OPEN

Original article

Nuclear Medicine Communications

Sensitivities evaluation of five radiopharmaceuticals in four common medullary thyroid carcinoma metastatic sites on PET/CT: a network meta-analysis and systematic review

Pengyu Li[a], Yujie Zhang[b], Tianfeng Xu[a], Jingqiang Zhu[a], Tao Wei[a,b] and Wanjun Zhao[a]

Objectives Detecting medullary thyroid carcinoma (MTC) metastatic lesions accurately is still a challenge for clinicians. PET/computed tomography (PET/CT) seems to be the most effective method in recent years. However, the sensitivity of each radiopharmaceutical varies greatly in different metastatic sites. We aim to investigate and compare five novel and common PET or PET/CT radiopharmaceutical sensitivities at the four most frequent metastatic sites by network meta-analysis.

Methods We searched for studies evaluating PET/CT radiopharmaceutical sensitivities at different metastatic sites in PubMed, Web of Science, Embase, and Cochrane Library. The risk bias was analyzed, and publication bias was accessed by funnel plot asymmetry tests. We performed both global inconsistency and local inconsistency tests by evaluating the agreement between direct and indirect comparisons. Then, we made pairwise meta-analyses and network meta-analyses for each metastatic site. Finally, we performed the surface under the cumulative ranking curves (SUCRA) and calculated the SUCRA values to rank the probability of each radiopharmaceutical being the most sensitive method.

Results In our results, 243 patients from 9 clinical studies which accessed sensitivities of different radiopharmaceuticals in MTC metastatic sites were included. For lymph nodes and liver, TF2/^{68}Ga-SSM288 showed the highest SUCRA values (0.974 in lymph nodes, 0.979 in liver). The SUCRA values for ^{18}F-DOPA and ^{68}Ga-SSA for bone metastatic lesions were nearly identical (0.301 and 0.319, respectively) and were higher than the other three radiopharmaceuticals. For lung lesions, ^{11}C-methionine had the highest SUCRA value (0.412).

Conclusion TF2/^{68}Ga-SSM288 had the best sensitivity in lymph nodes and liver lesions. ^{11}C-methionine was most sensitive in lung lesions. While ^{18}F-DOPA and ^{68}Ga-SSA had familiar sensitivities to be the best two radiopharmaceuticals. *Nucl Med Commun* 44: 1114–1125 Copyright © 2023 The Author(s). Published by Wolters Kluwer Health, Inc.

Nuclear Medicine Communications 2023, **44**:1114–1125

Keywords: medullary thyroid carcinoma, metastatic sites, network meta-analysis, PET/CT, radiopharmaceutical

[a]Department of Thyroid Surgery, West China Hospital, Sichuan University and [b]Laboratory of Thyroid and Parathyroid Disease, Frontiers Science Center for Disease-related Molecular Network, West China Hospital, Sichuan University, Chengdu, China

Correspondence to Wanjun Zhao, Department of Thyroid Surgery, West China Hospital, Sichuan University, No.37, Guoxue Alley, Chengdu 610041, China
Tel: +86 15208286983; fax: +86 85425932; Email: surgeonwei@163.com

Received 19 July 2023 **Accepted** 6 September 2023.

Introduction

Medullary thyroid carcinoma (MTC) is a rare neuroendocrine cancer that originates from parafollicular C cells (C-cells), accounting for 5% of all thyroid malignancies [1]. It most commonly presents as a solitary thyroid nodule in patients at their first diagnoses [2]. Though MTC has a low incidence, it shows high distant and local nodal metastatic rates of about 30–50% and 70–80% respectively, and accounts for 13.4% of all thyroid-related death [3–5]. Lymph nodes, lung, bone, and liver are the most common metastatic sites [6]. Surgery is the only potentially curative treatment for patients with MTC nowadays [2], while MTC is insensitive to chemotherapy and radiation therapy [7]. Re-operation, local treatments based on imaging findings (i.e. external beam radiotherapy, thermal ablations), and tyrosine kinase inhibitors can be used to treat progressive MTC [8] when MTC patients' tumors progressed with postoperative recurrence and metastases.

During the postoperative follow-up of MTC patients, Serum calcitonin (Ctn) and carcinoembryonic antigen (CEA), which are secreted by parafollicular C-cells, were frequently used as valuable tumor markers and monitoring indicators to detect metastases or recurrence [9]. Additionally, imaging methods have been used more regularly and regarded as an important following-up method in recent years. ATA (American Thyroid Association)

DOI: 10.1097/MNM.0000000000001773

guidelines [8] indicated that additional imaging procedures need to be used in patients with elevated postoperative Ctn greater than 150 pg/ml. Moreover, imaging techniques can show the precise location of the metastases or recurrence and the characteristics of lesions, whereas biochemical indicators only qualitatively evaluate metastatic recurrence [10]. Imaging findings can provide visual evidence for diagnosis and treatment selection.

In clinical practice, conventional imaging methods for MTC patients included ultrasonography, computed tomography (CT), and magnetic resonance imaging. These methods were inadequate since they can only morphologically demonstrate the local metastases or recurrence [11]. Meanwhile, these methods usually failed to detect distant metastatic or recurrent sites [8,12,13], making it difficult for clinicians to diagnose and treat tumor progression. PET imaging, either PET or hybrid PET/CT had the most encouraging results for detecting and localizing both local and distant recurrent or metastatic MTC lesions using various radiopharmaceuticals [14,15]. The recent 2020 EANM guidelines recommended particularly carrying out PET/CT scans in MTC patients with persistent or recurrent disease [14]. The common radiopharmaceuticals used in MTC were ^{18}F-FDG, ^{18}F-DOPA, and ^{68}Ga-SSA [16]. Various PET or PET/CT radiopharmaceuticals had different sensitivities in metastatic sites. Beheshti *et al.* [17] found that ^{18}F-DOPA PET could detect 94% of lesions, whereas only 62% of lesions were detected by ^{18}F-FDG PET. Verbeek *et al.* [18] indicated that ^{18}F-FDG was more effective than ^{18}F-DOPA at identifying patients with MTC biochemical progression. Souteiro *et al.* [19] found that ^{68}Ga-SSA was more sensitive than ^{18}F-FDG (69.2% vs. 53.9%, respectively). There is a wide variation between the findings of different studies, and there is no definitive conclusion about which radiopharmaceutical is the most sensitive method at different metastatic sites. Additionally, we found that only one meta-analysis was conducted by Lee *et al.* [20] about the overall detection rate of five different PET/CT radiopharmaceuticals in MTC 3 years ago. This meta-analysis only accessed the overall effects of PET or PET/CT radiopharmaceuticals. However, this meta-analysis did not assess the sensitivity of each radiopharmaceutical at different metastatic sites. Meanwhile, the explicit metastatic sites were also not discussed or analyzed in this meta-analysis. Which radiopharmaceutical was most sensitive or effective for different local or distant metastatic lesions is still unknown. Clinicians must consider how to choose an appropriate PET/CT radiopharmaceutical according to suspected local or distant metastatic lesions before deciding whether to operate again or pursue other treatment options [17,21,22], which was significant for the patient's prognosis. The objective of this network meta-analysis and systematic review is to investigate and compare sensitivities of the five novel and common PET/CT radiopharmaceuticals at the four most common recurrent or metastatic MTC sites (Lymph nodes, Bone, Lung, and Liver) for the first time. We also aim to provide evidence-based knowledge for clinicians to choose the most effective PET/CT imaging radiopharmaceutical when distinct local or distant metastases were found in MTC patients.

Materials and methods

This network meta-analysis and systematic review were designed and performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement for reporting systematic reviews and meta-analyses [23]. Ethics approval is not required for network meta-analyses and systematic reviews [24].

Data sources, search strategy

Two authors independently searched literature published in Pubmed, Web of Science, Embase, and Cochrane Library up to 11 April 2022. We used the following keywords in all fields as search strategy: (1) 'PET' or 'PET/computed tomography' or 'PET' or 'PET/CT', (2) 'medullary thyroid cancer' or 'medullary thyroid carcinoma', (3) 1 and 2. We considered possibly eligible studies for clinical researches. We also manually searched the researched lists of key articles for additional studies.

