Original article

Performance of ^{68}Ga-DOTA-SST PET/CT, octreoscan SPECT/CT and ^{18}F-FDG PET/CT in the detection of culprit tumors causing osteomalacia: a meta-analysis

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Objectives The objective of this study was to assess and compare the performance of ^{68}Ga-DOTA-conjugated-somatostatin-receptor-targeting-peptides (^{68}Ga-DOTA-SST) PET/CT, octreoscan-SPECT/CT and ^{18}F-FDG-PET/CT in the detection of tumor-induced osteomalacia (TIO).

Methods Relevant studies reporting the performance ^{68}Ga-DOTA-SST PET/CT, octreoscan-SPECT/CT and ^{18}F-FDG-PET/CT in TIO were identified by searching PubMed, EMBASE, and Web of Science (last updated June 2019). Two authors independently extracted the numbers of true and false positives, and true and false negatives. The pooled estimates on a per-patient basis were calculated with 95% confidence interval (CI) obtained using a random-effects model.

Results Fourteen studies comprising 346 patients were included in this meta-analysis. The meta-analysis provided the following results on a per-patient analysis. The pooled sensitivities of both ^{68}Ga-DOTA-SST PET/CT (90%, 95% CI 82–95%) and octreoscan-SPECT/CT (83%, 95% CI 75–89%) were found to be significantly higher ($P < 0.005$) than that of ^{18}F-FDG PET/CT (67%, 95% CI 53–80%). There was no statistically significant difference between the sensitivity of ^{68}Ga-DOTA-SST PET/CT and octreoscan-SPECT/CT ($P = 0.161$). Owing to the low number of articles with true negative findings, the pooled specificities were not calculated. A total of 287 tumors were identified in 287 patients according to the data the included studies offered. The majority of the tumors were located in the lower extremities (59.6%, 171/287), followed by craniofacial regions (24.0%, 69/287), torso (9.4%%, 27/287), and upper extremities (6.9%, 20/287).

Conclusion This meta-analysis demonstrates that somatostatin receptor-based imaging modalities outperformed ^{18}F-FDG PET/CT in the detection of TIO, with ^{68}Ga-DOTA-SST PET/CT performing slightly better than octreoscan-SPECT/CT. *Nucl Med Commun* 41: 370–376 Copyright © 2020 The Author(s). Published by Wolters Kluwer Health, Inc.

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Introduction

Tumor induced osteomalacia (TIO), also known as oncogenic osteomalacia, is an uncommon acquired paraneoplastic syndrome characterized by biochemical anomalies, such as hypophosphatemia and hyperphosphaturia, and manifested as long-term debilitating bone pain and muscle weakness [1]. The oncogenic osteomalacia is secondary to a phosphaturic mesenchymal tumor mixed connective tissue variant, which secretes fibroblast growth factor 23 (FGF23) and other phosphaturic proteins [2]. PMTMCTs are usually small, benign and slow-growing polymorphous neoplasms. The overproduction of FGF23 increases renal phosphate loss and decreases renal phosphate reabsorption, leading to hypophosphatemia and consequent osteomalacia [3]. The only curative therapy of the disease is complete resection of the responsible tumor or destruction via radiofrequency ablation [4,5]. PMTMCTs are rare neoplasms that approximately 53% of cases occurred within bones, 45% patients in soft tissue and 3% of patients in the skin [6]. Nevertheless, even with the recognition of TIO, the precise localization of the tumor can be challenging due to their small size and obscure anatomical situation [7]. In addition, the local symptoms directly caused by the slow-growing tumor are frequently overshadowed by the severe systematic symptoms of osteomalacia. These tumors prove to be difficult for conventional anatomy-based imaging techniques to detect.

