25, 27, 29, 31, 34] The risk of bias was high for patient selection in one study.[20] The applicability concerns was unclear for patient selection in one study,[18] for the index test in two studies,[21, 28] and for the reference standard in three studies.[17, 18, 20] The applicability concerns were high for patient selection in one study,[20] and for reference standard in six studies.[21, 22, 24, 29, 30, 33]

Diagnostic performance of ^{18}F-fluoride PET/CT

Eighteen studies reported the outcome of the patient-based analysis, of which five studies had equivocal image

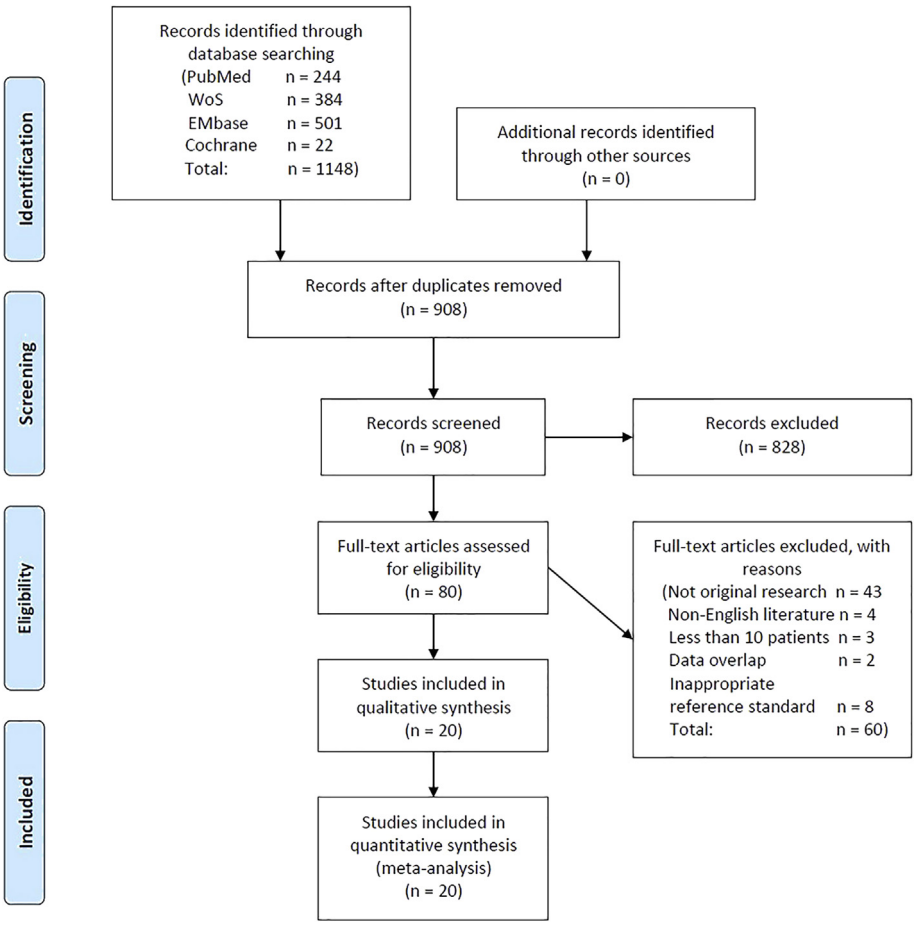

Figure 1 The PRISMA flow diagram of study selection.

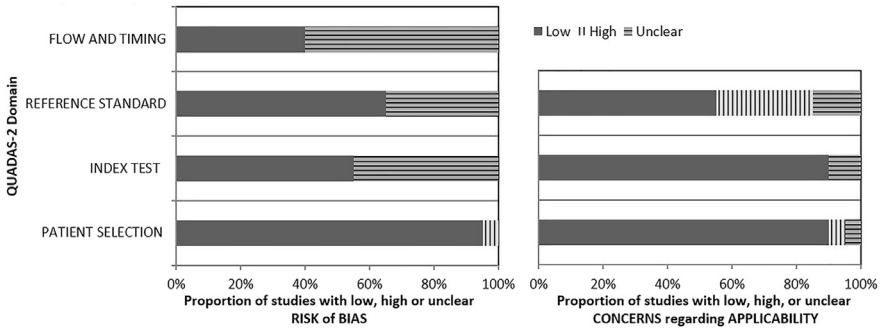

Figure 2 The risk of bias and applicability concerns of included studies.

