Diagnostic performance of ¹⁸F-FDG-PET/CT in DTC patients with thyroglobulin elevation and negative iodine scintigraphy: a meta-analysis

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Abstract

Purpose: To evaluate the accuracy of ¹⁸F-FDG-PET/CT for the detection of recurrent and/or metastatic diseases in differentiated thyroid cancer (DTC) patients with thyroglobulin elevation and negative iodine scintigraphy. Whether PET/CT with TSH stimulation (sPET/CT) had better diagnostic performance than PET/CT without TSH stimulation (nsPET/CT) in this scenario was also evaluated.

Methods: PubMed and Embase databases were searched for eligible studies from January 2001 to December 2018. Only studies with clearly stated reference standard (histopathology confirmation and/or clinical/imaging follow-up) were included. Publication bias was assessed by Deeks funnel plot. The pooled sensitivity, specificity, diagnostic odds ratio (DOR) and the area under the summary receiver-operating characteristics curve (AUC) for PET/CT was determined by random-effect analysis, respectively. sPET/CT and nsPET/CT were compared pairwise for all diagnostic estimate indexes using Z-test.

Results: We included 17 studies with 1195 patients in this meta-analysis. The pooled sensitivity, specificity, DOR and AUC for PET/CT on patient-based data were 0.86 (95% CI: 0.79–0.91), 0.84 (95% CI: 0.72–0.91), 31.00 (95% CI: 12.00–80.00) and 0.91 (95% CI: 0.88–0.93), respectively. There was high heterogeneity ($I^2 = 80\%$ for sensitivity, $I^2 = 82\%$ for specificity) and possible publication bias ($P = 0.01$). Z test did not detect statistically significant difference between sPET/CT and nsPET/CT for all the diagnostic estimate indexes (all $P > 0.05$).

Conclusions: On patient-based analysis, ¹⁸F-FDG-PET/CT has high diagnostic accuracy for the detection of recurrent and/or metastatic diseases in DTC patients with thyroglobulin elevation and negative iodine scintigraphy, but existing studies were limited by high heterogeneity and possible publication bias. The diagnostic performance of sPET/CT may be not superior to nsPET/CT.

European Journal of
Endocrinology
(2019) **181**, 93–102

Introduction

¹⁸F-FDG-PET/CT is primarily considered in high-risk differentiated thyroid cancer (DTC) patients with thyroglobulin elevation and negative iodine scintigraphy (1, 2). It can help to localize recurrent and/or metastatic diseases not detected by other imaging techniques, which is important to define the most appropriate management approach and may have a significant impact on survival (3, 4). During

the past two decades, numerous accuracy studies and two previous meta-analyses have reported favorable diagnostic performance for PET in evaluating DTC patients with thyroglobulin elevation and negative iodine scintigraphy (5, 6, 7, 8, 9, 10, 11). However, in recent years, with the installation of more hybrid PET/CT systems, the capability of this technique might be significantly improved by incorporating anatomical

information. Therefore, it is necessary to summarize the current evidence in the literature to update its value.

Thyroid-stimulating hormone (TSH) stimulation is a requirement of high levels of TSH (usually above 30 mIU/L) before radioactive iodine therapy to maximize the iodine uptake in cancerous thyroid cells. It can be achieved either endogenously by 4–6 weeks of thyroid hormone withdrawal (THW) or exogenously by instant administration of recombinant TSH (rhTSH). Theoretically, because high levels of TSH could also stimulate the cancerous thyroid cells to have higher metabolic demand and thus higher FDG uptake, PET/CT with TSH stimulation (sPET/CT) would detect more cancerous lesions than those without TSH stimulation (nsPET/CT) (12). However, although several studies have reported that the sensitivity of ¹⁸F-FDG-PET/CT may be slightly improved with TSH stimulation on a per-lesion basis, in clinical practice, the benefit of identifying additional small lesions remains to be proven (13). Moreover, TSH stimulation does not come without a price. Four to six weeks of THW induces iatrogenic hypothyroidism and consequent symptoms such as fatigue, decreased appetite, diminished motor skills, fluid retention and constipation, which will have noticeable negative effects on patients' quality of life and their psychometric functionality (14, 15). The use of rhTSH could avoid these deleterious effects for TSH stimulation, but it was relatively expensive and currently not commercially available in a large part of the world (16, 17).