Functional imaging modalities, such as PET and SPECT, have been utilized with various tracers to detect the culprit tumor inducing osteomalacia. The localization of TIO

using ^{18}F-FDG PET/CT have been described in several case reports and studies [8–11]. As these tumors are slowing growing and commonly small in size, the FDG uptake may be relatively low. TIOs are reported to overexpress somatostatin receptor, mainly subtype 2, allowing the use of somatostatin receptor imaging with PET or SPECT [12]. ^{68}Ga-DOTA-SST PET/CT has higher resolution, better physical characteristic and higher affinity for somatostatin receptor 2, 5 compared to octreoscan SPECT/CT [13]. Therefore, it is speculated that ^{68}Ga-DOTA-SST might have a higher sensitivity than octreoscan-SPECT/CT in detecting TIO [13]. However, evidence on the direct comparison of ^{68}Ga-DOTA-SST PET/CT and octreoscan-SPECT/CT, as well as ^{18}F-FDG PET/CT is limited. The aim of this meta-analysis is to assess and compare the efficacy of ^{68}Ga-DOTA-SST PET/CT with octreoscan-SPECT/CT and ^{18}F-FDG PET/CT in detecting TIO.

Materials and methods
Search strategy
We performed a comprehensive literature search on PubMed, EMBASE and Web of Science. The search algorithm used was based on the combination of the following keywords: 'tumor-induced osteomalacia OR oncogenic osteomalcia'; '18F-fluorodeoxyglucose OR FDG'; '68 Ga OR 68 gallium'; '99mTc-HYNIC-TO-COR ^{111}In-pentetreotide OR octreotide scintigraphy OR somatostatin receptor scintigraphy'. We placed no restrictions on the language or date of publication. Reference lists of the retrieved articles and relevant review articles were also checked to identify studies that may have been missed by the initial database search.

Study selection
Studies were included based on the following criteria: (1) ^{68}Ga-DOTA-SST or ^{18}F-FDG PET/CT or Octreoscan-SPECT/CT were performed in patients suspicious of TIO; (2) studies that reported the diagnostic performance data; (3) clinical studies that included at least five patients. The exclusion criteria were as follows: (1) review articles, cases, editorials or letters, comments, conference proceedings, preclinical studies, animal studies; (2) patients with recurrent TIO; (3) duplicate data; (4) non-original articles.

Data extraction and quality assessment
Study and clinicopathological characteristics were extracted from the selected studies using a standardized form. The methodologic quality of included studies was evaluated using the Quality Assessment of Diagnostic Accuracy Studies-2 tool (QUADAS-2) [14]. The QUADAS-2 tool primarily assesses four domains: risk of bias in patient selection; index test; reference standard; and the timing of the reference test. Data extraction and quality assessment were independently performed by two independent reviewers; any disagreements were resolved by consensus.

Statistical analysis
The reference standard employed by the included studies was either pathological diagnosis or clinical diagnosis. In certain articles where there were no false-positives (FPs) and true-negatives (TNs), the 'detection rate' was used as 'sensitivity'. From each included study, the number of true-positives, FPs, TNs and false-negatives were obtained on a per-patient basis if available. A random-effects model was used for statistical pooling of the data, taking into account the heterogeneity between studies. Heterogeneity among those eligible studies was assessed by the I^2 test. Heterogeneity was considered low if I^2 statistic was 25%, moderate if I^2 statistic was 50% and high if I^2 statistic was 75%. Since most of the studies did not apply a direct comparison among imaging methods, the Z test was used to find whether the pooled sensitivity was significantly different among imaging modalities [15–17]. For P value, the level of statistical significance was set to 0.05. All statistical analyses were performed using Meta-disc 1.4 software and SPSS version 21.

Results
Literature search and study characteristics
The process of selecting studies for the meta-analysis is shown in Fig. 1. A total of 370 articles were obtained through the initial search. After the removal of 192 duplicate articles and exclusion of 157 studies based on title and abstract review. There were 21 potentially eligible studies. Finally, 14 studies, comprising a total sample size of 346 patients with TIO met all inclusion criteria, and they were included in this meta-analysis. The summary of characteristics and statistics of the included studies are described in Tables 1 and 2. The imaging modalities used for TIO included ^{68}Ga-DOTA-SST PET/CT, ^{18}F-FDG PET/CT, ^{99m}Tc-HYNIC-TOC SPECT/CT and ^{111}In-pentetreotide SPECT/CT.