findings in 22 patients. The forest plots of pooled sensitivity, specificity, +LR, −LR, and DOR were shown in Fig 4 and Electronic Supplementary Material Fig S1, while the SROC curves were shown in Fig 5a,b, from which the pooled sensitivity, specificity, +LR, −LR, DOR, AUC and Q* of ^{18}F-fluoride PET/CT were 93% (95% confidence interval [CI], 91–96%), 95% (95% CI, 93–96%), 11.128 (95% CI, 7.293–16.982), 0.099 (95% CI, 0.067–0.146), 166.67 (95% CI, 97.628–284.52), 0.9741, and 0.9267, respectively, when the equivocal results were considered as negative for BM; and 96% (95% CI, 93–97%), 93% (CI, 91–95%), 9.731 (95% CI, 6.808–13.909), 0.075 (95% CI, 0.044–0.128), 161.93 (95% CI, 85.804–305.61), 0.9731, and 0.9250, respectively, when the equivocal results were considered as positive.

Eleven studies reported the outcome of the lesion-based analysis. Among them, three studies had equivocal image findings in 24 lesions. When these equivocal findings were considered as negative for BM, the pooled sensitivity, specificity, +LR, −LR, DOR, AUC and Q* were 93% (95% CI, 92–94%), 96% (95% CI, 95–97%), 17.932 (95% CI, 11.881–27.066), 0.097 (95% CI, 0.058–0.161), 204.71 (95% CI, 104.37–401.49), 0.9801, and 0.9375, respectively. When

Figure 3 Summary of the quality assessment of each study.

these equivocal results were regarded as positive, then the pooled sensitivity, specificity, +LR, −LR, DOR, AUC and Q* would be 94% (95% CI, 92–95%), 95% (95% CI, 94–96%), 16.440 (95% CI, 11.116–24.312), 0.092 (95% CI, 0.054–0.158), 218.35 (95% CI, 104.57–455.96), 0.9846, and 0.9464, respectively. Fig 6 and Electronic Supplementary Material Fig S2 demonstrated the forest plots of the pooled sensitivity and specificity, as well as +LR, −LR, and DOR respectively, and the SROC curves on lesion basis were shown in Fig 5c,d.

The results of the subgroup analysis are shown in Table 1. Due to the limited data, a subgroup analysis of all cancer types was not performed. On a patient basis, the subgroup analysis of prostate cancer, breast cancer, and various cancer was calculated. On a lesion basis, the available data could only support the subgroup analysis of prostate cancer and various cancers.

Comparison between ^{18}F-fluoride PET/CT and ^{99m}Tc-MDP BS

Seven studies comprising 368 patients compared the diagnostic accuracy of ^{18}F-fluoride PET/CT with ^{99m}Tc-MDP BS on a patient basis, but only three of the 20 compared these two methods on a lesion basis. Thus a comparison between was only conducted on the patient basis in this current meta-analysis. The pooled sensitivity of ^{18}F-fluoride PET/CT and ^{99m}Tc-MDP BS were 88% (95% CI, 81–93%) versus 65% (95% CI, 56–73%) when the equivocal results were regarded as negative for BM, and 92% (95% CI, 86–96%) versus 71% (95% CI, 62–79%) when the equivocal results were regarded as positive. The pooled specificity of ^{18}F-fluoride PET/CT and ^{99m}Tc-MDP BS were 96% (95% CI, 93–98%) versus 91% (95% CI, 87–95%) when the equivocal results were considered as negative, and 92% (95% CI, 88–95%) versus 77% (95% CI, 71–82%) when the equivocal results were considered as positive. Electronic Supplementary Material Figs S3 and S4 demonstrate the pooled +LR, −LR, and DOR of ^{18}F-fluoride PET/CT and ^{99m}Tc-MDP BS. Similarly, there existed obvious differences between these two imaging methods. The SROC curves of ^{18}F-fluoride PET/CT and ^{99m}Tc-MDP BS are shown in Fig 7, from obvious differences between them can be identified in terms of AUC and Q*, which implied the diagnostic accuracy of ^{18}F-fluoride PET/CT was higher than ^{99m}Tc-MDP BS. In fact, significant differences can be observed in sensitivity ($p<0.005$) and specificity ($p<0.05$) when the equivocal results were considered as positive; however, when they were considered negative for BM, the significant difference can only be observed in sensitivity ($p<0.005$), but not in specificity ($p=0.08$).