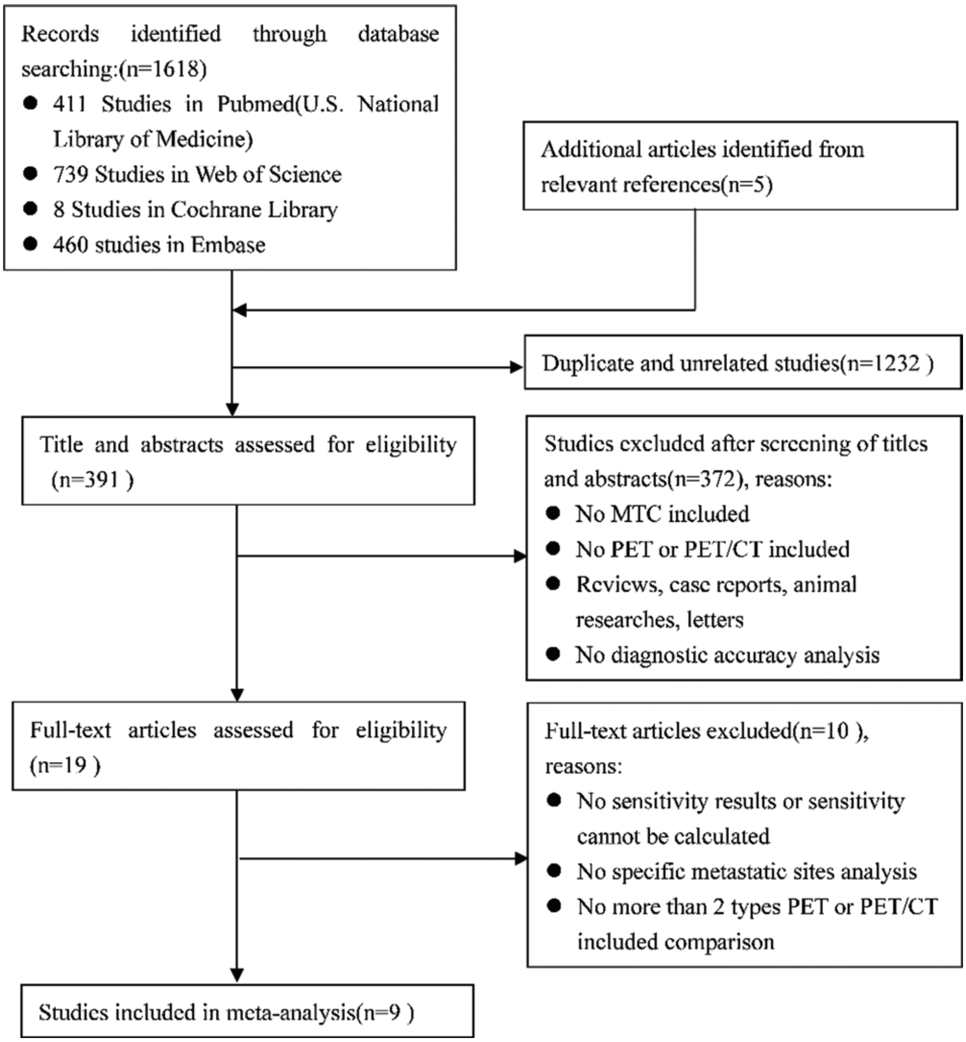
Study selection

The inclusion criteria for eligible studies were: (1) retrospective or prospective studies; (2) studies using PET or PET/CT; (3) studies with more than two radiopharmaceuticals; (4) patients with elevated Ctn or CEA verified as metastatic or recurrent MTC by positive findings of follow-up or histology; (5) studies with more than 10 patients; (6) studies analyzed at least one MTC recurrent or metastatic site; (7) available data of true-positive (TP) and false-negative (FN) numbers in each lesion-based analysis. Studies were excluded as follows: (1) the full text of studies could not be accessed online or by request to authors; (2) reviews, letters, case reports, and animal researches; (3) no clearly defined metastatic sites analysis; (4) original data of lesion-based analysis cannot be reached; (5) studies not in English.

Quality assessment and data extraction

The overall quality of the included studies in this review was critically appraised by 2 authors independently, based

Fig. 1



Search diagram for eligible studies of PET/CT radiopharmaceuticals' sensitivities at different metastatic sites.

on the 15-item modified Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) [25]. The QUADAS-2 tool primarily assesses 4 domains: risk of bias in Patient Selection, Index Test, Reference Standard, and Flow and Timing of reference test. Discrepancies between the selection of studies and in the data extraction, reviewers who were blinded to the journal, author, institution, and date of publication independently selected articles based on the inclusion criteria. Scores were assigned to study design characteristics and examination results using a standardized form based on the QUADAS-2 tool. We used Review Manager 5 (RevMan 5.4.1; Cochrane Collaboration, Oxford, UK) to assess the quality.

A standardized data form was used to extract all data for evaluation. The information we collected from each study included the first authorship, the publication year, the type of study, sample size, imaging method, radiopharmaceutical type, mean Ctn and CEA, overall diagnostic sensitivity, and included metastatic sites. Each study was analyzed to retrieve the numbers of TP and TN of the including radiopharmaceuticals in metastatic site analysis, according to the reference standard.

Publication of bias of individual studies

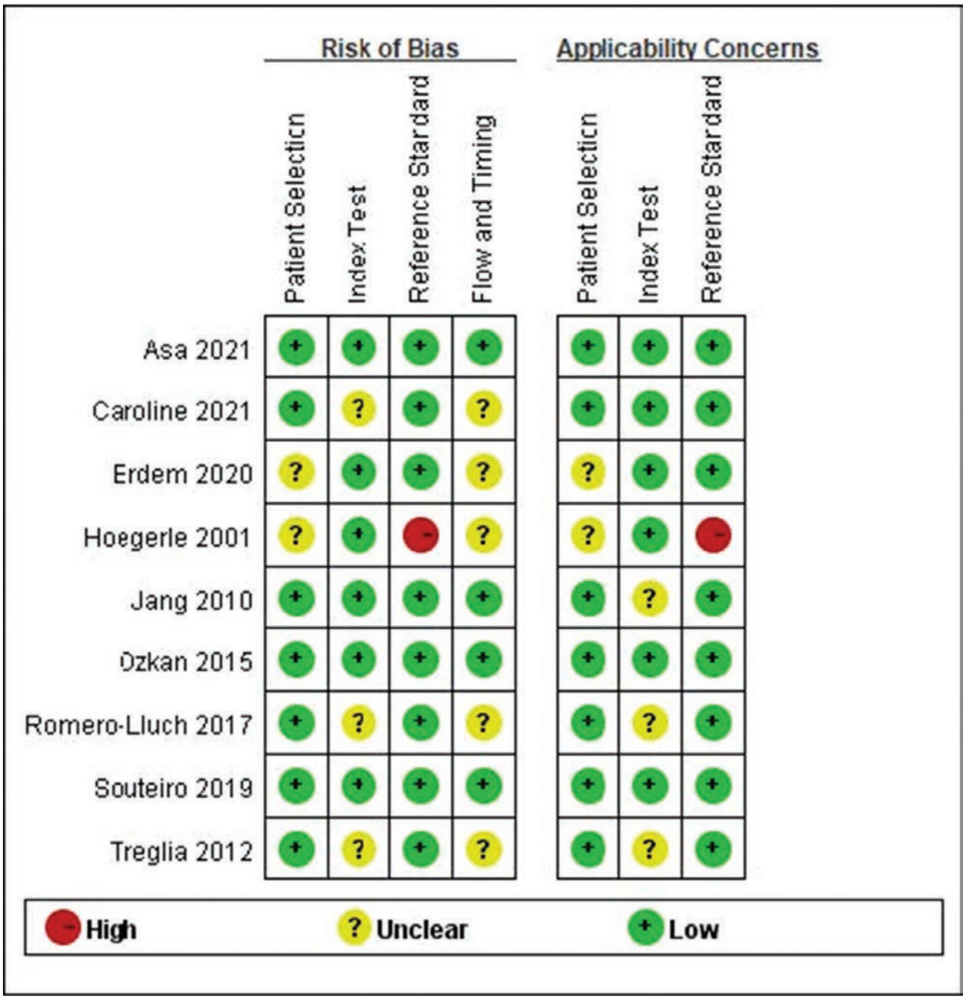
We used funnel plots to explain the publication bias. Asymmetry outcomes of funnel plots indicated publication bias. The funnel plots were generated through STATA version 17.0 software (Stata Corp LP, College Station, Texas, USA) [26].

Table 1 **Characteristics of the included studies**

Author\year	Country	S type	Sample size	Imaging method<? Char=Mixed?>	Radiopharmaceuticals	Mean Ctn (pg/ml)	Mean CEA(ng/ml)	Overall sensitivity					Included sites
								FDG	^{18}F-DOPA	^{68}Ga-SSA	^{11}C-methionine	TF$_2$/^{68}Ga IMP288	
Asa. *et al.* 2021 [33]	Turkey	P	46	PET/CT	^{18}F-DOPA;^{68}Ga-SSA	2031.9	68.3	\	87.90%	79.90%	\	\	1,2,3,4
Milin. *et al.* 2021 [32]	France	R	25	PET/CT	^{18}F-DOPA;TF$_2$/^{68}Ga IMP288	488	18	\	65%	\	\	92%	1,2,3,4
Erdem. *et al.* 2020	Turkey	R	73	PET/CT	^{18}F-FDG;^{68}Ga-SSA	\	\	72.40%	\	88.10%	\	\	1,2,3,4
Souteiro. *et al.* 2019 [19]	Portugal	R	13	PET/CT	^{18}F-FDG,^{68}Ga-SSA	828	19.31	76.10%	\	80.30%	\	\	1,2,3,4
Romero. *et al.* 2017 [34]	Spain	R	18	PET/CT	^{18}F-DOPA;^{18}F-FDG	311.1	11.6	57%	100%	\	\	\	1,3,4
Ozkan. *et al.* 2015 [37]	Turkey	R	22	PET/CT	^{18}F-FDG;^{68}Ga-SSA	871.5	11.2	51.70%	\	91.10%	\	\	1,2,3
Treglia. *et al.* 2012 [39]	Italy	R	18	PET/CT	^{18}F-DOPA;^{18}F-FDG;-^{68}Ga-SSA	2580	67.6	28%	85%	20%	\	\	1,3,4
Jang. *et al.* 2010 [41]	Korea	R	17	PET/CT	^{11}C-metheilin;^{18}F-FDG	370	13.8	79.50%	\	\	72.70%	\	1,2,3,4
Hoegerle. *et al.* 2001 [44]	Germany	P	11	PET	^{18}F-DOPA;^{18}F-FDG	1120.9	165.1	43.70%	87.50%	\	\	\	1

1, lymph nodes; 2, lung; 3, bone; 4, liver.
CEA, carcinoembryonic antigen; Ctn, serum calcitonin; P, prospective; PET/CT, PET computed tomography; R, retrospective.

