Endocrine (2012) 42:535–545
DOI 10.1007/s12020-012-9671-6

META-ANALYSIS

Detection rate of recurrent medullary thyroid carcinoma using fluorine-18 fluorodeoxyglucose positron emission tomography: a meta-analysis

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Received: 25 February 2012 / Accepted: 4 April 2012 / Published online: 17 April 2012

Abstract Several studies evaluated the diagnostic performance of fluorine-18 fluorodeoxyglucose (FDG) positron emission tomography (PET), and positron emission tomography/computed tomography (PET/CT) in detecting recurrent medullary thyroid carcinoma (MTC) with conflicting results. Aim of our study is to meta-analyze published data about this topic. A comprehensive computer literature search of studies published in PubMed/MEDLINE, Scopus, and Embase databases through December 2011 and regarding FDG PET or PET/CT in patients with suspected recurrent MTC was carried out. Pooled detection rate (DR) on a per patient-based analysis was calculated to measure the diagnostic performance of FDG PET and PET/CT in this setting. A sub-analysis considering PET device used, serum calcitonin, carcino-embryonic antigen (CEA), calcitonin doubling time (CTDT), and CEA doubling time (CEADT) values was also performed. Twenty-four studies comprising 538 patients with suspected recurrent MTC were included. DR of FDG PET or PET/CT in suspected recurrent MTC on a per patient-based analysis was 59 % (95 % confidence interval: 54–63 %). Heterogeneity between the studies was revealed. DR increased in patients with serum calcitonin $\geq$1,000 ng/L (75 %), CEA $\geq$5 ng/ml (69 %), CTDT <12 months (76 %), and CEADT <24 months (91 %). In patients with suspected recurrent MTC FDG PET and PET/CT are associated with a non-optimal DR since about 40 % of suspected recurrent MTC remain usually unidentified. However, FDG PET and PET/CT could modify the patient management in a certain number of recurrent MTC because these methods are often performed after negative conventional imaging studies. DR of FDG PET and PET/CT increases in patients with higher calcitonin and CEA values and lower CTDT and CEADT values, suggesting that these imaging methods could be very helpful in patients with more aggressive disease.

Keywords PET · PET/CT · ^{18}F-FDG · Fluorodeoxyglucose · Medullary thyroid carcinoma

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Introduction

Medullary thyroid carcinoma (MTC) is an uncommon and slow-growing neuroendocrine tumor that originates from parafollicular C cells secreting calcitonin. MTC accounts for approximately 5 % of thyroid carcinomas, occurring in either sporadic (75 % of cases) or familial forms (25 % of cases). This tumor is frequently aggressive; most frequent sites of metastatic disease are cervical and thoracic lymph nodes, lungs, liver, and bone. The mainstay of treatment for MTC is surgical resection that is the only strategy for potential cure; in patients with metastatic disease therapeutic options are limited as this tumor does not concentrate radioiodine and shows poor response to chemotherapy and external-beam radiation therapy [1].

Serum calcitonin represents the most sensitive and accurate tumor marker in the postoperative management and surveillance of MTC. In about one-third of patients with MTC lesions also carcino-embryonic antigen (CEA) levels may be increased and this finding has prognostic significance, as increased CEA levels are characteristic of advanced forms when the tumor tends to de-differentiation. Serum calcitonin and CEA doubling times (CEADTs) are efficient tools for assessing tumor progression and are useful prognostic factors of survival in patients with MTC

[1]. In the presence of a significant increase of serum calcitonin or CEA levels after surgery the search for locally residual/recurrent or metastatic disease by imaging is indicated [2]. According to the recommendations of the American Thyroid Association, these imaging modalities include neck ultrasound, neck and chest computed tomography (CT), liver-three phase contrast-enhanced CT or contrast-enhanced magnetic resonance imaging (MRI), bone scintigraphy and bone MRI of the spine and pelvis [2].

Currently, positron emission tomography (PET) or positron emission tomography/computed tomography (PET/CT) using fluorine-18 fluorodeoxyglucose (FDG, a glucose analog) and fluorine-18 dihydroxyphenylalanine (F-DOPA, a marker of intracellular decarboxylation) are most commonly used in cases of suspected recurrent MTC when conventional imaging modalities are often negative or inconclusive in the presence of rising levels of tumor markers. Several studies evaluated the diagnostic accuracy of FDG PET and PET/CT in patients with suspected recurrent MTC reporting a wide range of sensitivity and specificity. Furthermore, detection rate (DR) of these imaging methods seems to improve in patients with higher serum calcitonin and CEA levels [3, 4]. To date, a meta-analysis on this topic is lacking in the literature; therefore, the aim of this study is to meta-analyze published data on the diagnostic performance of FDG PET and PET/CT in patients with suspected recurrent MTC, in order to add evidence-based data in this setting.