Discussion

^{18}F-fluoride, which has a higher affinity and more rapid clearance than the BS tracer ^{99m}Tc-MDP,[35] was developed as a bone-specific PET tracer in the 1960s.[36] In recent years, numerous studies have demonstrated that ^{18}F-fluoride PET/CT can be used for early diagnosis,[37] quantitative analysis,[38] and response assessment[39] of various bone diseases. In the present study, meta-analyses were used to quantify the diagnostic value of ^{18}F-fluoride PET/CT for BM, and the results indeed validated the superior performance of ^{18}F-fluoride PET/CT compared to ^{99m}Tc-MDP BS in this field.

Sensitivity and specificity are the most important indicators for evaluating diagnostic performance. Whether equivocal outcomes were considered as positive or negative, the present meta-analysis has shown that ^{18}F-fluoride PET/CT has high pooled sensitivity and specificity both on a patient basis and a lesion basis, which is consistent with the results of most clinical trials. Similar to the previous meta-analysis,[10] ^{18}F-fluoride PET/CT showed both higher pooled sensitivity and specificity when compared with ^{99m}Tc-MDP BS; however, a significant difference could be observed in sensitivity ($p<0.005$), but not in specificity when the

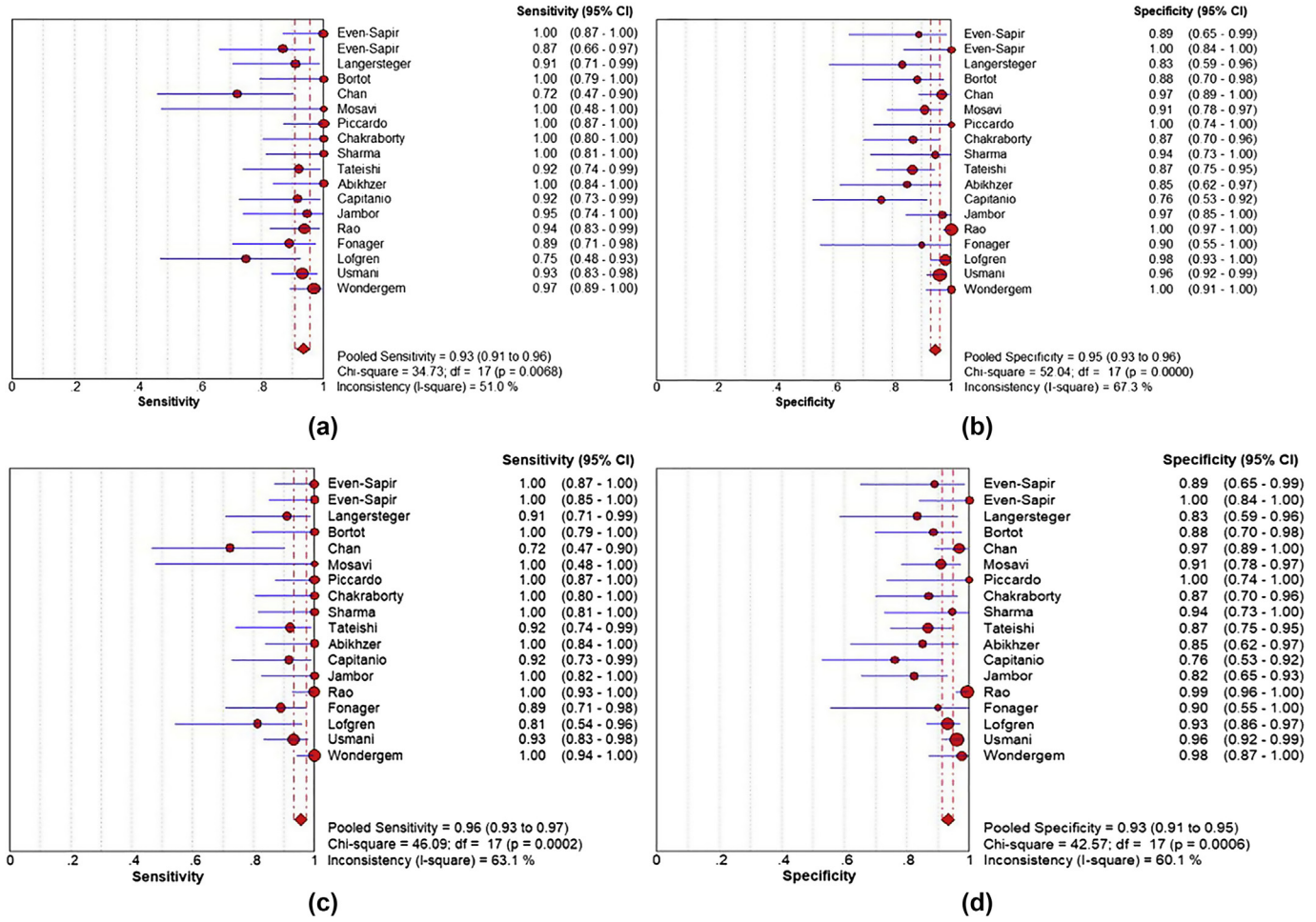

Figure 4 Forest plots of ^{18}F-fluoride PET/CT for detecting BM on patient basis. The pooled sensitivity (a) and specificity (b) when the equivocal image findings were regarded as negative for BM. The pooled sensitivity (c) and specificity (d) when the equivocal image findings were regarded as positive for BM.

equivocal results were considered as negative (p=0.08). In addition, an interesting phenomenon was that ^{99m}Tc-MDP BS has much more equivocal results compared with ^{18}F-fluoride PET/CT. In detail, seven studies compared these two imaging methods, among which three studies comprising 214 patients reported equivocal results, and 43 of 214 could not be diagnosed exactly by ^{99m}Tc-MDP BS, whereas there were only 15 patients that had equivocal results using ^{18}F-fluoride PET/CT. This phenomenon further demonstrated the superior diagnostic performance of ^{18}F-fluoride PET/CT over BS. It would also partially increase the fluctuations of pooled sensitivity and specificity of BS, leading to more uncertainty when comparing these two methods.