In the present study, we performed a meta-analysis to evaluate the accuracy of ¹⁸F-FDG-PET/CT for the detection of recurrent and/or metastatic diseases in DTC patients with thyroglobulin elevation and negative iodine scintigraphy. Whether sPET/CT had better diagnostic performance than nsPET/CT in this scenario was also evaluated.

Methods

This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (18) and specific suggestions for meta-analyses of studies investigating diagnostic accuracy were followed (19).

Data sources and search strategy

Two authors (W.Q. and B.L.) searched all available literature published from January 2001 (since the

inception of hybrid PET-CT systems) to December 2018 in the PubMed and Embase database using an algorithm based on a combination of terms: (1) 'PET' OR 'positron emission tomography' OR 'PET-CT' OR 'positron emission tomography-computed tomography' OR 'PET/CT' OR 'positron emission tomography/computed tomography'; (2) 'FDG' OR 'fluorodeoxyglucose'; (3) 'differentiated thyroid cancer' OR 'papillary thyroid carcinoma' OR 'follicular thyroid carcinoma'; (4) 'Tg' OR 'thyroglobulin'; (5) 'radioiodine' OR 'radioactive iodine' OR '¹³¹I' OR 'I-131'. Additional key words identified during the searching process were incorporated into the searching strategies. The reference lists of identified publications were also hand-searched for potential relevant studies.

Study selection

Studies were eligible for inclusion if all of the following criteria applied: (a) the diagnostic performance of ¹⁸F-FDG-PET/CT in DTC patients with thyroglobulin elevation and negative iodine scintigraphy to detect recurrent and/or metastatic diseases could be clearly identified in the study or subsets of the study; (b) the data were sufficient (i.e., patient number above 10) to construct a 2×2 contingency table; (c) the reference standard was histopathology confirmation and/or clinical/imaging follow-up and was clearly stated in the article. The exclusion criteria were (a) duplicated articles; (b) case reports, abstract, letters, review or meta-analyses; (c) clearly irrelevant titles and abstracts; (d) non-English full-text articles; (e) studies in which CT was not integrated with PET.

Using the aforementioned inclusion and exclusion criteria, three researchers (W.Q., Z.G. and Z.Y.) independently screened titles and abstracts of the retrieved articles and then evaluated the full-text version of the remaining articles to determine their eligibility for inclusion. Disagreements between the researchers were resolved by discussion, or if necessary, by a fourth party.

Quality assessment

Two reviewers (J.B. and M.Q.) independently assessed the quality of the included studies based on the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool (20). Each study was evaluated based on the following domains: patient selection, index test, reference standard and, flow and timing. These domains were then evaluated according to the risk of bias and were rated regarding applicability as 'high', 'low' or 'unclear'. Disagreements

between the reviewers were resolved by discussion, or if necessary, by a third party.

Data extraction

Two reviewers (B.L. and Z.G.) independently conducted data extraction for all included articles. The extracted data included the first author, study characteristics (year, country, study design, data style, TSH stimulation and TSH level), patient characteristics (numbers of patients, male percentage, mean age, Tg level and histology) and technical aspects (^{18}F -FDG dose, fast time and reference standard). Disagreements between the reviewers were resolved by discussion, or if necessary, by a third party. For each study, the absolute numbers of true-positive, true-negative, false-positive and false-negative data were also extracted on a per-patient basis.

Diagnostic performance analyses

Our primary analysis assessed the overall diagnostic performance of ^{18}F -FDG-PET/CT incorporating all the included studies. Our secondary analysis investigated the diagnostic performance of ^{18}F -FDG-PET/CT according to whether TSH stimulation was prepared or not by analyzing available extracted data. Pair-wise comparison for the diagnostic estimate indexes was performed between sPET/CT and nsPET/CT.

Statistical analysis

The pooled sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR) and diagnostic odds ratio (DOR) were presented as estimates with 95% confidence intervals (CIs) by using random-effect analysis. The summary receiver-operating characteristic (SROC) curves were constructed and the area under the curve (AUC) was calculated.

Heterogeneity among pooled studies was assessed by use of Cochrane Q and I^2 statistic. Values of I^2 equal to 25, 50 and 75% were assumed to represent low, moderate and high heterogeneity, respectively. In case of substantial heterogeneity, meta-regression analysis was performed to explore the potential source of heterogeneity and the covariates were (1) study design (prospective vs retrospective); (2) patient number included (>40 vs ≤ 40); (3) fast time (≥ 4 h vs ≥ 6 h); (4) TSH stimulation (with vs without); (5) ethnicity (Asian vs Caucasian); (6) FTC percent (>10 vs $\leq 10\%$); (7) mean Tg value (>50 ng/mL vs ≤ 50 ng/mL); (8) reference standard

(histopathology alone vs others). The threshold effect between sensitivity and 1-specificity was calculated with Spearman correlation coefficient. Publication bias was assessed by Deeks funnel plot.

