RESEARCH

Diagnostic performance of PET in thyroid cancer with elevated anti-Tg Ab

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Abstract

We aimed to explore the role of the diagnostic accuracy of F-18 fluorodeoxyglucose positron emission tomography/computed tomography (PET/CT) for the detection of recurrent and/or metastatic diseases in differentiated thyroid cancer (DTC) patients with progressively and/or persistently elevated TgAb levels and negative radioactive iodine whole-body scan (RI-WBS) through a systematic review and meta-analysis. The MEDLINE, EMBASE and Cochrane Library database, from the earliest available date of indexing through June 30, 2017, were searched for studies evaluating the diagnostic performance of F-18 FDG PET/CT for the detection of recurrent and/or metastatic diseases in DTC patients with progressively and/or persistently elevated TgAb levels and negative RI-WBS. We determined the sensitivities and specificities across studies, calculated positive and negative likelihood ratios (LR+ and LR–). Across 9 studies (515 patients), the pooled sensitivity for F-18 FDG PET/CT was 0.84 (95% CI; 0.77–0.89) a pooled specificity of 0.78 (95% CI; 0.67–0.86). Likelihood ratio (LR) syntheses gave an overall positive likelihood ratio (LR+) of 3.8 (95% CI; 2.5–5.7) and negative likelihood ratio (LR–) of 0.21 (95% CI; 0.14–0.30). The pooled diagnostic odds ratio (DOR) was 18 (95% CI; 10–34). The area (AUC) under the hierarchical summary receiver-operating characteristic (HCROC) curve was 0.88 (95% CI; 0.85–0.90). F-18 FDG PET or PET/CT demonstrated moderate sensitivity and specificity for the detection of recurrent and/or metastatic diseases in DTC patients with progressively and/or persistently elevated TgAb levels and negative RI-WBS.

Key Words

- ▶ positron emission tomography
- ▶ PET/CT
- ▶ thyroid neoplasm
- ▶ anti-thyroglobulin antibody

Endocrine-Related Cancer
(2018) **25**, 643–652

Introduction

Differentiated thyroid cancers (DTC) account for 1% of all malignant tumors and are the most common malignant endocrine tumor. In the United States, an estimated 14,400 men and 42,470 women will be diagnosed with thyroid cancer and 920 men and 1090 women will die of the disease at 2017 (Siegel *et al.* 2017). Serum thyroglobulin (Tg)

measurement and neck ultrasonography are considered to be the mainstays of postoperative follow-up in DTC patients (Haugen *et al.* 2016). Also, Tg is an important biological marker of persistent and/or recurrent disease after total thyroidectomy and radioactive iodine-131 ablation (RIA) in DTC patients.

Anti-thyroglobulin autoantibodies (TgAb) are known to be more common in DTC patients, especially in papillary thyroid cancer (PTC) compared with the general population (Kumar *et al.* 1994, Souza *et al.* 2003). Also, TgAb could interfere with serum Tg measurement and compromises the clinical utility of Tg monitoring of DTC patients for recurrence (Spencer *et al.* 2005, 2011, Kim *et al.* 2010). Theoretically, TgAb might be produced as a result of presence of thyroid tissue presence. Therefore, increasing serum TgAb levels during the follow-up of DTC patients appear to be a good biomarker for persistent or recurrent DTC patients with undetectable serum Tg levels. Some previous studies demonstrated these relationships in DTC patients (Tsushima *et al.* 2013, Durante *et al.* 2014, Hsieh & Wang 2014). On the contrary, some other studies could not find these phenomenon (Kumar *et al.* 1994, Görges *et al.* 2005).

F-18 fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) is a functional imaging tool for the detection, staging and management of various cancers. F-18 FDG PET/CT has emerged as an important tool for the management of patients with DTC and is most valuable in patients with increasing Tg levels with a negative radioactive iodine whole-body scan (RI-WBS) after RIA (Joensuu & Ahonen 1987, Abraham & Schöder 2011). According to the ATA guidelines, F-18 FDG PET/CT should be performed only when unstimulated Tg levels exceed 10 ng/mL (ATA Taskforce 2009).