Because likelihood ratios are considered to have greater clinical significance [40], the likelihood ratios of ^{18}F-fluoride PET/CT on a patient and a lesion basis were analysed. It is generally believed that the positive likelihood ratio >10, or the negative likelihood ratio <0.1 indicates a relatively high accuracy.[41] In this meta-analysis, only on a patient basis, when the equivocal result was considered positive, then the positive likelihood ratio was <10 (+LR=9.731). In other circumstances, all +LR and −LR satisfied the requirement of high accuracy. DOR is another indicator to describe diagnostic performance, which can combine results from different studies into summary estimates with increased precision. The values of DOR ranges from 0 to infinity, with higher values indicating better discriminatory test performance of this diagnostic method.[42, 43] In this meta-analysis, when the equivocal imaging findings of ^{18}F-fluoride PET/CT were regarded as negative or positive respectively, the DOR values were 166.7 and 161.93 on the patient basis, and 204.71 and 218.35 on the lesion basis. Thus, there is sufficient confidence to indicate that ^{18}F-fluoride PET/CT has superior diagnostic value for detecting BM.

A number of imaging methods can detect BM in addition to ^{18}F-fluoride PET/CT and ^{99m}Tc-MDP BS, but no definitive conclusion has been made as to which method has the best diagnostic performance. A recent meta-analysis compared MRI, CT, PET, BS, and SPECT in detecting vertebral metastases, and the results showed that MRI was the best technique on both on a patient basis and a lesion basis.[44] Another earlier meta-analysis conducted by Yang *et al.* demonstrated a different result. They found that PET and MRI were comparable and both significantly more accurate than CT and BS for the diagnosis of BM;[45] however, most of these previous meta-analysis chose 2-[^{18}F]-fluoro-2-deoxy-