We conducted a Z test to pair-wisely compare the difference in sensitivity, specificity, PLR, NLR, DOR and AUC between sPET/CT and nsPET/CT. All statistical analyses were conducted with Stata 15.1 (Stata Corporation).

Results

Literature search and study selection

The initial search retrieved 1005 articles, and 908 were excluded upon review of titles and abstracts. The remaining 97 articles were carefully assessed by full-text and another 80 were excluded for the following reasons: case reports, abstracts, letters, reviews or meta-analysis ($n=8$); articles not available or not in English ($n=2$); data not retrievable for analysis ($n=33$); insufficient reference standard ($n=1$); less than 10 patents ($n=3$); PET study without CT ($n=31$) and with only scan-based data ($n=2$). Finally, 17 articles (21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37) including data on the diagnostic performance of ^{18}F -FDG-PET/CT in DTC patients with thyroglobulin elevation and negative iodine scintigraphy were eligible for further analysis. A PRISMA flow diagram of the study selection process is shown in Fig. 1.

Study description and quality assessment

The study and patient characteristics of the 17 articles comprising 1195 patients are summarized in Table 1. Among them, seven were conducted with TSH stimulation, three without TSH stimulation, five with both and two not described.

The results of summary risk of bias and applicability concerns of each study are shown in Supplementary Fig. 1 (see section on supplementary data given at the end of this article). The quality of the included studies was considered satisfactory.

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

Patient-based diagnostic performance was reported in all 17 studies comprising 1195 patients. The pooled sensitivity, specificity, PLR, NLR and DOR for PET/CT were 0.86 (95% CI: 0.79–0.90), 0.84 (95% CI: 0.72–0.91),

Figure 1

The PRISMA flow diagram of study selection.

5.20 (95% CI: 2.90–9.50), 0.17 (95% CI: 0.11–0.27) and 31.00 (95% CI: 12.00–80.00), respectively. Figure 2 shows the forest plots of the sensitivity and specificity of PET/CT for detection of recurrent and/or metastatic diseases. The I^2 values for sensitivity and specificity were 80% (95% CI=71.59–89.05) and 82% (95% CI=74.44–89.68), respectively. Figure 3 shows the SROC curve and the AUC was 0.91 (95% CI: 0.88–0.93).

Because heterogeneity between studies was high for both sensitivity and specificity, with no evidence of a threshold effect given the negative direction of the negative correlation ($\rho=-0.224$, $P=0.372$), meta-regression analysis was performed to explore other

sources of heterogeneity. The result indicated that patient number included ($P=0.02$ for sensitivity) and reference standard ($P=0.02$ for specificity) might be the sources of heterogeneity (Table 2).

An asymmetrical funnel plot indicated possible publication bias ($P=0.01$) in this study, although there might be other explanations such as variations in methodology, patients, reference standard, study design and chance (38) (Supplementary Fig. 2).

Lesion-based diagnostic performance was reported in two studies including 152 lesions, but meta-analytic summary diagnostic estimate indexes could not be calculated due to the small number of included studies.

Table 1 Study and patient characteristic of the included studies.