Several previous studies have evaluated the diagnostic accuracy of F-18 FDG PET or PET/CT for the detection of recurrent and/or metastatic diseases in DTC patients with negative RI-WBS and elevated TgAb level with variable diagnostic accuracy (Seo *et al.* 2010, Ozkan *et al.* 2012, 2013, Qiu *et al.* 2017). The purpose of the current study is to meta-analyze the published data on the diagnostic accuracy of F-18 FDG PET or PET/CT for the detection of recurrent and/or metastatic diseases in DTC patients with progressively and/or persistently elevated TgAb levels and negative RI-WBS.

Materials and methods

Data sources and search strategy

We conducted electronic English-language literature searches of MEDLINE via PubMed, EMBASE and Cochrane Library database from the earliest available date of indexing through June 30, 2017. We also hand-searched the reference lists of identified publications for

additional studies. We used a search algorithm based on a combination of terms: (1) 'PET' OR 'positron emission tomography' OR 'positron emission tomography/computed tomography' OR 'PET/CT' 'positron emission tomography-computed tomography' OR 'PET-CT'; and (2) 'Thyroid neoplasms' OR 'Thyroid cancer' OR 'Papillary thyroid cancer' OR 'Follicular thyroid cancer' and (3) 'Anti-thyroglobulin antibody' OR 'Anti-TG'.

Study selection

The inclusion criteria for relevant studies were as follows: whole-body F-18 FDG PET or PET/CT had been used to identify the recurrent and/or metastatic diseases in patients with elevated TgAb and negative RI-WBS; sufficient data to reassess sensitivity and specificity of F-18 FDG PET or PET/CT or absolute numbers of true-positive, true-negative, false-positive and false-negative data had been presented; and no data overlap.

Duplicate publications were excluded, as were publications such as review articles, case reports, conference papers and letters, which do not contain the original data. Two researchers independently reviewed titles and abstracts of the retrieved articles, applying the above-mentioned selection criteria. Articles were rejected if clearly ineligible. The same four researchers then independently evaluated the full-text version of the included articles to determine their eligibility for inclusion.

Data extraction and quality assessment

Information about basic study (authors, year of publication and country of origin), study design (prospective or retrospective), patients' characteristics and technical aspects were collected.

Each study was analyzed to retrieve the number of true-positive (TP), true-negative (TN), false-positive (FP) and false-negative (FN) findings of F-18 FDG PET or PET/CT for the detection of recurrent and/or metastatic diseases in patients with elevated TgAb and negative RI-WBS, according to the reference standard. Only studies providing such complete information were finally included in the meta-analysis.

Quality of the included studies was assessed based on 15-item modified Quality Assessment of Diagnostic Accuracy Studies (QUADAS2) (Whiting *et al.* 2011). Two reviewers independently assessed each potentially eligible study and assigned them as a quality rating of 'good', 'fair' or 'poor'. Quality assessment was conducted

based on following criteria: study design and presence of bias including selection, performance, recording and reporting bias. Studies with high risk of bias were defined as poor quality, presence of moderate risk (did not affect the results) as fair quality, and those with minimal risk as good quality. Disagreements were settled with consensus decision. Disagreement between the 2 authors was resolved by discussion.

Data synthesis and analysis

All data from each eligible study were extracted. Categorical variables are presented as frequencies or percentages, and continuous variables are presented as mean values unless stated otherwise. Measures of the diagnostic performance, including sensitivity, specificity and diagnostic odds ratios (DORs), are reported as point estimates with 95% confidence intervals (CIs). A DOR can be calculated as the ratio of the odds of positivity in a disease state relative to the odds of positivity in the non-disease state, with higher values indicating better discriminatory test performance (Glas *et al.* 2003). Between-study statistical heterogeneity was assessed using I^2 and the Cochrane Q test on the basis of the random-effects analysis (Thompson 1994). Publication bias was examined using the effective sample size funnel plot and associated regression test of asymmetry described by Deeks *et al.* (2005). We used the bivariate random-effects model for analysis and pooling of the diagnostic performance measures across studies,