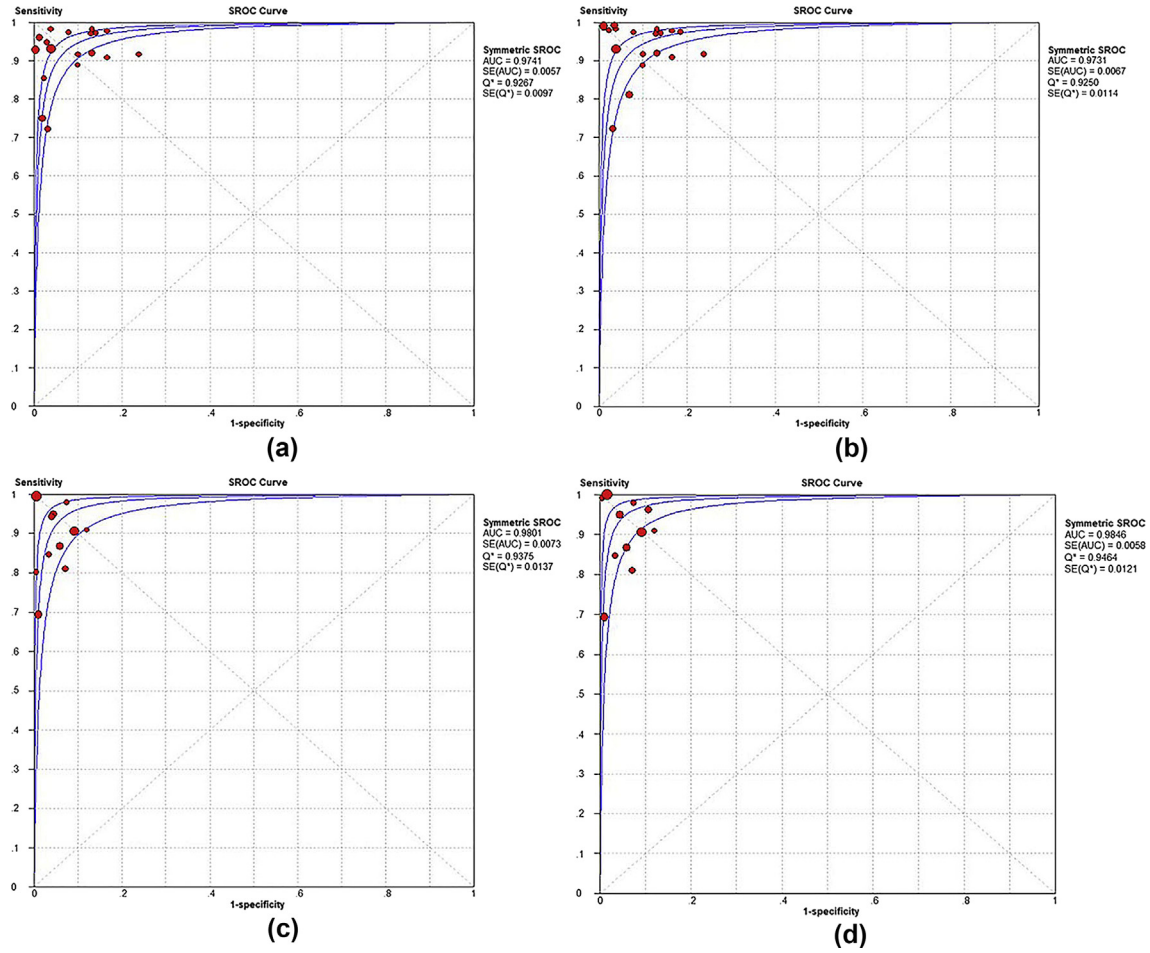

Figure 5 SROC curves of ^{18}F-fluoride PET/CT for detecting BM on patient basis when the equivocal results were considered as negative (a) or positive (b), respectively, and on lesion basis when the equivocal results were considered as negative (a) or positive (b), respectively.

D-glucose (FDG) to represent PET imaging, some of them confound all PET tracers while the diagnostic value of different tracers might be completely different. In fact, ^{18}F-FDG is not a bone-specific tracer and this may cause difficulties in differentiating progressive disease from post-therapy healing in clinical practice.[6] In addition, the diagnostic accuracy of ^{18}F-fluoride has been proved to be better than ^{18}F-FDG.[10] There were too few studies about other imaging methods (such as CT, MRI, SPECT, and ^{18}F-FCH) that fulfilled the present inclusion criteria to enable a review of all imaging methods. It is also worth noting that several studies have demonstrated a significant difference between ^{18}F-fluoride PET and ^{18}F-fluoride PET/CT in detecting BM,[15, 16, 20] but they were not clearly differentiated in the previous meta-analysis.[10] In the present meta-analysis, the focus was on the comparison of ^{18}F-fluoride PET/CT and ^{99m}Tc-MDP BS, and was formulated rigorously and inclusion criteria were implemented, and ^{18}F-fluoride PET from ^{18}F-fluoride PET/CT was excluded, resulting in more credible clinical evidence to illustrate the diagnostic performance of ^{18}F-fluoride PET/CT.