Quality assessment
Regarding the patient selection domain, 10 studies had a high risk of bias because they were retrospective and did not provide information about consecutive enrollment [18–27]. Regarding the index test domain, the included studies were all classified as unclear because they lacked information about whether they were interpreted without the knowledge of the reference standard. Even so, we believe that the index test interpretation was made without knowing the reference standard result because the surgical resection of the suspected TIO could only be performed when imaging techniques detect suspicious culprit tumor. Regarding the reference standard domain, in the same way, all studies showed a high risk of bias, as it was unclear whether reference standard interpretation was blinded to the index test results. Regarding the flow and timing domain, all studies had a high risk of bias, as the PET-reference standard interval was not provided. The applicability of the included studies was adequate and all classified as low.

Fig. 1
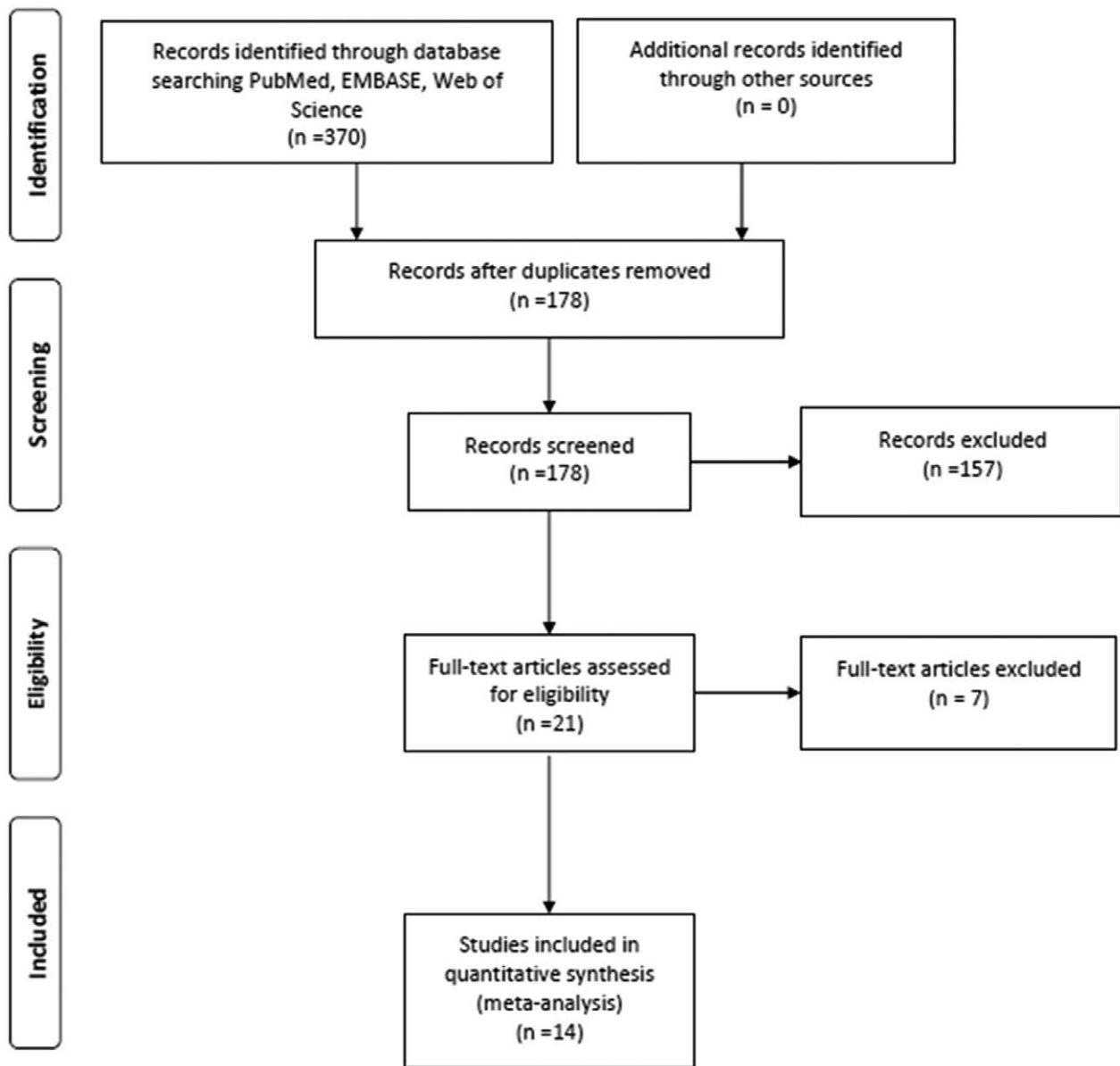
Flowchart diagram presenting the selection of eligible studies.