Reference	Study characteristic					Patient characteristic			
	Country	Study design	Data style	TSH stimulation	TSH level (mIU/L)	Patients, n	% Males (male/female)	Mean age (range)	Tg (ng/mL)
(37)	Thailand	Retro	PB	Yes	>30	38	42.1 (16/22)	47.9 (24–79)	(11.6–5055)
(34)	Korea	Retro	PB	Yes and No	US>30 WS: NA	75	NA	NA	(2.1–496.2)
(35)	Turkey	Retro	PB	NA	NA	104	26.9 (28/76)	46.4 (11–79)	14.4 ± 4.71
(36)	Turkey	Retro	PB	NA	NA	165	31.5 (52/113)	47.0 (13–80)	180 (2–3340)
(33)	Turkey	Retro	PB	No	<2	90	34.4 (31/59)	44.1 (17–88)	NA
(31)	India	Pro	PB	Yes	>30	62	40.3 (25/37)	42.5 (12–68)	275 ± 480.7
(32)	Turkey	Retro	PB	Yes	>30	71	25.4 (18/53)	42.6 (18–62)	14 (4–569)
(28)	Switzerland	Retro	PB	No	0.2 (0.01–0.2)	102	NA	NA	PP: 6.7 (0.7–73.6) PN: 1.8 (0.5–4.9)
(30)	Germany	Retro	PB	Yes	≥5	103	NA	NA	PP (3462 ± 19523) PN (37 ± 250)
(29)	Turkey	Retro	PB	Yes and No	US>30 WS: NA	49	NA	NA	Mean: 74.9
(24)	Germany	Retro	PB	Yes and No	US>30 WS: NA	30	40.0 (12/18)	44.4 (12–82)	28.1 (2.2–8663)
(27)	Turkey	Pro	PB	Yes and No	US: NA WS: <0.1	105	36.2 (38/67)	51.7 (13–83)	US: 166.5 ± 507.4 WS: 28.3 ± 105.5
(26)	Thailand	Pro	PB	Yes and No	US>30 WS: NA	30	26.7 (8/22)	52 (29–79)	US: 142.61 ± 196.63 WS: 12.56 ± 16.65
(25)	Switzerland	Pro	PB and LB	No	NA	42	19.6 (9/37)	41.5 (19–78)	RP: 9.4 (1.6–104.6) RN: 3.0 (1.0–7.2)
(23)	France	Pro	PB	Yes	73 ± 64	44	36.4 (16/28)	51 (9–83)	25 ± 68
(22)	France	Pro	PB	Yes	>30	45	31.1 (14/31)	55 (14–80)	0.4–1978
(21)	Germany	Pro	PB and LB	Yes	>30	40	NA	56.8 (NA)	>2

FTC, follicular thyroid cancer; LB, lesion based; NA, not available; PB, patient based; PN, PET/CT negative; PP, PET/CT positive; Pro, prospective; PTC, papillary thyroid cancer; Retro, retrospective; RN, reference standard negative; RP, reference standard positive; US, under TSH stimulation; WS, without TSH stimulation.

Comparison of diagnostic performance between sPET/CT and nsPET/CT

The pooled sensitivity, specificity, PLR, NLR, DOR and AUC for sPET/CT and nsPET/CT were 0.83 (95% CI: 0.70–0.92) and 0.84 (95% CI: 0.77–0.90), 0.77 (95% CI: 0.46–0.93) and 0.84 (95% CI: 0.67–0.93), 3.61 (95% CI: 1.25–10.45) and 5.18 (95% CI: 2.34–11.48), 0.22 (95% CI: 0.10–0.46) and 0.19 (95% CI: 0.12–0.29), 16.76 (95% CI: 3.24–86.52) and 27.83 (95% CI: 8.74–88.65) and 0.88 (95% CI: 0.84–0.90) and 0.89 (95% CI: 0.86–0.91), respectively. Table 3 showed that Z test did not detect statistically significant difference between sPET/CT and nsPET/CT for all the diagnostic estimate indexes during pair-wise comparison (All $P > 0.05$).

Discussion

The findings of our meta-analysis indicate that ¹⁸F-FDG-PET/CT has high diagnostic accuracy for detection of recurrent and/or metastatic diseases in DTC patients with thyroglobulin elevation and negative iodine scintigraphy, with a sensitivity of 0.86 (95% CI: 0.79–0.91), a specificity of 0.84 (95% CI: 0.72–0.91) and an AUC of 0.91 (95% CI: 0.88–0.93). The PLR value of 5.20 (95% CI: 2.90–9.50) suggested that patients with recurrent and/or metastatic disease have a five times greater chance of positive PET/CT results than patients without the disease, whereas the NLR value of 0.17 (95% CI: 0.11–0.27) indicated that patients without recurrent and/or metastatic disease have a six times (1/0.17) greater chance of negative PET/CT results than patients with the disease. The DOR value, which is an accuracy parameter that combines sensitivity and specificity data into a single measure, pointed to a similar direction with the AUC results (39). Considering that a DOR value of 1.0 indicates that the test does not discriminate between patients with and without the disease, in this meta-analysis, we have a DOR value of 31.00 (95% CI: 12.00–80.00).