as well as comparisons between different index tests (Reitsma *et al.* 2005, Hamza *et al.* 2008). The bivariate model estimates pairs of logit transformed sensitivity and specificity from studies, incorporating the correlation that might exist between sensitivity and specificity. We also used the model to create hierarchical summary receiver-operating characteristic curves and to estimate the area under the curve (Rutter & Gatsonis 2001). When statistical heterogeneity was substantial, we performed meta-regression to identify potential sources of bias (Lijmer *et al.* 1999) using freeware of Meta-disc (Meta-DiSc, version 1.4, Universidad Complutense, Madrid, Spain). Meta-regression was performed to examine the potential source of the heterogeneity and the covariates were (1) ethnicity (Asian vs Caucasian), (2) detection device (PET vs PET/CT), (3) cancer type (PTC vs PTC and FTC) and (4) titer of TgAb (Continuous variable).

Pooled estimates were also calculated for subgroups of studies that were defined according to specific study designs. Two-sided $P \leq 0.05$ was considered statistically significant. Statistical analyses were performed with midas command in commercial software programs (STATA, version 13.1; StataCorp LP).

Ethical approval

Institutional review board approval was not required because we only performed data analysis based on the published studies.

Table 1 Characteristics of the included studies.

Authors (year)	Country	Device	Analysis	Patient number	Cancer type	Age	Male/female	F-18 FDG dose (MBq)	Mean TgAb (IU/mL, range)	TgAb measure	Study design
Asa <i>et al.</i> (2014)	Turkey	PET/CT	PB	40	PTC FTC	43.1	8/32	NA	1101.2 (150–4000)	ECLIA	R
Bogsrud <i>et al.</i> (2011)	USA	PET	PB	17	PTC FTC	51.5	9/8	740	416 (10–6500)	ECLIA	R
Chung <i>et al.</i> (2002)	Korea	PET	PB	26	PTC	41.1	1/25	370	983.2 (25–7439)	RIA	R
Kingpetch <i>et al.</i> (2011)	Thai	PET/CT	PB	22	PTC FTC	NA	NA	227.5–455.4	414.6	RIA	R
Ozkan <i>et al.</i> (2012)	Turkey	PET/CT	PB	31	PTC	50.1	4/27	370	472.9 (27–4000)	RIA	R
Ozkan <i>et al.</i> (2013)	Turkey	PET/CT	PB	10	PTC	NA	NA	370	663.4 (71.3–4000)	RIA	R
Qiu <i>et al.</i> (2017)	China	PET/CT	PB	82	PTC	48	32/50	3–4 MBq/kg	479 (98–3726)	ECLIA	R
Viedma <i>et al.</i> (2011)	Spain	PET	LB	11	PTC	NA	NA	370–434	200	ECLIA	R
Seo <i>et al.</i> (2010)	Korea	PET/CT	PB	276	PTC FTC	NA	NA	370–555	NA	RIA	R

ECLIA, electrochemiluminescence immunoassay; FTC, follicular thyroid cancer; LB, lesion-based; NA, not available; PB, patient based; PTC, papillary thyroid cancer; R, retrospective; RIA, radioimmunoassay.

Figure 1

Flow chart of the search for eligible studies on the diagnostic performance of F-18 FDG PET or PET/CT for detection of recurrent and/or metastatic diseases in DTC patients with progressively and/or persistently elevated TgAb levels and negative RI-WBS.