Fig. 2

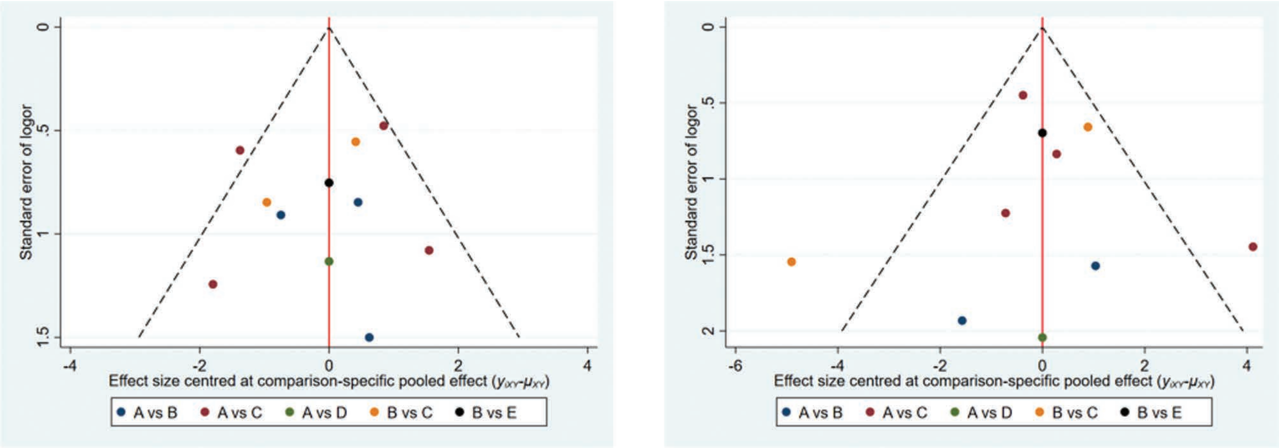


	Risk of Bias				Applicability Concerns		
	Patient Selection	Index Test	Reference Stardard	Flow and Timing	Patient Selection	Index Test	Reference Stardard
Asa 2021	+	+	+	+	+	+	+
Caroline 2021	+	?	+	?	+	+	+
Erdem 2020	?	+	+	?	?	+	+
Hoegerle 2001	?	+	-	?	?	+	-
Jang 2010	+	+	+	+	+	?	+
Ozkan 2015	+	+	+	+	+	+	+
Romero-Lluch 2017	+	?	+	?	+	?	+
Souteiro 2019	+	+	+	+	+	+	+
Treglia 2012	+	?	+	?	+	?	+

- High
? Unclear
+ Low

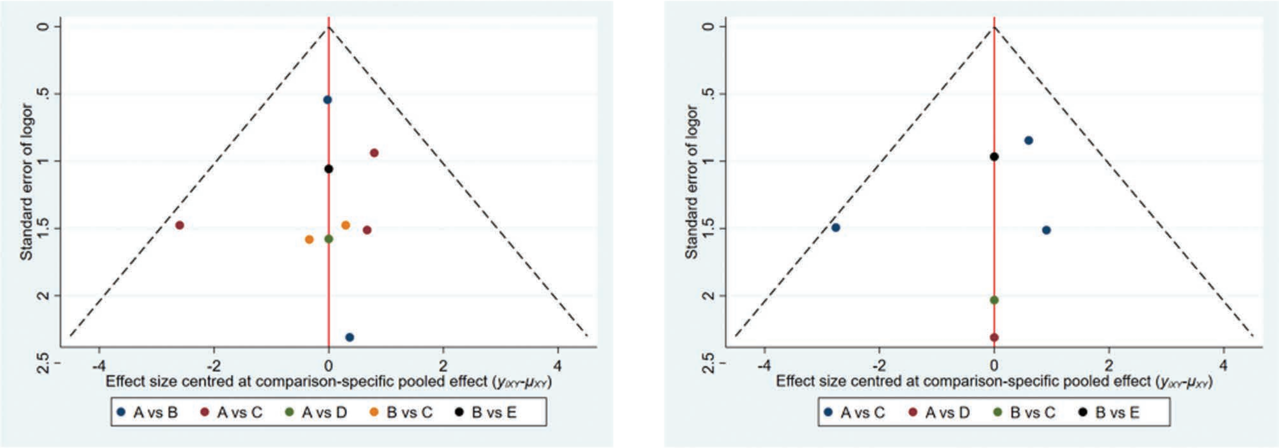
Risk bias and applicability concerns summary based on 15 items QUADAS-2. [Risk bias of applicability concerns of each study according to Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2). The overall quality of the included studies was deemed satisfactory.].

Fig. 3



Lymph nodes

Bone



Liver

Lung

Publication bias of included studies with sensitivity analysis at different metastatic sites. [Funnel plot for PET imaging with 5 different radiopharmaceuticals for the sensitivity in each site of metastatic MTC with different analytic criteria. In all 4 metastatic sites network meta-analyses, individual studies are distributed symmetrically and towards the top, there was no evidence of publication bias. (a) ^{18}F-FDG; (b) ^{18}F-DOPA; (c) ^{68}Ga-SSA; (d) ^{11}C-methionine; (e) TF$_2$/^{68}Ga-IMP288.].

Network meta-analysis

The network meta-analysis was performed for different radiopharmaceuticals in metastatic MTC. We analyzed four metastatic sites (lymph nodes, lung, liver, and bone) respectively. For each site, we first generated network geometry. The network geometry showed the direct or indirect interventions between RCTs, and the edges' width and the nodes' size revealed the number of articles. After that, we performed an overall inconsistency test, the level of global inconsistency was computed according to the type of between-radiopharmaceutical comparison for all cases. Meanwhile, we used the node-splitting method for the local inconsistency test, in which each radiopharmaceutical was individually examined, and the outcomes of direct and indirect comparisons were statistically tested. The inconsistency was remarkable when the *P*-value was < 0.05 in both the overall and local inconsistency test, which meant the transitivity of data is not statistically significant. Then, we made a network meta-analysis and generated a league table of five PET/CT radiopharmaceuticals in each metastatic site. The league table contained the relative effectiveness [odd ratio (OR) value] and its uncertainty (95% confidence interval) for each pair of interventions. Finally, based on a Bayesian approach, we performed surface under the cumulative ranking curve (SUCRA) to determine the probability of each PET pharmaceutical being the best in different metastatic sites. The SCURA value presented the probability that each radiopharmaceutical will be the most sensitive modality in distinct metastatic sites. The radiopharmaceutical will rank higher if the SUCRA value is greater. We also integrated the SUCRA plot into a single figure to display the ranking probability more concisely.

Statistical analysis

All data from each eligible study was extracted in Excel 2016 (Microsoft Corporation, Redmond, CA). We used STATA version 17.0 software (Stata Corp LP) to make pairwise meta-analyses for direct comparisons of radiopharmaceuticals before network meta-analyses, and the results showed the estimation value of the OR and 95% credible intervals (95% CI) of sensitivity for each metastatic site. Heterogeneity was analyzed using a χ^2 test, with a Pc value of less than 0.05 suggesting significant heterogeneity. In addition, an I^2 statistic was adopted to evaluate the degree of heterogeneity [27,28]. Based on Cochrane's Handbook, a rough classification of the I^2 index is as follows: low heterogeneity (0–40%), moderate heterogeneity (30–60%), substantial heterogeneity (50–90%), and considerable variability (75–100%). The $Pc < 0.05$ or $I^2 > 50\%$ for heterogeneity would be considered significant differences. Based on the results, different method models would be chosen. A random-effects model was regularly used whether the n Pc value was larger than 0.05 or I^2 was less than 50%; otherwise, a fixed-effect model would be performed. Finally, we performed the Bayesian network meta-analysis and specific graphical analysis as mentioned above; R software 4.1.0 (R Foundation for Statistical Computing) and STATA version 17.0 software (Stata Corp LP) were used according to previous studies [26,29,30].

Results

Literature search and selection of studies

After the comprehensive computerized search was performed and references lists were extensively cross-checked, our research yielded 1618 records on or before April 11, 2022, including 411 articles from Pubmed, 739 articles from Web of Science, 460 articles in Embase, 8 articles from Cochrane Library, 5 articles from references. Excluding the duplicates, unrelated topics, unoriginal clinical studies, non-English articles, and studies without original data, 19 full-text articles [3,12,17,19,31–44] were assessed for possibly eligible. Finally, 9 studies [3,19,32–34,37,39,41,44] were selected because of the eligibility for the systematic review and network meta-analysis. There were 10 articles excluded due to the following reasons: We removed 4 full-text articles [17,34,40,42] because the original sensitivity data (TP and FN) could not be reached or calculated; In addition, 6 studies [12,31,35,36,38,43] that only used one PET/CT radiopharmaceutical were also excluded. There were no additional studies found by screening the references of these articles. The detailed procedure of study selection in the current meta-analysis is shown in Fig. 1.