According to the SNM procedure guideline, the effective dose of ^{18}F-fluoride is 0.024 mSv/MBq, which means for a typical activity of 370 MBq, the effective dose is 8.9 mSv for ^{18}F-fluoride. The effective dose of ^{99m}Tc-MDP is 0.0057 mSv/MBq, so for a typical activity of 925 MBq, the effective dose is 5.3 mSv. Thus, the radiation dose of ^{18}F-fluoride is 70% higher than that of ^{99m}Tc-MDP;[46] however, Ohnona *et al.* found that halving the injected ^{18}F-fluoride activity recommended by the SNM practice guideline did not result in loss of information and adversely affect the visual detection of significant foci. This reduction in injection activity leads to a significant decrease in the effective dose, which would become less than or equal to that of ^{99m}Tc-MDP, while providing better image quality after a shorter waiting time. This evidence supported the development of ^{18}F-fluoride PET/CT for the functional detection of BM.[47] In view of the large difference between the cost of ^{18}F-fluoride PET/CT and ^{99m}Tc-MDP BS in different countries, it is difficult to directly compare the cost, but the cost of ^{18}F-fluoride PET/CT is indeed higher than that of ^{99m}Tc-MDP BS; however, regarding the high surgical expense that can be avoided by more accurate diagnostic methods, the additional cost of PET/CT seems reasonable.[48] In addition, with the increasing availability of PET/CT imaging systems and the number of commercial distribution centres for PET radiotracers, the

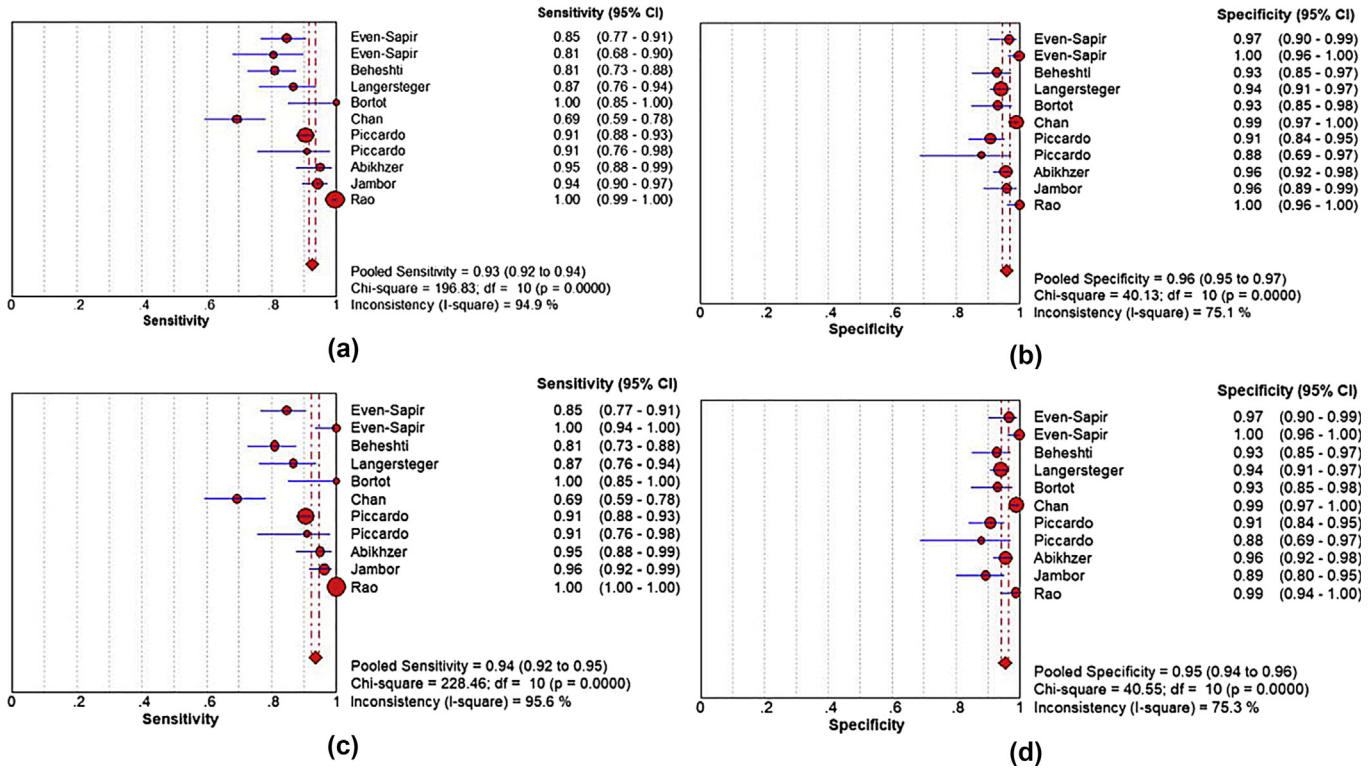

Figure 6 Forest plots of ^{18}F-fluoride PET/CT for detecting BM on lesion basis. The pooled sensitivity (a) and specificity (b) when the equivocal results were considered as negative. The pooled sensitivity (c) and specificity (d) when the equivocal results were considered as positive.