Our patient-based results were slightly better than that reported in a meta-analysis conducted by Dong *et al.* (8), which presented a sensitivity of 0.84, a specificity of 0.84 and an AUC of 0.89 by analyzing 17 studies with 571 patients performed by PET alone without CT. However, this should be interpreted cautiously because the small differences observed may be largely due to the variations between imaging techniques, study populations and methodological qualities of the selected studies. For example, 14 of 17 our included PET/CT studies were

Figure 2

Forest plot of pooled sensitivity and specificity of ¹⁸F-FDG-PET/CT for detection of recurrent and/or metastatic diseases in DTC patients with thyroglobulin elevation and negative iodine scintigraphy.

published after 2012, whereas 14 of 17 their included PET studies were reported before 2001. It is possible that this slight superiority for PET/CT might be attributed to the improvement of emerging PET device over the years, rather than the additional information provided by CT. Up until now, studies directly comparing PET and PET/CT in the same patient series have been scarce due to worries of limited benefit and unnecessary radiation to the patients (21). But still, prospective studies with more robust design are needed in this area.

In a meta-analysis by Ma *et al.* (40), seven prospective controlled clinical trials comprising 168 DTC patients who were referred to PET or PET/CT for thyroglobulin elevation and negative iodine scintigraphy were analyzed to evaluate the effects of TSH stimulation on the uptake of FDG. When comparing sPET scans to nsPET scans, this meta-analysis revealed statistically significant difference in the number of patients with PET true-positive lesions and the number of the PET-detected lesions. In a prospectively designed study, Leboulleux *et al.* (13) assessed the impact of rhTSH administration on ¹⁸F-FDG-PET/CT in 63 DTC patients with thyroglobulin elevation and negative iodine scintigraphy. They found that the use of rhTSH significantly increased the number of lesions detected, but the numbers of patients in whom any lesion was detected were not different between sPET/CT scans and nsPET/CT scans. However, despite their positive view on performing TSH stimulation before PET scans, both articles did not offer the diagnostic performance results because of difficulty in defining reference standard and the lack of follow-up data. In our meta-analysis, we

include studies with clearly stated reference standard (histopathology confirmation and/or clinical/imaging follow-up). Both sPET/CT and nsPET/CT maintained high diagnostic performance and we did not detect statistically significant difference between sPET/CT and nsPET/CT for all the diagnostic estimate indexes during pair-wise comparison (All $P > 0.05$). These results indicated that on a

Figure 3

SROC curve of ¹⁸F-FDG-PET/CT for detection of recurrent and/or metastatic diseases in DTC patients with thyroglobulin elevation and negative iodine scintigraphy.

Clinical Study	W Qichang, B Lin and others	¹⁸ F-FDG-PET/CT in DTC patients	181:1	99
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Table 2 Subgroup analysis of the diagnostic performance of ¹⁸F-FDG-PET/CT.

Covariate/Subgroup	Number of studies	Meta-analytic summary estimate			
		Sensitivity (95% CI)	P value*	Specificity (95% CI)	P value*
Study design			0.06		0.14
Prospective	7	0.86 (0.77, 0.95)		0.78 (0.59, 0.96)	
Retrospective	10	0.86 (0.79, 0.93)		0.87 (0.77, 0.96)	
Patient number			0.02		0.93
>40	13	0.85 (0.78, 0.92)		0.84 (0.75, 0.94)	
≤40	4	0.93 (0.85, 1.00)		0.82 (0.59, 1.00)	
Fast time [#]			0.08		
≥6 h	10	0.87 (0.80, 0.94)		0.89 (0.80, 0.98)	0.26
≥4 h	5	0.91 (0.83, 0.98)		0.73 (0.49, 0.97)	
TSH stimulation [#]			0.11		0.34
Yes	7	0.83 (0.73, 0.93)		0.81 (0.67, 0.95)	
No	3	0.88 (0.78, 0.99)		0.88 (0.74, 1.00)	
Ethnicity			0.42		0.57
Asian	4	0.92 (0.84, 0.99)		0.90 (0.78, 1.00)	
Caucasian	13	0.85 (0.78, 0.92)		0.81 (0.71, 0.92)	
FTC percent [#]			0.07		0.96
>10%	7	0.87 (0.78, 0.96)		0.82 (0.67, 0.98)	
≤10%	6	0.88 (0.79, 0.97)		0.79 (0.59, 0.99)	
Mean Tg value [#]			0.49		0.85
>50 ng/mL	3	0.87 (0.77, 0.97)		0.87 (0.69, 1.00)	
≤50 ng/mL	6	0.81 (0.71, 0.91)		0.85 (0.71, 0.99)	
Reference standard			0.74		0.02
Histopathology alone	1	0.83 (0.57, 1.00)		0.29 (0.00, 0.78)	
Others	16	0.86 (0.80, 0.90)		0.86 (0.78, 0.93)	