Study description and characteristics

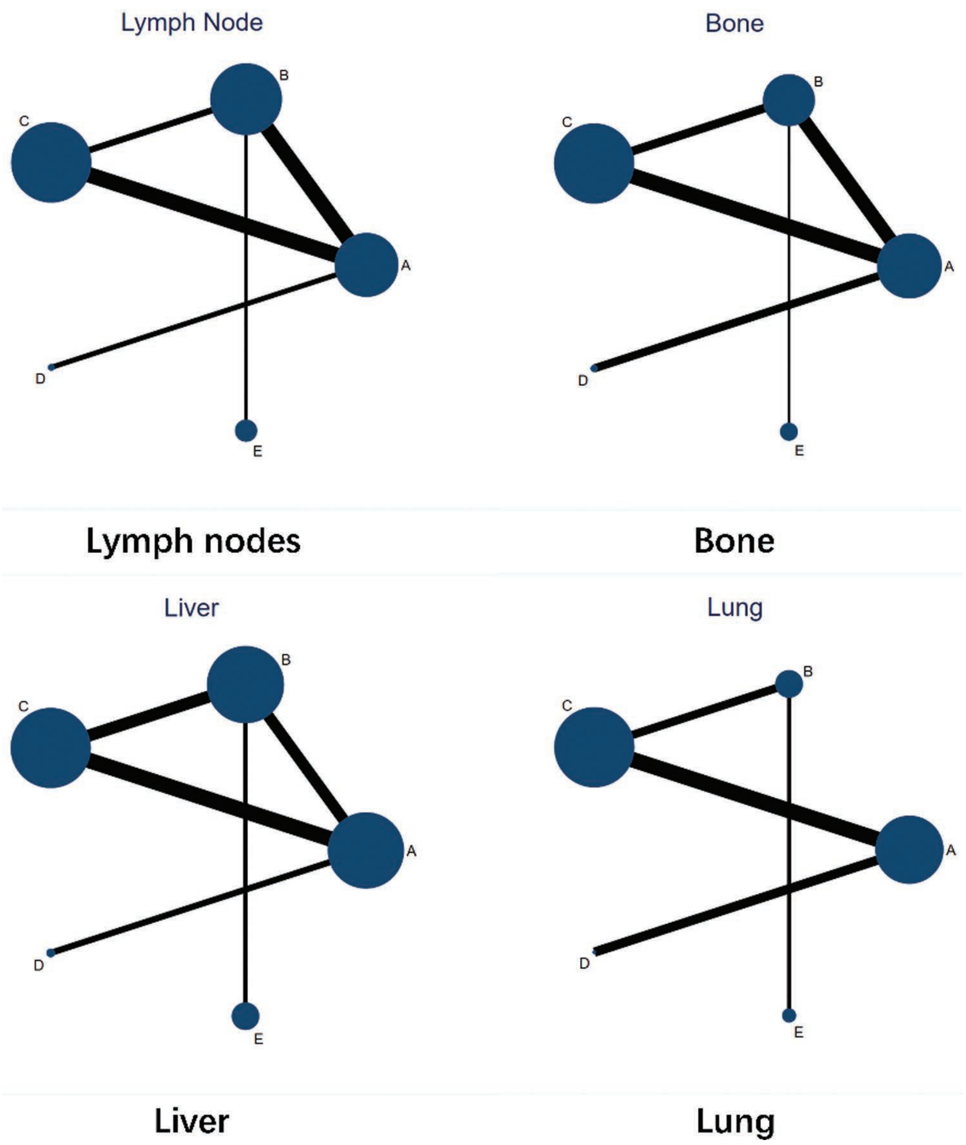
The basic characteristics of the included studies were presented in Table 1. A total of 243 patients with 5 different PET radiopharmaceuticals were included for sensitivity analysis in MTC. We conducted all analyses based on the sensitivity data of each metastatic site. Among 9 included studies, 7 were published in European countries, while 2 were published in Asian countries. There were 2 prospective [33,44] and 7 retrospective studies [3,19,32,34,37,39,41]. Of 9 studies, 8 studies [3,19,32–34,37,39,41] acquired images with a PET/CT scanner, whereas 1 study [44] used PET scanner. ^{18}F-DOPA PET or PET/CT was performed in 5 studies [32–34,39,44], whereas ^{68}Ga-SSA was performed in 5 studies [3,19,33,37,39], and ^{18}F-FDG was

Table 2 **Pairwise meta-analysis results for the direct comparison between two radiopharmaceuticals**

		Heterogeneity			95% CI	
Comparisons	k	I^2	Pc	OR	Lower	Upper
Lymph nodes						
A vs. B	3	0%	<0.001	0.04	0.01	0.14
B vs. C	2	45.9%	<0.001	10.95	4.41	27.19
A vs. C	4	76.2%	0.118	0.29	0.06	1.37
A vs. D	1	NA	NA	0.13	0.01	1.15
E vs. B	1	NA	NA	16.99	3.88	74.35
Bone						
A vs. B	2	9.5%	0.004	0.04	0.00	0.35
B vs. C	2	91%	0.919	1.32	0.01	288.58
A vs. C	4	67.9%	0.122	0.28	0.06	1.40
B vs. E	1	NA	NA	5.44	1.39	21.33
Liver						
A vs. B	2	0%	<0.001	0.14	0.05	0.42
B vs. C	2	0%	<0.001	202.51	22.75	1802.79
A vs. C	3	50.2%	0.4	2.42	0.31	19.08
A vs. D	1	NA	NA	55.86	2.53	1231.23
E vs. B	1	NA	NA	24.00	3.02	190.66
Lung						
A vs. C	3	53.4%	0.274	2.11	0.11	42.26
B vs. E	1	NA	NA	2.40	0.36	15.94

A, ^{18}F-FDG; B, ^{18}F-DOPA; C, ^{68}Ga-SSA; D, ^{11}C-methionine; E, TF2/^{68}Ga-IMP28; CI indicates confidence interval; DT, doubling time; k, number of effect sizes; I^2, Higgins' I^2; NA, not available; OR, odds ratio; Pc, Cochrane Q statistics *P*-value.

Fig. 4



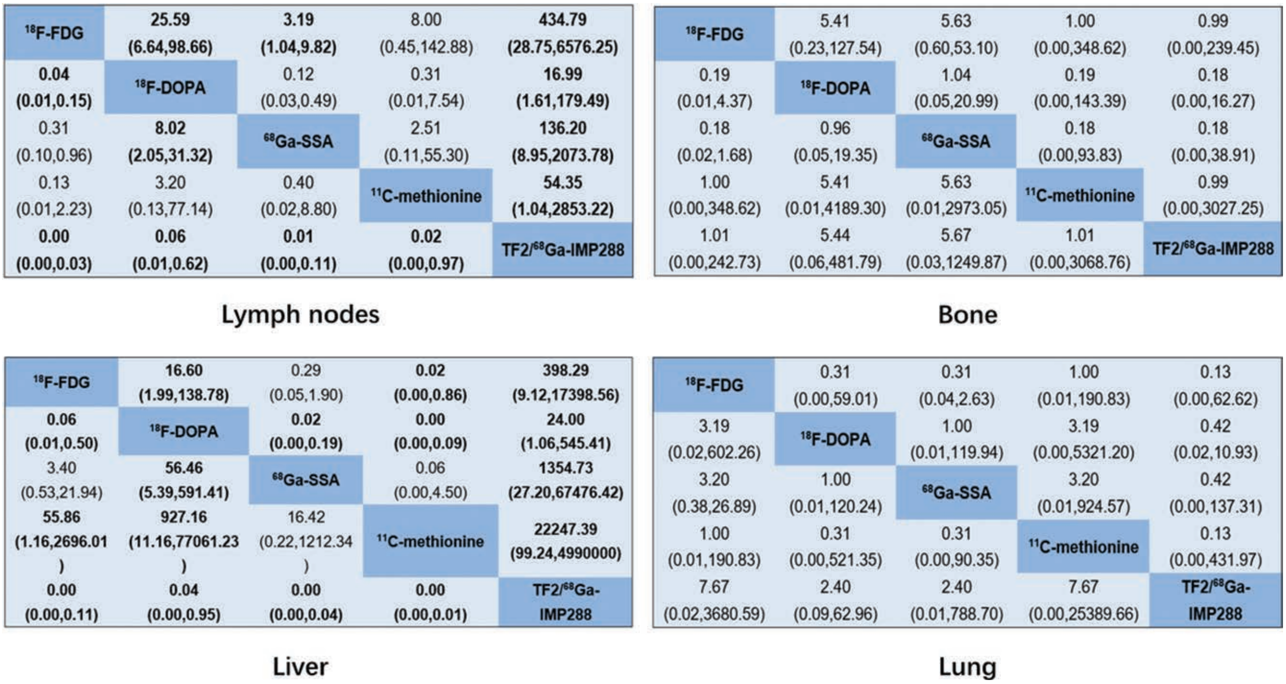
Evidence network plot of 5 different PET radiopharmaceuticals for the sensitivity in each metastatic site of recurrent MTC. [The edges' width and the nodes' size showed the number of articles. ^{18}F-FDG, ^{18}F-DOPA, and ^{68}Ga-SSA were included in more studies than ^{11}C-methionine and TF2/^{68}Ga-IMP28. (a) ^{18}F-FDG; (b) ^{18}F-DOPA; (c) ^{68}Ga-SSA; (d) ^{11}C-methionine; (e) TF2/^{68}Ga-IMP288.]