Table 1
The results of subgroup analysis of combined ^{18}F-fluoride positron-emission tomography (PET)/computed tomography (CT) based on the sites of primary tumours.

Cancer type	No. of data sets	Sensitivity (%)	Specificity (%)	+LR	−LR	DOR
Patient basis[a]						
Overall	18	95.6 (93.3–97.2)	93.1 (91.2–94.8)	9.731 (6.808–13.909)	0.075 (0.044–0.128)	161.93 (85.804–305.61)
VC	5	94.8 (89.6–97.9)	92.8 (89.5–95.3)	9.774 (5.523–17.296)	0.084 (0.038–0.187)	170.71 (72.874–399.88)
PC	5	96.4 (91.9–98.8)	93.3 (87.6–96.9)	10.436 (5.012–21.733)	0.067 (0.023–0.199)	200.62 (38.476–1046.1)
BC	3	97.2 (90.3–99.7)	84.9 (72.4–93.3)	5.132 (2.553–10.319)	0.065 (0.022–0.198)	122.67 (16.294–923.53)
Patient basis[b]						
Overall	18	93.4 (90.8–95.5)	94.6 (92.8–96.1)	11.128 (7.293–16.982)	0.099 (0.067–0.146)	166.67 (97.628–284.52)
VC	5	93.3 (87.7–96.9)	95.8 (93.0–97.7)	15.777 (7.979–31.199)	0.087 (0.034–0.225)	279.53 (113.69–687.26)
PC	5	92.9 (87.3–96.5)	94.0 (88.6–97.4)	10.998 (4.228–28.608)	0.100 (0.058–0.174)	132.96 (38.185–462.96)
BC	3	97.2 (90.3–99.7)	84.9 (72.4–93.3)	5.132 (2.553–10.319)	0.065 (0.022–0.198)	122.67 (16.294–923.53)
Lesion basis[a]						
Overall	11	93.5 (92.4–94.5)	95.5 (94.3–96.5)	16.440 (11.116–24.312)	0.092 (0.054–0.158)	218.35 (104.57–455.96)
VC	3	92.2 (88.5–95.0)	93.2 (89.3–96.1)	12.564 (7.392–21.356)	0.070 (0.020–0.248)	204.28 (92.099–453.10)
PC	4	87.6 (83.1–91.3)	94.8 (92.5–96.6)	13.426 (7.068–25.504)	0.126 (0.059–0.271)	118.58 (35.380–397.44)
Lesion basis[b]						
Overall	11	92.7 (91.5–93.7)	95.9 (94.7–96.8)	17.932 (11.881–27.066)	0.097 (0.058–0.161)	204.71 (104.37–401.49)
VC	3	91.1 (87.3–94.1)	95.4 (91.8–97.7)	18.043 (10.276–31.681)	0.085 (0.032–0.225)	264.97 (110.38–636.02)
PC	4	83.6 (78.6–87.8)	94.8 (92.5–96.6)	13.191 (7.402–23.453)	0.181 (0.139–0.237)	88.130 (45.160–171.99)

The data in parentheses represents 95% confidence intervals.
+LR, positive likelihood ratio; −LR, negative likelihood ratio; DOR, diagnostic odds ratio; VC, various cancer; PC, prostate cancer; BC, breast cancer.
[a] Data were calculated when the equivocal results were considered as positive.
[b] Data were calculated when the equivocal results were considered as negative.

high cost could be partially ameliorated by increasing patient throughput and avoiding additional separate CT examinations.[49]

The present meta-analysis had several limitations. First, as a bone biopsy from all lesions was not ethical and practical, the included studies did not have a fully unified standard reference, which is a common obstacle for all research evaluating the diagnostic performance of different imaging methods in the detection of BM.[43] Most of the included studies used clinical and imaging follow-up for at least 6 months to confirm the presence of BM, while the diversity of clinical and imaging methods used in different