*P value of meta-regression analysis to explore possible sources of heterogeneity. [#]Fast time, TSH stimulation, FTC percent and Mean Tg value were not available in 2, 7, 4 and 8 studies, respectively.

per-patient basis, TSH stimulation might not significantly improve the diagnostic capacity of PET/CT. As a matter of fact, several previous studies have reported similar results (22, 23, 34). Taken into consideration the patients' arduous THW experience and the high cost of rhTSH, it might be worth evaluating whether TSH stimulation could be omitted for PET/CT to assess DTC patients with thyroglobulin elevation and negative iodine scintigraphy. However, ultimately, this question needed to be weighed according to resulting changes in clinical management,

as well as knowledge on possible treatments and patients' corresponding prognosis. Therefore, in this regard, further well-designed studies evaluating the actual additional patients' oncological benefit to perform a sPET/CT are still needed.

There are several limitations to the present meta-analysis. Firstly, funnel plots showed that there was possible publication bias ($P=0.01$), which implied that studies with significant findings were more likely to be published and thus might affect the pooled results.

Table 3 Pair-wise comparison for the diagnostic estimate indexes between sPET/CT and nsPET/CT.

Modality	Sensitivity	Specificity	Positive LR	Negative LR	DOR	AUC
sPET/CT						
95% CI	0.83 (0.70, 0.92)	0.77 (0.46, 0.93)	3.61 (1.25, 10.45)	0.22 (0.10, 0.46)	16.76 (3.24, 86.52)	0.88 (0.84, 0.90)
P het	<0.001	<0.001	<0.001	<0.001	<0.001	
I ²	83%	86%	95%	80%	100%	
nsPET/CT						
95% CI	0.84 (0.77, 0.90)	0.84 (0.67, 0.93)	5.18 (2.34, 11.48)	0.19 (0.12, 0.29)	27.83 (8.74, 88.65)	0.89 (0.86, 0.91)
P het	0.27	0.01	<0.001	0.10	<0.001	
I ²	22%	69%	62%	48%	100%	
Z-test						
Z	0.15	0.51	0.47	-0.30	0.38	0.50
P	0.44	0.31	0.32	0.38	0.35	0.31

AUC, area under the curve; CI, confidence interval; DOR, diagnostic odds ratio; LR, likelihood ratio; P het, P heterogeneity.

Secondly, there was high heterogeneity of sensitivity and specificity between studies and this indicated a lack of consistency for our results. Our subgroup analysis revealed that patient number included ($P=0.02$) and reference standard ($P=0.02$) might be the sources of heterogeneity. Thirdly, the included studies used different criteria as their reference standard, with most depending on the changing course of Tg and results of follow-up imaging, in combination with histology or cytology results. Only one study used exclusively histopathologic findings (29). Fourthly, only patient-based data was included in our meta-analysis. However, in the study selection process, we found that studies reporting lesion-based data for PET/CT were very few ($n=2$) and this precludes further diagnostic performance analysis. This is understandable because it is hardly practical or ethical to acquire histopathologic information of every PET-detected lesion and small lesions might not have much clinical significance if there is already a verified large one. Finally, because there is a tendency for higher risk patients to perform sPET/CT, the disease status in this group could be more severe than that of nsPET/CT. This might introduce bias when comparisons were performed for diagnostic accuracy.

In conclusion, ¹⁸F-FDG-PET/CT has high diagnostic accuracy in evaluating DTC patients with thyroglobulin elevation and negative iodine scintigraphy on patient-based analysis, but existing studies were limited by high heterogeneity and possible publication bias. The diagnostic performance of sPET/CT may be not superior to nsPET/CT.

Supplementary data

This is linked to the online version of the paper at <https://doi.org/10.1530/EJE-19-0261>.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this study.

Funding

This work was supported by the Young Researcher Fund of Science and Technology Department of Jilin Province (Grant number: 20170520027JH) and the 13th Five-year Plan of Education Department of Jilin Province (Grant number: JJKH20190070KJ).

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Received 8 April 2019

Revised version received 14 May 2019

Accepted 19 May 2019