Quantitative synthesis

From the included study protocols, six used ^{68}Ga-DOTA-SST PET/CT [21,23,24,28–30], two ^{18}F-FDG PET/CT [26,31], two octreoscan-SPECT/CT [18,32], two ^{68}Ga-DOTA-SST PET/CT, ^{18}F-FDG PET/CT and octreoscan-SPECT/CT [20,33], one used ^{68}Ga-DOTA-SST and ^{18}F-FDG PET/CT [22], and one used ^{18}F-FDG PET/CT and octreoscan-SPECT/CT [19] as index test examinations. For each study, the metrics of sensitivity and specificity were obtained. Due to the low number of articles providing TN and FP findings, pooled specificity was not calculated in this meta-analysis. The sensitivity

values, with the corresponding 95% confidence intervals (CIs), were calculated for all included studies (Fig. 2). The pooled sensitivities of both ^{68}Ga-DOTA-SST PET/CT (90%; 95% CI 82–95%) and octreoscan-SPECT/CT (83%; 95% CI 75–89%) were found to be significantly higher ($P < 0.005$) than that of ^{18}F-FDG PET/CT (67%; 95% CI 53–80%). The pooled sensitivity of ^{68}Ga-DOTA-SST PET/CT was higher than that of octreoscan-SPECT/CT, but the difference was not statistically significant ($P = 0.161$). The random-effects model was used because of moderate to substantial heterogeneity among the included studies ($I^2 = 66.9\%$ for ^{68}Ga-DOTA-SST PET/

Table 1 Characteristics of studies included in the meta-analysis

Author	Year	Country	Prospective	Consecutive enrollment	No. patient	Index test
Jan de Beur *et al.*	2002	USA	Prospective	NR	11	^{111}In-pentetreotide
Jing *et al.*	2013	China	Retrospective	NR	183	^{99m}Tc-HYNIC-TOC
Clifton-Bligh *et al.*	2013	USA	Retrospective	Consecutive	6	^{68}Ga-DOTATATE
Chong *et al.*	2013	USA	NR	NR	27	^{18}F-FDG/^{111}In-pentetreotide
Breer *et al.*	2014	Germany	Retrospective	Consecutive	5	^{68}Ga-DOTATATE
Jadhav *et al.*	2014	India	Retrospective	NR	9	^{99m}Tc-HYNIC-TOC/^{18}F-FDG/^{68}Ga-DOTATATE
Zhang *et al.*	2015	China	Retrospective	NR	43	^{68}Ga-DOTATATE
Agrawal *et al.*	2015	India	Retrospective	NR	6	^{18}F-FDG/^{68}Ga-DOTATATE
El-Maouche *et al.*	2016	USA	Prospective	NR	11	^{18}F-FDG/^{68}Ga-DOTATATE/^{111}In-pentetreotide
Jain *et al.*	2016	India	Prospective	NR	8	^{18}F-FDG
Bhavani *et al.*	2016	India	NR	NR	10	^{68}Ga-DOTANOC
Satyaraddia *et al.*	2017	India	Retrospective	NR	8	^{68}Ga-DOTATATE
Paquet *et al.*	2018	Switzerland	Retrospective	Consecutive	14	^{68}Ga-DOTATOC
Jagtap *et al.*	2011	India	Retrospective	NR	5	^{18}F-FDG

NR, not reported.