performed in 7 studies [3,19,34,37,39,41,44]. One study [41] with ^{11}C-methionine PET/CT and another study [32] with TF2 and ^{68}Ga-labeled IMP288 immuno-PET were also included. Detecting and localizing sensitivity of lymph nodes were available in all 9 studies [3,19,32–34,37,39,41,44], whereas liver lesions were available in 7 studies [3,19,32–34,39,41], bone lesions were available in 8 studies [3,19,32–34,37,39,41] and lung lesions were available in 6 studies [3,19,32,33,37,41]. The average value of serum calcitonin (Ctn) and CEA in 8 studies [19,32–34,37,39,41,44] was 1213.3 pg/ml and 44.5 ng/ml, respectively. There was 1 study [3] with no original Ctn and CEA data. All patients in these studies had elevated Ctn or CEA. The overall sensitivity of each PET radiopharmaceutical was also shown in Table 1.

Study quality assessment and publication bias

Results of the QUADAS-2 assessment are presented in Fig. 2. The quality of studies varied from moderate to high. The quality of the included studies was deemed satisfactory. The statistical approaches for the publication bias or small-study effect in 9 studies are shown in Fig. 3. In all 4 metastatic sites network meta-analyses, individual studies are distributed symmetrically about the combined effect size and toward the top of the graph. Thus,

Fig. 5



^{18}F-FDG	**25.59** **(6.64,98.66)**	**3.19** **(1.04,9.82)**	8.00 (0.45,142.88)	**434.79** **(28.75,6576.25)**
0.04 **(0.01,0.15)**	**^{18}F-DOPA**	0.12 (0.03,0.49)	0.31 (0.01,7.54)	**16.99** **(1.61,179.49)**
0.31 (0.10,0.96)	**8.02** **(2.05,31.32)**	**^{68}Ga-SSA**	2.51 (0.11,55.30)	**136.20** **(8.95,2073.78)**
0.13 (0.01,2.23)	3.20 (0.13,77.14)	0.40 (0.02,8.80)	**^{11}C-methionine**	**54.35** **(1.04,2853.22)**
0.00 **(0.00,0.03)**	**0.06** **(0.01,0.62)**	**0.01** **(0.00,0.11)**	**0.02** **(0.00,0.97)**	**TF2/^{68}Ga-IMP288**

Lymph nodes

^{18}F-FDG	5.41 (0.23,127.54)	5.63 (0.60,53.10)	1.00 (0.00,348.62)	0.99 (0.00,239.45)
0.19 (0.01,4.37)	**^{18}F-DOPA**	1.04 (0.05,20.99)	0.19 (0.00,143.39)	0.18 (0.00,16.27)
0.18 (0.02,1.68)	0.96 (0.05,19.35)	**^{68}Ga-SSA**	0.18 (0.00,93.83)	0.18 (0.00,38.91)
1.00 (0.00,348.62)	5.41 (0.01,4189.30)	5.63 (0.01,2973.05)	**^{11}C-methionine**	0.99 (0.00,3027.25)
1.01 (0.00,242.73)	5.44 (0.06,481.79)	5.67 (0.03,1249.87)	1.01 (0.00,3068.76)	**TF2/^{68}Ga-IMP288**

Bone

^{18}F-FDG	**16.60** **(1.99,138.78)**	0.29 (0.05,1.90)	**0.02** **(0.00,0.86)**	**398.29** **(9.12,17398.56)**
0.06 **(0.01,0.50)**	**^{18}F-DOPA**	**0.02** **(0.00,0.19)**	**0.00** **(0.00,0.09)**	**24.00** **(1.06,545.41)**
3.40 (0.53,21.94)	**56.46** **(5.39,591.41)**	**^{68}Ga-SSA**	0.06 (0.00,4.50)	**1354.73** **(27.20,67476.42)**
55.86 **(1.16,2696.01)**	**927.16** **(11.16,77061.23)**	16.42 (0.22,1212.34)	**^{11}C-methionine**	**22247.39** **(99.24,4990000)**
0.00 **(0.00,0.11)**	**0.04** **(0.00,0.95)**	**0.00** **(0.00,0.04)**	**0.00** **(0.00,0.01)**	**TF2/^{68}Ga-IMP288**

Liver

^{18}F-FDG	0.31 (0.00,59.01)	0.31 (0.04,2.63)	1.00 (0.01,190.83)	0.13 (0.00,62.62)
3.19 (0.02,602.26)	**^{18}F-DOPA**	1.00 (0.01,119.94)	3.19 (0.00,5321.20)	0.42 (0.02,10.93)
3.20 (0.38,26.89)	1.00 (0.01,120.24)	**^{68}Ga-SSA**	3.20 (0.01,924.57)	0.42 (0.00,137.31)
1.00 (0.01,190.83)	0.31 (0.00,521.35)	0.31 (0.00,90.35)	**^{11}C-methionine**	0.13 (0.00,431.97)
7.67 (0.02,3680.59)	2.40 (0.09,62.96)	2.40 (0.01,788.70)	7.67 (0.00,25389.66)	**TF2/^{68}Ga-IMP288**

Lung

Network Meta-analysis results of 5 different radiopharmaceutical sensitivities in each metastatic site. (Each column in the table showed the OR value and 95% confidence interval between the two radiopharmaceuticals.).

Table 3 **SCURA values of five PET/CT radiopharmaceuticals sensitivities in four metastatic MTC sites**

Radiopharmaceutical	Lymph nodes	Bone	Liver	Lung
A	0.000	0.011	0.000	0.283
B	0.005	0.301	0.021	0.158
C	0.000	0.319	0.000	0.037
D	0.021	0.218	0.000	0.412
E	0.974	0.151	0.979	0.110

A, ^{18}F-FDG; B, ^{18}F-DOPA; C, ^{68}Ga-SSA; D, ^{11}C-methionine; E, TF2/^{68}Ga-IMP28.

there was no obvious evidence of publication bias in the current network meta-analysis.

Pairwise meta-analysis

We performed a direct paired comparison of 5 types of radiopharmaceuticals for detection sensitivity in 4 metastatic sites (lymph nodes, lung, liver, and bone). As shown in Table 2, the estimated odds ratio (OR) and 95% confidence interval (95% CI) of pairwise meta-analysis for the sensitivity of metastatic MTC were analyzed. For both lymph nodes and liver metastatic lesions, TF2/^{68}Ga-IMP288 had a relatively high sensitivity (Lymph nodes: OR, 16.99; 95% CI, 3.88–74.35; Liver: OR, 24.00; 95% CI, 3.02–190.66). While for bone lesions, ^{18}F-DOPA had a high detection sensitivity (OR, 1.32; 95% CI, 0.01–288.58). However, there was no relationship between the 2 individual meta-analyses for lung lesions, so the pairwise meta-analysis result was missing.

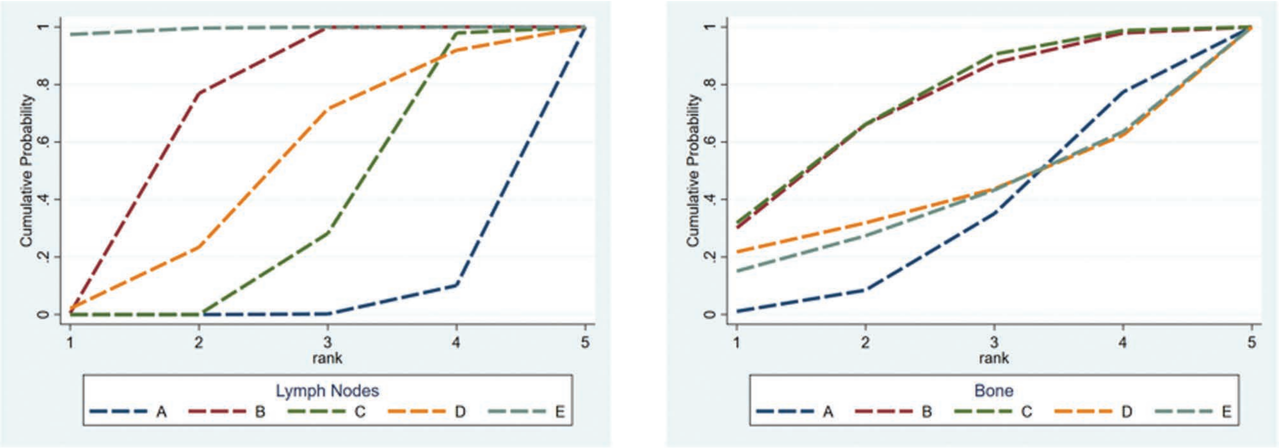
Evidence network and inconsistency test

The evidence network map for each metastatic site was shown in Fig. 4. A greater number of MTC patients were detected by the ^{18}F-FDG, ^{18}F-DOPA, and ^{68}Ga-SSA; these tests had comparatively more investigations. We performed a global inconsistency test in 4 metastatic sites by an overall inconsistency model. All p values of analyzed sites were larger than 0.05 (bone 0.44, liver 0.07, lymph nodes 0.42), except for lung lesions, which was not applicable for the inconsistency model because of no loop in lung analysis (Fig. 4). In the local inconsistency test, node-splitting results showed consistency among the direct and indirect evidence of all outcomes. All p values of other sites were larger than 0.05 except for ^{18}F-DOPA vs. ^{18}F-FDG and ^{18}F-DOPA vs. ^{68}Ga-SSA in lung lesions. Therefore, the consistency model was mainly applied in the current study.