Results

Literature search and selection of studies

After the comprehensive computerized search was performed and references lists were extensively cross-checked, our research yielded 44 records, of which 16 duplicated records were excluded after reviewing the title and abstract. Also, non-relevant 15 abstracts, 2 case reports, 1 review article were excluded. Remaining 10 full-text articles were assessed for eligibility and 1 article was excluded due to unavailability of sufficient numerical data ($n=9$) for the calculation of sensitivity and specificity of F-18 FDG PET or PET/CT for the detection of recurrent and/or metastatic diseases in DTC patients with progressively and/or persistently elevated TgAb levels and negative RI-WBS. Finally, 9 studies were selected and were eligible for the systematic review and meta-analysis, and no additional studies were found screening the references of these articles (Chung *et al.* 2002, Seo *et al.* 2010, Bogsrud *et al.* 2011, Kingpetch *et al.* 2011, Viedma *et al.* 2011, Ozkan *et al.* 2012, 2013, Asa *et al.* 2014, Qiu *et al.* 2017). The characteristics of the included studies are presented in Table 1. The detailed procedure of study selection in the meta-analysis is shown in Fig. 1.

Figure 2

Results of Deeks's funnel plot of asymmetry test for publication bias. Non-significant slope indicates that no significant bias was found. ESS: effective sample size. 1, Qiu *et al.* 2017; 2, Ozkan *et al.* 2013; 3, Ozkan *et al.* 2012; 4, Kingpetch *et al.* 2011; 5, Seo *et al.* 2010; 6, Viedma *et al.* 2011; 7, Bogsrud *et al.* 2011; 8, Asa *et al.* 2014; 9, Chung *et al.* 2002.

Study description, quality and publication bias

We conducted all analyses based on per-patient data and/or per-lesion data analysis. Among those 9 studies included in the current review, 8 studies conducted patient-based analysis of F-18 FDG PET/CT (Chung *et al.* 2002, Seo *et al.* 2010, Bogsrud *et al.* 2011, Kingpetch *et al.* 2011, Ozkan *et al.* 2012, 2013, Asa *et al.* 2014, Qiu *et al.* 2017). The other study conducted lesion-based analysis (Viedma *et al.* 2011). There were a total of 515 patients in the included studies, and the age ranged from 17 to 82 years. A total 50 patients were male, and 142 patients were female. The four studies did not report the number of male and female patients in their population (Seo *et al.* 2010, Kingpetch *et al.* 2011, Viedma *et al.* 2011, Ozkan *et al.* 2013). Of all 9 studies enrolled patients retrospectively. Six studies used PET/CT (Seo *et al.* 2010, Kingpetch *et al.* 2011, Ozkan *et al.* 2012, 2013, Asa *et al.* 2014, Qiu *et al.* 2017) and other studies (Chung *et al.* 2002, Bogsrud *et al.* 2011, Viedma *et al.* 2011) used PET as imaging device in their studies. The principal characteristics of the 9 studies

	Risk of Bias				Applicability Concerns		
	Patient Selection	Index Test	Reference Standard	Flow and Timing	Patient Selection	Index Test	Reference Standard
Asa 2014	—	?	+	+	?	+	?
Bogsrud 2011	—	+	+	+	+	?	+
Chung 2002	—	?	+	+	+	+	+
Kingpetch 2011	—	?	?	?	?	+	+
Ozkan 2012	+	+	+	+	+	?	+
Ozkan 2013	—	+	+	+	+	+	+
Qiu 2017	?	+	+	+	+	+	+
Sanz 2011	—	?	+	+	?	+	+
Seo 2010	—	+	+	+	+	+	+

High
 Unclear
 Low

Figure 3

Risk of bias and applicability concerns summary.

included in the meta-analysis are included in Table 1. To assess a possible publication bias, Deeks's funnel plot asymmetry tests were designed. The non-significant slope indicates that no significant bias was found. The *P* value was 0.85 (Fig. 2).

Methodological quality assessment

Figure 3 shows the risk of bias and applicability concerns summary and overall, the quality of the included studies was deemed satisfactory.