Table 2 Summary of statistics of included articles

Author	Patients	Index test	True-positive	False-positive	False-negative	True-negative	Sensitivity (%)	Specificity (%)
Jing *et al.*	183	Octreoscan SPECT/CT	69	1	11	102	86.30	99.10
Clifton-Bligh *et al.*	6	^{68}Ga-DOTATATE PET/CT	6	NA	0	NA	100	NA
Chong *et al.*	31	^{18}F-FDG PET/CT	14	7	2	4	88	36
		Octreoscan SPECT/CT	18	7	1	4	94.70	36.40
Breer *et al.*	5	^{68}Ga-DOTATATE PET/CT	5	NA	0	NA	100	NA
Jadhav *et al.*	9	^{68}Ga-DOTATATE PET/CT	7	NA	0	NA	100	NA
		Octreoscan SPECT/CT	6	NA	0	NA	100	NA
		^{18}F-FDG PET/CT	4	NA	4	NA	50	NA
Zhang *et al.*	43	^{68}Ga-DOTATATE PET/CT	32	1	0	10	100	90.9
Agrawal *et al.*	6	^{68}Ga-DOTATATE PET/CT	5	NA	1	NA	83.30	NA
		^{18}F-FDG PET/CT	2	NA	2	NA	50	NA
El-Maouche *et al.*	11	^{68}Ga-DOTATATE PET/CT	6	NA	5	NA	54.50	NA
		Octreoscan SPECT/CT	4	NA	7	NA	36.30	NA
		^{18}F-FDG PET/CT	4	NA	7	NA	36.30	NA
Jain *et al.*	8	^{18}F-FDG PET/CT	7	NA	1	NA	87.55	NA
Bhavani *et al.*	10	^{68}Ga-DOTANOC PET/CT	9	NA	1	NA	90	NA
Satyaraddia *et al.*	8	^{68}Ga-DOTATATE PET/CT	8	NA	0	NA	100	NA
Paquet *et al.*	14	^{68}Ga-DOTATOC PET/CT	8	1	3	2	73	66.7
Jagtap *et al.*	5	^{18}F-FDG PET/CT	4	NA	1	NA	80	NA
Jan de Beur *et al.*	7	Octreoscan SPECT/CT	5	NA	2	NA	71	NA

NA, not available.

CT, 77.4% for octreoscan-SPECT/CT and 56.8% for ^{18}F-FDG PET/CT). A total of 287 tumors were identified in 287 patients according to the data the included studies offered. We found that most of the tumors were located in the lower extremities (59.6%, 171/287), followed by craniofacial regions (24.0%, 69/287), torso (9.4%, 27/287) and upper extremities (6.9%, n = 20/287).

Discussion

Functional imaging methods have played a significant role in the detection of suspicious lesions of TIO. Several studies have used ^{68}Ga-DOTA-SST PET/CT, octreoscan-SPECT/CT and ^{18}F-FDG PET/CT in patients with TIO and reported favorable results. But only a few of them have compared these diagnostic techniques in the same group of patients. And these studies have limited power as they only enrolled small number of patients. This might be due to that TIO is a rare disease, for which large cohort studies are usually not feasible. Meta-analysis is regarded as an appropriate method to tackle this problem. Therefore, we have pooled reported data of the

published studies in order to assess and compare the efficacy of ^{68}Ga-DOTA-SST PET/CT, octreoscan-SPECT/CT and ^{18}F-FDG PET/CT in detecting TIO.