Network meta-analysis of five radiopharmaceuticals in four metastatic sites

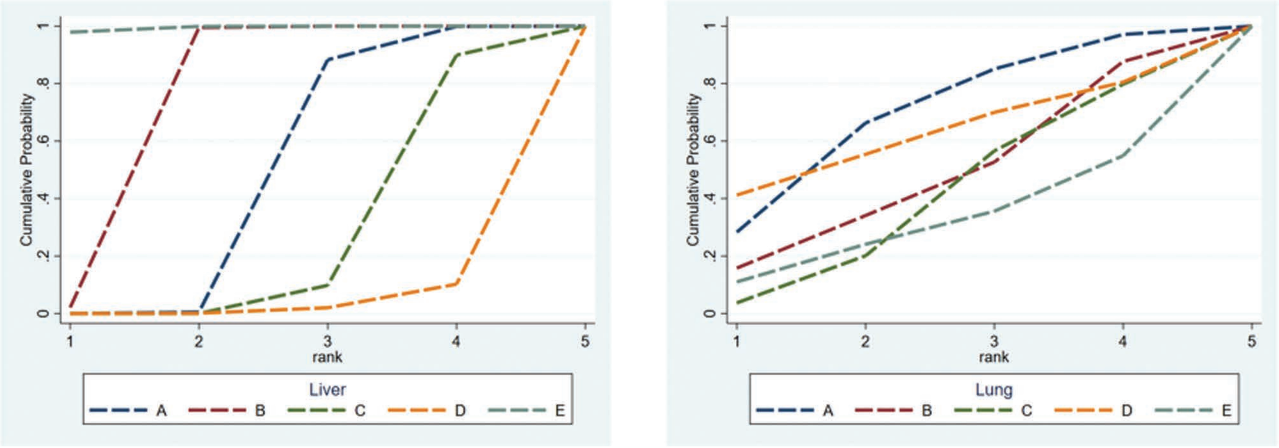
Figure 5 shows the network meta-analysis results of 5 radiopharmaceuticals in 4 metastatic sites. For detecting and localizing both lymph nodes and liver metastatic lesions, the PET/CT with TF2/^{68}Ga-IMP288 was significantly better than other radiopharmaceuticals (OR, 16.99; 95% CI, 1.61–179.49. OR, 24.00; 95% CI, 1.06–545.41, respectively). The ^{68}Ga-SSA and ^{18}F-DOPA showed approximately the same efficacy and they were relatively better than the other 3 radiopharmaceuticals for bone

Fig. 6



Lymph nodes

Bone



Liver

Lung

SUCRA plots of five radiopharmaceutical sensitivities in each metastatic site. (SUCRA plots showed the cumulative probability of each radiopharmaceutical to rank first to fifth. The most effective radiopharmaceutical had the highest level at the 'RANK 1' site. (a) ^{18}F-FDG; (b) ^{18}F-DOPA; (c) ^{68}Ga-SSA; (d) ^{11}C-methionine; (e) TF2/^{68}Ga-IMP288.).

lesions (OR, 1.04; 95% CI, 0.05–20.99). For lung lesions, ^{18}F-FDG and ^{11}C-methionine showed almost the same efficacy and they were better than the other 3 radiopharmaceuticals although the difference was statistically insignificant (OR, 1.00; 95% CI, 0.01–190.83).

The corresponding SUCRA values and Bayesian ranking probabilities of five different radiopharmaceuticals for each metastatic site were shown in Table 3 and Fig. 6. TF2/^{68}Ga-IMP288 ranked first at both lymph nodes (SUCRA value: 0.974) and liver (SUCRA value: 0.979) metastatic lesions. Meanwhile, ^{18}F-DOPA (SUCRA value: 0.301) and ^{68}Ga-SSA (SUCRA value: 0.319) were approximately the same which meant the highest probability of ranking first in bone lesions. ^{11}C-methionine showed the best ranking in detecting and localizing lung metastatic lesions (SUCRA value: 0.412).

Discussion

Though MTC was not common in thyroid carcinoma, its high recurrent and metastatic rate made patient management difficult in clinical practice. Many studies had reported that PET/CT showed better efficacy than conventional imaging methods in detecting metastatic or recurrent MTC lesions [45]. However, different radiopharmaceuticals had different sensitivities in various metastatic sites [46]. Although one meta-analysis reported an extremely cursory outcome of different radiopharmaceuticals 3 years ago, there was no systematic review and network meta-analysis for different radiopharmaceutical sensitivities at different sites of local or distant metastatic lesions. The radiopharmaceuticals included in that meta-analysis were not all commonly used in clinical practice, and it did not analyze the sensitivities of radiopharmaceuticals at common metastatic sites. It is still unknown which radiopharmaceutical is the most sensitive technique in different metastatic locations. As far as we know, our study is the first network meta-analysis that compared sensitivities of five novel and common PET/CT radiopharmacology in the four most common metastatic sites (Lymph nodes; Lung; Bone; Liver). We aimed to provide knowledge-based evidence for clinicians to choose a proper PET/CT radiopharmaceutical for different metastases and improve the diagnosis and treatment for MTC patients.

In our study, TF2/^{68}Ga-IMP288 showed the maximum probability to be the best PET/CT radiopharmaceutical for both lymph nodes and liver metastatic lesions. While the highest probability of ranking first for bone lesions was indicated by the similar sensitivities between ^{18}F-DOPA and ^{68}Ga-SSA. For detecting and localizing lung lesions, ^{11}C-methionine had the most probability to be the most effective radiopharmaceutical. We hypothesized that these findings might be caused by the different imaging mechanisms used by different PET/CT radiopharmaceuticals in detecting tumor lesions.

TF2 is an engineered bispecific mAb that can recognize human CEA and histamine-succinyl-glycine motif. IMP288 is a hapten that can be marked by radionuclides [47]. TF2/^{68}Ga-IMP288 immuno-PET was first reported in metastatic MTC by *Milin* [48], and it was the most sensitive and effective method compared to ^{18}F-DOPA and other conventional imaging. Meanwhile, immuno-PET was the newest method in nuclear medicine and showed more encouraging results than common PET or PET/CT in clinical practice [49,50]. It is currently one of the most promising areas in nuclear medicine research. Our network meta-analysis indicated that immuno-PET with TF2/^{68}Ga-IMP288 showed the best efficacy in lymph nodes and liver lesions. While in bone and lung metastatic lesions, TF2/^{68}Ga-IMP288 had a lower ranking than other common radiopharmaceuticals. The possible reason for this discovery is TF2/^{68}Ga-IMP288 combines the benefits of TF2's high targeting ability and the imaging features of ^{68}Ga-IMP288. Therefore, when lymph nodes and liver metastatic lesions secret more CEA, these sites could attract more TF2/^{68}Ga-IMP288. A growing number of studies about immuno-PET and TF2/^{68}Ga-IMP288 are now being carried out to provide further knowledge and evidence [51].

^{18}F-DOPA accumulates and decarboxylates in neuroendocrine tumors which can be transferred into tumor cells through L-amino acid transporters. ^{18}F-FDG was known as a tumor radiopharmaceutical by participating in the Glucose metabolism of tumor cells. In previous studies, ^{18}F-DOPA showed better efficacy than ^{18}F-FDG in recurrent and metastatic MTC. ^{18}F-FDG is used as a complementary method of ^{18}F-DOPA in these patients [52]. In our network meta-analysis results, we found the same conclusion. ^{18}F-DOPA ranked best and had almost the same efficiency as ^{68}Ga-SSA in bone metastatic lesions, while ^{18}F-FDG ranked in last place. And in the other 3 metastatic sites except for lung lesions, ^{18}F-DOPA ranked higher than ^{18}F-FDG. Intracellular decarboxylation of ^{18}F-DOPA is a feature of the neuroendocrine origin of MTC. We can assume that a higher ^{18}F-DOPA uptake is relative to a higher degree of cell differentiation, this might explain the better performance of ^{18}F-DOPA than ^{18}F-FDG [53].

^{68}Ga-somatostatin analog is another common radiopharmaceutical used in MTC. However, there is still an unclear conclusion compared with ^{18}F-DOPA and ^{18}F-FDG because of limited studies with other PET radiopharmaceuticals [34]. In our network meta-analysis results, ^{68}Ga-SSA and ^{18}F-DOPA are almost tied for first in detecting bone metastatic lesions. Beyond that, ^{18}F-DOPA was better than ^{68}Ga-SSA in all other sites. While ^{68}Ga-SSA seems to have similar sensitivity with ^{18}F-FDG except for bone lesions. Our discovery indicated that ^{68}Ga-SSA may be used as another complementary method for ^{18}F-DOPA or can be the first choice for detecting suspicious bone metastatic lesions.