Diagnostic accuracy of F-18 FDG PET or PET/CT

The diagnostic performance results of F-18 PET/CT of the 9 included studies in the meta-analysis are presented in Fig. 4 and Table 2. The pooled sensitivity for F-18 FDG PET/CT was 0.84 (95% CI; 0.77–0.89) without heterogeneity

($I^2=0.00$, 95% CI=0.00–100.00) and a pooled specificity of 0.78 (95% CI; 0.67–0.86) with heterogeneity ($I^2=57.63$, 95% CI=26.25–89.02). LR syntheses gave an overall positive likelihood ratio (LR+) of 3.8 (95% CI; 2.5–5.7) and negative likelihood ratio (LR–) of 0.21 (95% CI; 0.14–0.30). The pooled DOR was 18 (95% CI; 10–34). Forest plots of the sensitivity and specificity of F-18 FDG PET/CT for the detection of recurrent and metastatic lesions are shown in Fig. 4. Figure 5 shows hierarchical summary receiver-operating characteristic (ROC) curve and indicates that the areas under the curve was 0.88 (95% CI; 0.85–0.90), indicating moderate diagnostic accuracy.

Heterogeneity evaluation and meta-regression analysis

Between-study heterogeneity was present for specificity among studies of F-18 FDG PET or PET/CT for the

Figure 4

Forest plot of pooled sensitivity and specificity of F-18 FDG PET or PET/CT for detection of recurrent and/or metastatic diseases in DTC patients with progressively and/or persistently elevated TgAb levels and negative RI-WBS. Summary of sensitivity and specificity of F-18 FDG PET or PET/CT was 0.84 (95% confidence interval (CI); 0.77–0.89) and 0.78 (95% CI; 0.67–0.86), respectively. (Q: Cochran's Q ; P : P is the percentage of observed total variation between studies.)

detection of recurrent and/or metastatic diseases. A meta-regression analysis was performed to explore other sources of heterogeneity in the studies of F-18 FDG PET or PET/CT. Meta-regression showed that the device (PET vs PET/CT) was the major source of heterogeneity in the meta-analysis (Table 3).

Discussion

It is known that persistent and/or a rising TgAb level after total thyroidectomy and RIA is a risk factor of recurrent/persistent disease of DTC (Seo *et al.* 2010, Hsieh & Wang 2014). Also, elevated TgAb may be alternative biological marker of the recurrent and/or metastatic disease (Seo *et al.* 2010). Durante *et al.* reported that PTC patients with positive serum TgAb titer during the first year after primary treatment were more likely to have persistent/recurrent disease than those who were consistently TgAb-negative and negative titers at 1 year may be associated with more favorable outcomes (Durante *et al.* 2014). Also, Kim *et al.* demonstrated that serum TgAb

levels measured at 6–12 months after remnant ablation could predict recurrence in patients with undetectable Tg values (Kim *et al.* 2008). In patients with undetectable Tg and positive TgAb values, a change in TgAb concentration during the early postoperative period may be a prognostic indicator of recurrence (Kim *et al.* 2008).

F-18 FDG PET/CT is used in the postoperative surveillance of DTC, mainly after RIA in patients with elevated serum Tg levels but negative RI-WBS (ATA Taskforce 2009). A recent meta-analysis of the diagnostic value of F-18 FDG PET or PET/CT in DTC patients who showed with elevated serum Tg post-thyroidectomy and negative RI-WBS demonstrated that these imaging techniques had a good diagnostic accuracy, with pooled sensitivity and specificity values of 88.5 and 84.7% respectively (Dong *et al.* 2009). They concluded that F-18 FDG PET is especially effective in detecting patients with elevated Tg levels and normal RI-WBS and F-18 FDG PET/CT is a more sensitive method in the follow-up of DTC recurrence or metastases, particularly in those with negative RI-WBS (Dong *et al.* 2009).

Table 2 Diagnostic performance of F-18 FDG PET or PET/CT for the detection of recurrent and/or metastatic diseases in differentiated thyroid cancer patients with elevated TgAb and negative radioactive iodine whole-body scan.