As expected, results of quantitative indirect comparison of pooled estimates showed that ^{68}Ga-DOTA-SST PET/CT exhibited the highest sensitivity in the detection of TIO, followed by octreoscan-SPECT/CT and ^{18}F-FDG PET/CT. Both somatostatin receptor-based functional imaging modalities had significant higher sensitivity than ^{18}F-FDG PET/CT. ^{18}F-FDG is the most widely used radiotracer in nuclear medicine and also the first PET tracer reported in literature to be used in the detection of TIO [9]. The reported sensitivity of ^{18}F-FDG PET/CT of published studies in detecting TIO varied greatly from 36.3 to 88%, with the pooled sensitivity being 67% and also the lowest among the three imaging modalities in this meta-analysis. This result might suggest the limitation in its utility. The relatively poor performance of ^{18}F-FDG PET/CT might be mainly due to the benign nature and low metabolic activity of the mesenchymal tumors associated with TIO [31].

Fig. 2
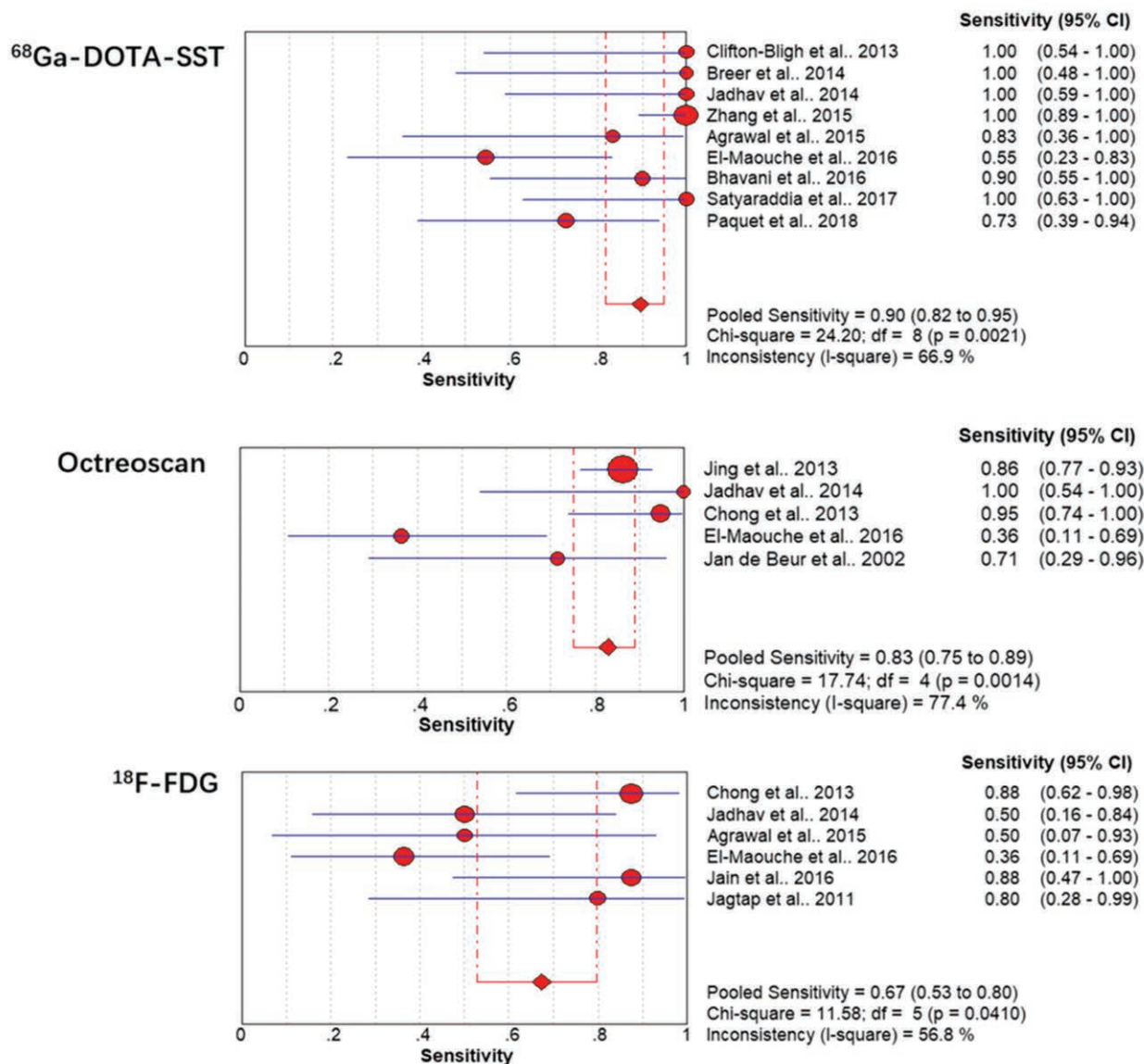
Forest plot of individual study results showing estimates of sensitivity and 95% CI. CI, confidence interval.