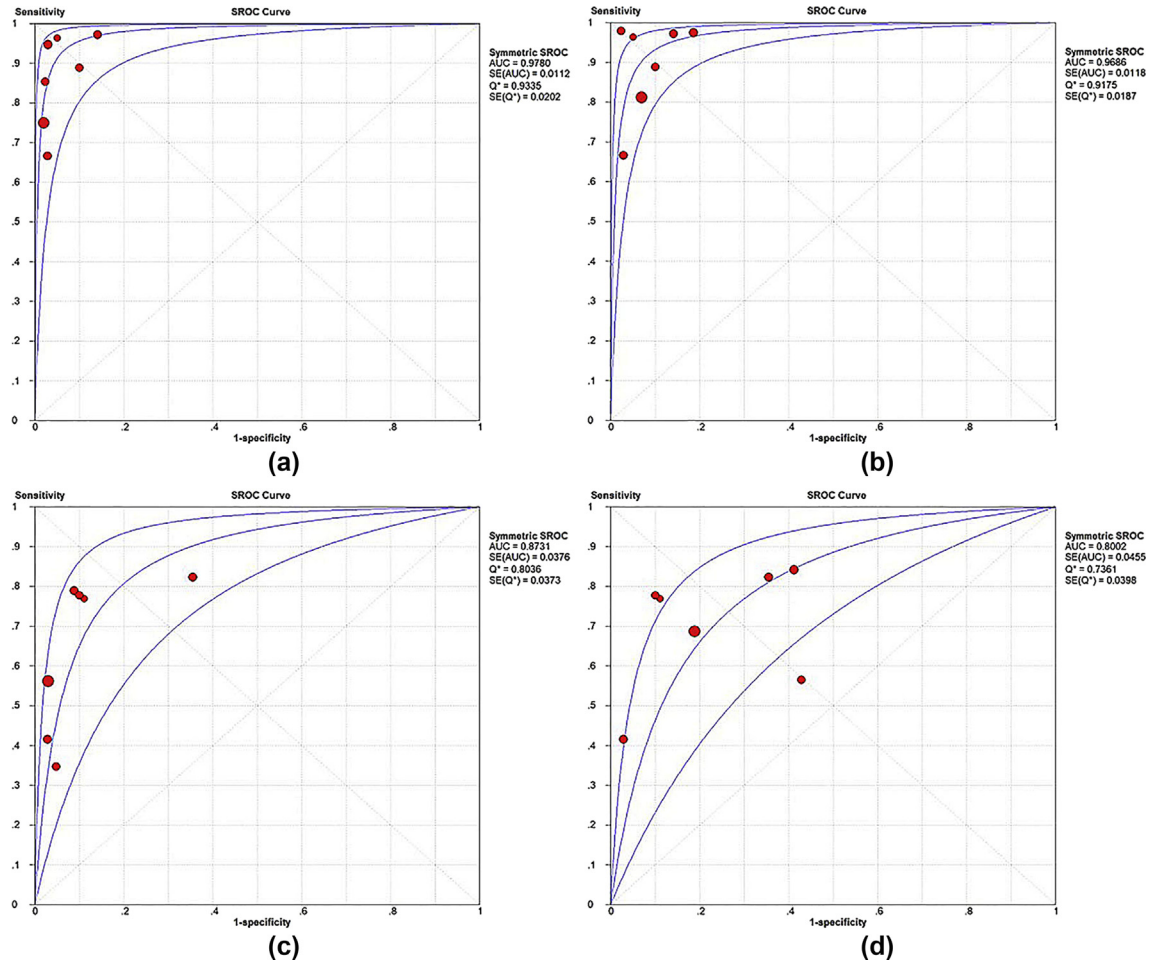

Figure 7 SROC curves of ^{18}F-fluoride PET/CT on patient basis when the equivocal results were regarded as negative (a) or positive (b). SROC curves of ^{99m}Tc-MDP BS on patient basis when the equivocal results were regarded as negative (c) or positive (d).

studies might increase the heterogeneity. Second, the results of subgroup analysis based on the different sites of primary tumours were not highly reliable because of the large variety of primary tumours and the limited number of studies. Therefore, whether the differences in the diagnostic accuracy of ^{18}F-fluoride PET/CT for different primary tumours were due to tumour sites or just because of the limited data could not be determined. Third, although a quality assessment of the included studies was conducted, selection bias, publication bias, verification bias, or work-up differences between the studies might still exist in the original studies.

In conclusion, the present meta-analysis demonstrated the superior diagnostic performance of ^{18}F-fluoride PET/CT in the detection of BM on both a patient and lesion basis. Besides, ^{18}F-fluoride PET/CT showed both higher sensitivity and higher specificity as well as less equivocal results when compared with ^{99m}Tc-MDP BS, indicating that ^{18}F-fluoride PET/CT is a more reliable method for detecting BM.

Declarations of interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

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