Authors (year)	Test results, number of patients or lesions				95% CI			
	True positive	False positive	False negative	True negative	Sensitivity	Specificity	PPV	NPV
Asa <i>et al.</i> (2014)	27	3	7	3	0.79 (0.62–0.91)	0.50 (0.12–0.88)	0.9 (0.72–0.97)	0.3 (0.08–0.65)
Bogsrud <i>et al.</i> (2011)	10	0	2	5	0.83 (0.52–0.98)	1.00 (0.48–1.00)	1.0 (0.66–1.00)	0.71 (0.30–0.95)
Chung <i>et al.</i> (2002)	11	1	2	12	0.85 (0.55–0.98)	0.92 (0.64–1.00)	0.92 (0.59–0.99)	0.86 (0.56–0.97)
Kingpetch <i>et al.</i> (2011)	6	6	0	10	1.00 (0.54–1.00)	0.63 (0.35–0.85)	0.5 (0.22–0.78)	1.0 (0.66–1.00)
Ozkan <i>et al.</i> (2012)	12	4	2	13	0.86 (0.57–0.98)	0.76 (0.50–0.93)	0.75 (0.47–0.92)	0.87 (0.58–0.98)
Ozkan <i>et al.</i> (2013)	6	2	0	2	1.00 (0.54–1.00)	0.50 (0.07–0.93)	0.75 (0.36–0.96)	1.0 (0.19–1.00)
Qiu <i>et al.</i> (2017)	54	5	10	13	0.84 (0.73–0.92)	0.72 (0.47–0.90)	0.92 (0.81–0.97)	0.57 (0.34–0.76)
Viedma <i>et al.</i> (2011)	7	1	0	3	1.00 (0.59–1.00)	0.75 (0.19–0.99)	0.88 (0.47–0.99)	1.0 (0.31–1.00)
Seo <i>et al.</i> (2010)	28	32	9	207	0.76 (0.59–0.88)	0.87 (0.82–0.91)	0.47 (0.34–0.59)	0.96 (0.92–0.98)
Combined	161	54	32	268	0.84 (0.77–0.89)	0.78 (0.67–0.86)	0.75 (0.68–0.80)	0.89 (0.85–0.92)

CI, confidence interval; NPV, negative predictive value; PPV, positive predictive value.

However, few studies reported the clinical usefulness of F-18 FDG PET or PET/CT for the detection of recurrent and/or metastatic diseases in DTC patients with elevated serum TgAb and negative RI-WBS after total thyroidectomy and RIA. According to the current systematic review and meta-analysis, F-18 FDG PET or PET/CT has moderate diagnostic accuracy for the detection of recurrent and/or metastatic diseases in these patients group with an area under the ROC curve of 0.88 (95% CI; 0.85–0.90). F-18 FDG PET or PET/CT demonstrated a sensitivity of 0.84 (95% CI; 0.77–0.89) and a specificity of 0.78 (95% CI; 0.67–0.86). A recent study by Qiu *et al.* investigated the diagnostic accuracy of F-18 FDG PET/CT for detection of recurrent and/or metastatic diseases in DTC patients with elevated serum TgAb and negative RI-WBS and reported 84% sensitivity, 72% specificity, 92% positive predictive value (PPV), 57% negative predictive value (NPV) and 82% accuracy (Qiu *et al.* 2017). They suggested that F-18 FDG PET/CT should be performed routinely in PTC patients with negative Tg, negative I-131 WBS at first post-ablation and progressively increased TgAb level, especially when span for progressively increased TgAb level ≥ 3 years and/or progressively increased TgAb value up to 150IU/mL (Qiu *et al.* 2017). Chung *et al.* first investigated the clinical usefulness of F-18 FDG PET in patients elevated serum TgAb levels (Chung *et al.* 2002). In their study, F-18 FDG PET showed a sensitivity, specificity and accuracy of 84.6, 92.3 and 88.4%, respectively (Chung *et al.* 2002). Asa *et al.* investigated the diagnostic usefulness

of F-18 FDG PET/CT in 40 patients with negative Tg and persistent/progressive elevated TgAb titers (Asa *et al.* 2014). On the basis of the total 16 patients with available final diagnoses, the sensitivity, specificity, PPV,