The overexpression of somatostatin receptor with a predominance of subtype 2 in these tumors made it possible for the utility of somatostatin receptor-based functional scans [12]. Somatostatin receptor-based imaging techniques include ^{99m}Tc-HYNIC-TOC SPECT/CT, and ^{111}In-pentetreotide SPECT/CT and ^{68}Ga-DOTA-SST PET/CT. To the best of our knowledge, only two studies with 20 subjects have performed a direct comparison between octreoscan-SPECT/CT and ^{68}Ga-DOTA-TATE PET/CT in patients with TIO [20,33]. The reported sensitivities of octreoscan-SPECT/CT and ^{68}Ga-DOTA-TATE PET/CT were 100% vs. 100% and 36.3% vs. 55%, respectively. However, the conclusions of these two studies are not solid due to the limited subjects enrolled. The strength of the current meta-analysis is the quantitative indirect comparison of the performance of octreoscan-SPECT/CT and ^{68}Ga-DOTA-SST PET/CT involving a large sample size. There was no statistically significant difference between the sensitivity of ^{68}Ga-DOTA-SST PET/CT and octreoscan-SPECT/CT ($P = 0.161$). Therefore, octreoscan-SPECT/CT is a valuable alternative to ^{68}Ga-DOTA-SST PET/CT in clinic. Still, wherever available, ^{68}Ga-DOTA-SST PET/CT should be preferred in light of the better physical characteristics and spatial resolution it offers than octreoscan-SPECT/CT.

The majority of the tumors were located in the lower extremities, followed by craniofacial regions, torso and upper extremities. The results are consistent with previously published studies [18,21,34]. More relevant researches are still needed to find out the underlying explanation for the location of tumors.

There are considerable limitations in this meta-analysis. Over half of the included studies are retrospective in nature, which might lead to overestimation of outcomes. Only one study performed a direct comparison among the three imaging modalities. Positive result publication bias is a major concern, because significant or favorable study results are easier to be published. Pooled specificity was not calculated in this meta-analysis, because most studies did not provide TN and FP findings. There are no other measures of diagnostic accuracy, including specificity, positive predictive value, negative predictive value and Diagnostic Odds Ratio, presented other than sensitivity data. Another major limitation is the lack of valid reference standard test and time and flow of imaging interpretation because all studies did not report whether reference standard was blinded to the index test and not specify the exact time interval between PET imaging and biopsy or surgery. There were heterogeneities in study design, patient selection, sample size, imaging acquisition among the included studies.

Conclusion

Tumor localization is a crucial step in the management of TIO. This meta-analysis demonstrates that somatostatin receptor-based imaging modalities outperformed ¹⁸F-FDG PET/CT in the detection of TIO, with ⁶⁸Ga-DOTA-SST PET/CT performing slightly better than octreoscan-SPECT/CT.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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