^{11}C-methionine is a commonly used amino acid tracer. It has been used in rectal, breast, lung, and prostate cancers, because methionine is necessary for protein synthesis, and its derivatives S-adenosyl methionine are accelerated in tumor cells [54–56]. Although it was not commonly used in MTC, our results show the best sensitivity in detecting and localizing lung metastatic lesions. However, its performance was limited at other sites. More studies about ^{11}C-methionine needed to be launched to provide more data and evidence to validate our results.

This network meta-analysis and systematic review had some limitations. First, we only evaluated sensitivities without specificity of five radiopharmaceuticals in four sites, because most of the studies involved sensitivity only. The specificity was not mentioned in these original clinical studies. Meanwhile, sensitivity was important to avoid the missed-diagnosis rate (reduce the false-negative rate) [57–60]. Secondly, there was an unequal number of clinical trials for each radiopharmaceutical. This may be the result of the limited number of original studies due to the low incidence of MTC and the fact that some radiopharmaceuticals are still in the clinical research stage (e.g. TF2/^{68}Ga-IMP288 and ^{11}C-methionine). Despite the unequal number of studies objectively present, our results from the inconsistency test indicated low inconsistency and strong transitivity between studies. Consequently, our outcomes were credible. We expect more studies for evaluating the sensitivity of different PET/CT radiopharmaceuticals in different distant metastatic sites will be carried out to provide more convincible evidence.

Conclusion

In conclusion, TF2/^{68}Ga-IMP288 PET or PET/CT showed the best performance for detecting and localizing lymph nodes and liver metastatic lesions of MTC. ^{18}F-DOPA and ^{68}Ga-SSA had a familiar performance and showed a higher SUCRA than other radiopharmaceuticals for bone metastatic lesions. For lung metastatic lesions, ^{11}C-methionine had the best performance among the 5 radiopharmaceuticals. Additionally, more multi-center clinical trials on radiopharmaceutical sensitivities in detecting and localizing metastatic sites were expected to be carried out in the future.

Acknowledgements

We confirm that all methods were carried out in accordance with the relevant guidelines and regulations in the manuscript.

The 1 3 5 Project for Disciplines of Excellence, West China Hospital, Sichuan University (Grant No. ZYJC21033) and the National Natural Science Foundation of China (Grant No.32101188), and General Project of Science and Technology Department of Sichuan Province (Grant No. 2021YFS0102), China.

Pengyu Li: Literature search and selection of studies; Data extraction and analysis; Writing- original draft. Yujie Zhang: Literature search; Data extraction; Assisting the analysis. Tianfeng Xu: Data check; Assisting data extraction. Jingqiang Zhu: Data extraction and Methodology. Tao Wei: Writing- review and editing; Data check; Conceptualization. Wanjun Zhao: Selection of studies; Writing- review, and editing; Conceptualization. All authors contributed to the critical revision of the paper and approved the final manuscript for publication.

Data statement: The original data included in our analysis are publicly available on Pubmed, DOI: [1] 10.1967/s002449912220; [2] 10.1007/s12020-019-01846-8; [3] 10.2967/jnumed.120.252791; [4] 10.1007/s12149-021-01627-2; [5] 10.1007/s00259-017-3759-4; [6] 10.1097/MNM.0000000000000240; [7] 10.1007/s00259-011-2031-6; [8] 10.1507/endocrj.k10e-258; [9] 10.1007/s002590000404.

Conflicts of interest

There are no conflicts of interest.

References

1 Romei C, Ciampi R, Elisei R. A comprehensive overview of the role of the RET proto-oncogene in thyroid carcinoma. *Nat Rev Endocrinol* 2016; **12**:192–202.

2 Cabanillas ME, McFadden DG, Durante C. Thyroid cancer. *Lancet* 2016; **388**:2783–2795.

3 Şahin OE, Uslu-Beşli L, Asa S, Sağer S, Sönmezoğlu K. The role of (68) Ga-DOTATATE PET/CT and (18)F-FDG PET/CT in the follow-up of patients with medullary thyroid cancer. *Hell J Nucl Med* 2020; **23**:321–329.

4 Moley JF. Medullary thyroid carcinoma: management of lymph node metastases. *J Natl Compr Canc Netw* 2010; **8**:549–556.

5 Call JA, Caudill JS, McIver B, Foote RL. A role for radiotherapy in the management of advanced medullary thyroid carcinoma: the Mayo Clinic experience. *Rare Tumors* 2013; **5**:e37.

6 Hadoux J, Pacini F, Tuttle RM, Schlumberger M. Management of advanced medullary thyroid cancer. *Lancet Diabetes Endocrinol* 2016; **4**:64–71.

7 Werner RA, Schmid J-S, Higuchi T, Javadi MS, Rowe SP, Märkl B, *et al*. Predictive value of (18)F-FDG PET in patients with advanced medullary thyroid carcinoma treated with vandetanib. *J Nucl Med* 2018; **59**:756–761.

8 Wells SA, Jr, Asa SL, Dralle H, Elisei R, Evans DB, Gagel RF, *et al*.; American Thyroid Association Guidelines Task Force on Medullary Thyroid Carcinoma. Revised American Thyroid Association guidelines for the management of medullary thyroid carcinoma. *Thyroid* 2015; **25**:567–610.

9 Filetti S, Durante C, Hartl D, Leboulleux S, Locati LD, Newbold K, *et al*.; ESMO Guidelines Committee. Electronic address: clinicalguidelines@esmo.org. Thyroid cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up†. *Ann Oncol* 2019; **30**:1856–1883.

10 Elisei R, Pinchera A. Advances in the follow-up of differentiated or medullary thyroid cancer. *Nat Rev Endocrinol* 2012; **8**:466–475.

11 Castinetti F, Taïeb D. Positron emission tomography imaging in medullary thyroid carcinoma: time for reappraisal? *Thyroid* 2021; **31**:151–155.

12 Szakáll S, Jr, Esik O, Bajzik G, Repa I, Dabasi G, Sinkovics I, *et al*. 18F-FDG PET detection of lymph node metastases in medullary thyroid carcinoma. *J Nucl Med* 2002; **43**:66–71.

13 Frank-Raue K, Raue F, Buhr HJ, Baldauf G, Lorenz D, Ziegler R. Localization of occult persisting medullary thyroid carcinoma before microsurgical reoperation: high sensitivity of selective venous catheterization. *Thyroid* 1992; **2**:113–117.

14 Giovanella L, Treglia G, Iakovou I, Mihailovic J, Verburg FA, Luster M. EANM practice guideline for PET/CT imaging in medullary thyroid carcinoma. *Eur J Nucl Med Mol Imaging* 2020; **47**:61–77.

15 Mosci C, Iagaru A. PET/CT imaging of thyroid cancer. *Clin Nucl Med* 2011; **36**:e180–e185.

16 Marcus C, Whitworth PW, Surasi DS, Pai SI, Subramaniam RM. PET/CT in the management of thyroid cancers. *AJR Am J Roentgenol* 2014; **202**:1316–1329.

17 Beheshti M, Pöcher S, Vali R, Waldenberger P, Broinger G, Nader M, *et al*. The value of 18F-DOPA PET-CT in patients with medullary thyroid carcinoma: comparison with 18F-FDG PET-CT. *Eur Radiol* 2009; **19**:1425–1434.

18 Verbeek HH, Plukker JTM, Koopmans KP, de Groot JWB, Hofstra RMW, Muller Kobold AC, *et al*. Clinical relevance of 18F-FDG PET and 18F-DOPA PET in recurrent medullary thyroid carcinoma. *J Nucl Med* 2012; **53**:1863–1871.

19 Souteiro P, Gouveia P, Ferreira G, Belo S, Costa C, Carvalho D, *et al*. (68) Ga-DOTANOC and (18)F-FDG PET/CT in metastatic medullary thyroid carcinoma: novel correlations with tumoral biomarkers. *Endocrine* 2019; **64**:322–329.

20 Lee SW, Shim SR, Jeong SY, Kim S-J. Comparison of 5 different pet radiopharmaceuticals for the detection of recurrent medullary thyroid carcinoma: a network meta-analysis. *Clin Nucl Med* 2020; **45**:341–348.

21 Viola D, Elisei R. Management of medullary thyroid cancer. *Endocrinol Metab Clin North Am* 2019; **48**:285–301.

22 Raue F, Frank-Raue K. Thyroid cancer: risk-stratified management and individualized therapy. *Clin Cancer Res* 2016; **22**:5012–5021.

23 Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, *et al*. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *Bmj* 2009; **339**:b2700.

24 Li J, Zhong D, Ye J, He M, Liu X, Zheng H, *et al*. Rehabilitation for balance impairment in patients after stroke: a protocol of a systematic review and network meta-analysis. *BMJ Open* 2019; **9**:e026844.

25 Whiting PF, Rutjes AWS, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, *et al*.; QUADAS-2 Group. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med* 2011; **155**:529–536.