Figure 5

Hierarchical summary receiver-operating characteristic (HSROC) curves of F-18 FDG PET or PET/CT for the detection of recurrent and/or metastatic diseases in DTC patients with progressively and/or persistently elevated TgAb levels and negative RI-WBS. 1, Qiu *et al.* 2017; 2, Ozkan *et al.* 2013; 3, Ozkan *et al.* 2012; 4, Kingpetch *et al.* 2011; 5, Seo *et al.* 2010; 6, Viedma *et al.* 2011; 7, Bogsrud *et al.* 2011; 8, Asa *et al.* 2014; 9, Chung *et al.* 2002.

Table 3 Effects of moderators.

Variables	Coef.*	SE	DOR	95% CI		P†
Ethnicity (Asian vs Caucasian)	−0.421	0.234	0.660	0.310	1.380	0.169
Device (PET vs PET/CT)	−1.265	0.273	0.280	0.120	0.670	0.019
Cancer type (PTC vs PTC and FTC)	0.329	0.220	1.390	0.690	0.280	0.232
TgAb (continuous variable)	−0.001	0.000	1.000	1.000	1.000	0.089

Ethnicity (0, Asian vs 1, Caucasian); device (0, PET vs 1, PET/CT); cancer type (0, PTC vs 1, PTC and FTC).

*Regression coefficient; †P value of random effect meta-regression using maximum likelihood estimation (ML) between-study variances and the weighted least squares of study size for regression model estimation.

NPV and the accuracy were 78.5, 50, 91.6, 25 and 75%, respectively (Asa *et al.* 2014). They concluded from the available data that F-18 FDG PET/CT can be effectively used in the detection of recurrence/metastasis in the follow-up of patients with DTC and negative serum Tg and a persistently/progressively increased TgAb level (Asa *et al.* 2014).

Interestingly, Chiovato *et al.* investigated whether complete removal of thyroid antigens results in the abatement of humoral thyroid autoimmunity. They showed that the persistence of thyroid peroxidase or thyroglobulin antibodies may be a marker of incomplete cure in many patients with differentiated thyroid carcinoma (Chiovato *et al.* 2003). Also, they concluded that the complete ablation of thyroid tissue with its antigenic components results in the disappearance of antibodies to all major thyroid antigens, thus supporting the concept that continued antibody production depends on the persistence of autoantigen in the body (Chiovato *et al.* 2003).

We should consider some limitations of the current meta-analysis. The inter-study heterogeneity was noticed in the current meta-analysis. The included studies were statistically heterogeneous in their estimates of specificity in the current study. We tried to overcome this limitation by using random-effects model that incorporates uncertainties arising because of inter-study variation, as well as performing meta-regression. To minimize bias in 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, and scores were assigned to study design characteristics and examination results by using a standardized form that was based on the QUADAS2 tool. Also, publication bias is a major concern in all meta-analyses as studies reporting significant findings are more likely to be published than those reporting non-significant results. We assessed the publication bias in our analysis by using funnel plots, which showed very little evidence of asymmetry ($P=0.85$).

Conclusion

F-18 FDG PET or PET/CT demonstrated moderate sensitivity and specificity for the detection of recurrent and/or metastatic diseases in DTC patients with progressively and/or persistently elevated TgAb levels and negative RI-WBS. At present, the literature regarding the use of F-18 FDG PET or PET/CT for this purpose remains still limited; thus, further large multicenter studies would be necessary to substantiate the diagnostic accuracy of F-18 FDG PET or PET/CT for the detection of recurrent and/or metastatic diseases in DTC patients with progressively and/or persistently elevated TgAb levels and negative RI-WBS.

Declaration of interest

The authors of this manuscript declare no relationships with any companies whose products or services may be related to the subject matter of the research reported.

Funding

This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

Informed consent

Written informed consent was not required for this study because it is a meta-analysis based on the studies that have been published.

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Received in final form 16 March 2018

Accepted 20 March 2018

Accepted Preprint published online 20 March 2018