26 Shim S, Yoon B-H, Shin I-S, Bae J-M. Network meta-analysis: application and practice using Stata. *Epidemiol Health* 2017; **39**:e2017047.

27 Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002; **21**:1539–1558.

28 Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *Bmj* 2003; **327**:557–560.

29 Shim SR, Kim S-J, Lee J, Rücker G. Network meta-analysis: application and practice using R software. *Epidemiol Health* 2019; **41**:e2019013.

30 Rouse B, Chaimani A, Li T. Network meta-analysis: an introduction for clinicians. *Intern Emerg Med* 2017; **12**:103–111.

31 Hayes AR, Crawford A, Al Riyami K, Tang C, Bomanji J, Baldeweg SE, *et al*. Metastatic medullary thyroid cancer: the role of 68gallium-DOTA-somatostatin analogue PET/CT and peptide receptor radionuclide therapy. *J Clin Endocrinol Metab* 2021; **106**:e4903–e4916.

32 Bodet-Milin C, Faivre-Chauvet A, Carlier T, Ansquer C, Rauscher A, Frampas E, *et al*. Anti-CEA pretargeted immuno-PET shows higher sensitivity than DOPA PET/CT in detecting relapsing metastatic medullary thyroid carcinoma: post hoc analysis of the iPET-MTC study. *J Nucl Med* 2021; **62**:1221–1227.

33 Asa S, Sonmezoglu K, Uslu-Besli L, Sahin OE, Karayel E, Pehlivanoglu H, *et al*. Evaluation of F-18 DOPA PET/CT in the detection of recurrent or metastatic medullary thyroid carcinoma: comparison with GA-68 DOTA-TATE PET/CT. *Ann Nucl Med* 2021; **35**:900–915.

34 Yamaga LYI, Cunha ML, Campos Neto GC, Garcia MRT, Yang JH, Camacho CP, *et al*. (68)Ga-DOTATATE PET/CT in recurrent medullary thyroid carcinoma: a lesion-by-lesion comparison with (111)In-octreotide SPECT/CT and conventional imaging. *Eur J Nucl Med Mol Imaging* 2017; **44**:1695–1701.

35 Romero-Lluch AR, Cuenca-Cuenca JI, Guerrero-Vázquez R, Martínez-Ortega AJ, Tirado-Hospital JL, Borrego-Dorado I, *et al*. Diagnostic utility of PET/CT with (18)F-DOPA and (18)F-FDG in persistent or recurrent medullary thyroid carcinoma: the importance of calcitonin and carcinoembryonic antigen cutoff. *Eur J Nucl Med Mol Imaging* 2017; **44**:2004–2013.

36 De Luca S, Fonti R, Camera L, Salvatore B, Faggiano A, Ciarmiello A, *et al*. Multimodal imaging with (18)F-FDG-PET/CT and (111)In-Octreotide SPECT in patients with metastatic medullary thyroid carcinoma. *Ann Nucl Med* 2016; **30**:234–241.

37 Archier A, Heimburger C, Guerin C, Morange I, Palazzo FF, Henry J-F, *et al*. (18)F-DOPA PET/CT in the diagnosis and localization of persistent medullary thyroid carcinoma. *Eur J Nucl Med Mol Imaging* 2016; **43**:1027–1033.

38 Ozkan ZG, Kuyumcu S, Uzum AK, Gecer MF, Ozel S, Aral F, *et al*. Comparison of 68Ga-DOTATATE PET-CT, 18F-FDG PET-CT and 99mTc-(V) DMSA scintigraphy in the detection of recurrent or metastatic medullary thyroid carcinoma. *Nucl Med Commun* 2015; **36**:242–250.

39 Jiang J, Yang Z, Zhang Y, Xu X, Wang M, Hu S, *et al*. Clinical value of [(18) F]FDG-PET/CT in the detection of metastatic medullary thyroid cancer. *Clin Imaging* 2014; **38**:797–801.

40 Treglia G, Castaldi P, Villani MF, Perotti G, de Waure C, Filice A, *et al*. Comparison of 18F-DOPA, 18F-FDG and 68Ga-somatostatin analogue PET/CT in patients with recurrent medullary thyroid carcinoma. *Eur J Nucl Med Mol Imaging* 2012; **39**:569–580.

41 Marzola MC, Pelizzo MR, Ferdeghini M, Toniato A, Massaro A, Ambrosini V, *et al*. Dual PET/CT with (18)F-DOPA and (18)F-FDG in metastatic medullary thyroid carcinoma and rapidly increasing calcitonin levels: Comparison with conventional imaging. *Eur J Surg Oncol* 2010; **36**:414–421.

42 Jang HW, Choi JY, Lee JI, Kim HK, Shin HW, Shin JH, *et al*. Localization of medullary thyroid carcinoma after surgery using (11)C-methionine PET/CT: comparison with (18)F-FDG PET/CT. *Endocr J* 2010; **57**:1045–1054.

43 Koopmans KP, de Groot JWB, Plukker JTM, de Vries EGE, Kema IP, Sluiter WJ, *et al*. 18F-dihydroxyphenylalanine PET in patients with biochemical evidence of medullary thyroid cancer: relation to tumor differentiation. *J Nucl Med* 2008; **49**:524–531.

44 de Groot JW, Links TP, Jager PL, Kahraman T, Plukker JTM. Impact of 18F-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) in patients with biochemical evidence of recurrent or residual medullary thyroid cancer. *Ann Surg Oncol* 2004; **11**:786–794.

45 Hoegerle S, Altehoefer C, Ghanem N, Brink I, Moser E, Nitzsche E. 18F-DOPA positron emission tomography for tumour detection in patients with medullary thyroid carcinoma and elevated calcitonin levels. *Eur J Nucl Med* 2001; **28**:64–71.

46 Brauckhoff K, Biermann M. Multimodal imaging of thyroid cancer. *Curr Opin Endocrinol Diabetes Obes* 2020; **27**:335–344.

47 Schlumberger M, Garcia C, Hadoux J, Klain M, Lamartina L. Functional imaging in thyroid cancer patients with metastases and therapeutic implications. *Presse Med* 2022; **51**:104113.

48 Rossi EA, Goldenberg DM, Cardillo TM, McBride WJ, Sharkey RM, Chang C-H. Stably tethered multifunctional structures of defined composition made by the dock and lock method for use in cancer targeting. *Proc Natl Acad Sci U S A* 2006; **103**:6841–6846.

49 Bodet-Milin C, Faivre-Chauvet A, Carlier T, Rauscher A, Bourgeois M, Cerato E, *et al*. Immuno-PET using anticarcinoembryonic antigen bispecific antibody and 68ga-labeled peptide in metastatic medullary thyroid carcinoma: clinical optimization of the pretargeting parameters in a first-in-human trial. *J Nucl Med* 2016; **57**:1505–1511.

50 Wei W, Rosenkrans ZT, Liu J, Huang G, Luo Q-Y, Cai W. ImmunoPET: concept, design, and applications. *Chem Rev* 2020; **120**:3787–3851.

51 Dun Y, Huang G, Liu J, Wei W. ImmunoPET imaging of hematological malignancies: From preclinical promise to clinical reality. *Drug Discov Today* 2022; **27**:1196–1203.

52 Alauddin MM, Khawli LA. Advances in immuno-PET for the detection of cancer and assessment of response to therapy. *Curr Med Chem* 2021; **28**:647–672.

53 Kauhanen S, Schalin-Jäntti C, Seppänen M, Kajander S, Virtanen S, Schildt J, *et al*. Complementary roles of 18F-DOPA PET/CT and 18F-FDG PET/CT in medullary thyroid cancer. *J Nucl Med* 2011; **52**:1855–1863.

54 Thomas CM, Asa SL, Ezzat S, Sawka AM, Goldstein D. Diagnosis and pathologic characteristics of medullary thyroid carcinoma-review of current guidelines. *Curr Oncol* 2019; **26**:338–344.

55 Jana S, Blaufox MD. Nuclear medicine studies of the prostate, testes, and bladder. *Semin Nucl Med* 2006; **36**:51–72.

56 Lindholm P, Lapela M, Någren K, Lehikoinen P, Minn H, Jyrkkiö S. Preliminary study of carbon-11 methionine PET in the evaluation of early response to therapy in advanced breast cancer. *Nucl Med Commun* 2009; **30**:30–36.

57 Hsieh HJ, Lin S-H, Lin K-H, Lee C-Y, Chang C-P, Wang S-J. The feasibility of 11C-methionine-PET in diagnosis of solitary lung nodules/masses when compared with 18F-FDG-PET. *Ann Nucl Med* 2008; **22**:533–538.

58 Saah AJ, Hoover DR. 'Sensitivity' and 'specificity' reconsidered: the meaning of these terms in analytical and diagnostic settings. *Ann Intern Med* 1997; **126**:91–94.

59 Rex DK, Rahmani EY, Haseman JH, Lemmel GT, Kaster S, Buckley JS. Relative sensitivity of colonoscopy and barium enema for detection of colorectal cancer in clinical practice. *Gastroenterology* 1997; **112**:17–23.

60 Parikh R, Mathai A, Parikh S, Chandra Sekhar G, Thomas R. Understanding and using sensitivity, specificity and predictive values. *Indian J Ophthalmol* 2008; **56**:45–50.