Methods

Search strategy

A comprehensive computer literature search of the PubMed/MEDLINE, Scopus, and Embase databases was carried out to find relevant published articles on the diagnostic performance of FDG PET and PET/CT in patients with recurrent MTC on the basis of increased serum calcitonin levels after primary surgery. We used a search algorithm based on a combination of the terms: (a) ''PET'' OR "positron emission tomography" AND (b) "medullary" OR "thyroid." No beginning date limit was used; the search was updated until December 31, 2011. To expand our search, references of the retrieved articles were also screened for additional studies. No language restriction was used.

Study selection

Studies or subsets in studies investigating the diagnostic performance of FDG PET or PET/CT in patients with recurrent/residual MTC were eligible for inclusion. Only those studies or subsets in studies that satisfied all of the following criteria were included: (a) FDG PET or PET/CT performed in patients with suspected recurrent MTC after primary surgery; (b) sample size of at least six patients with MTC.

The exclusion criteria were: (a) articles not within the field of interest of this review; (b) review articles, editorials or letters, comments, conference proceedings; (c) case reports or small case series (sample size of <6 patients with recurrent/residual MTC); (d) insufficient data to reassess the diagnostic performance of FDG PET or PET/CT on a per patient-based analysis from individual studies; (e) possible data overlapping (in such cases the most complete article was included in the meta-analysis).

Two researchers independently reviewed the titles and abstracts of the retrieved articles, applying the inclusion and exclusion criteria mentioned above. Articles were rejected if they were clearly ineligible. The same two researchers then independently reviewed the full-text version of the remaining articles to determine their eligibility for inclusion. Disagreements were resolved in a consensus meeting.

Data abstraction

For each included study, information was collected concerning basic study (author names, journal, year of publication, country of origin), patient characteristics (number of patients with suspected recurrent/residual MTC performing FDG PET or PET/CT, mean age, sex), technical aspects (study design, device used, radiopharmaceutical injected dose, time interval between radiopharmaceutical injection and image acquisition, acquisition protocol, image analysis and reference standard used). For each study, the number of recurrent MTC patients detected by FDG PET or PET/CT were recorded. Patients evaluated with FDG PET or PET/CT before surgery were excluded from the analysis.

Quality assessment

Two independent reviewers evaluated the methodology of the selected studies using the quality assessment tool for diagnostic accuracy studies (QUADAS) [5]. This 14-items tool is composed by five items related to verification bias, three items related to review bias, two items relating to generalizability and context and spectrum bias, and four to reporting. Reviewers, who were blinded to the purposes of the meta-analysis, recorded a score of "1" for "yes" and "0" for "no" for each of the 14 items; all disagreements were resolved by means of consensus.

Statistical analyses

DRs of FDG PET or PET/CT were calculated on a per patient-based analysis. We considered as positive a patient with at least one lesion detected by FDG PET or PET/CT.

DR was determined from the number of patients with recurrent MTC detected by FDG PET or PET/CT (A) and the number of patients performing FDG PET or PET/CT (B), according to the following formula: DR = $(A)/(B)$. Sub-analysis considering serum calcitonin, CEA, calcitonin doubling time (CTDT), and CEADT values were performed. Furthermore, a sub-analysis considering PET device used was carried out.

We used a random effect model for statistical pooling of the data. Pooled data are presented with 95 % confidence intervals (95 % CI). A I-square statistic was performed to test for heterogeneity between studies. Statistical analyses were performed using Meta-DiSc statistical software.

Results

Literature search

The comprehensive computer literature search from the PubMed/MEDLINE, Scopus, and Embase databases revealed 1,285 articles. Reviewing titles and abstracts, 1,252 articles were excluded: 1,156 because they were not in the field of interest of this review, 76 as reviews or editorials, 20 as case reports or small case series.

Thirty-three articles were selected and retrieved in full-text version; no additional study was found screening the references of these articles. From these 33 articles potentially eligible for inclusion, after reviewing the full-text article, two studies were excluded because DR of FDG PET or PET/CT could not be calculated on a per patient-based analysis for insufficient data [6, 7]; moreover, seven articles were excluded for possible data overlapping [8–14]. Finally, 24 studies, comprising a total sample size of 538 patients with MTC met all inclusion and exclusion criteria, and they were included in this meta-analysis [15–38] (Fig. 1). The characteristics of the included studies are presented in Tables 1 and 2.

Quality assessment

Overall, the studies included in this meta-analysis have shown moderate methodological quality according to QUADAS [5]. Studies scored between 7/14 and 12/14 with a median score of 9/14. The index test and the reference standard were often interpreted without blinding, and this represents the most critical issue about the methodological quality of the included studies.

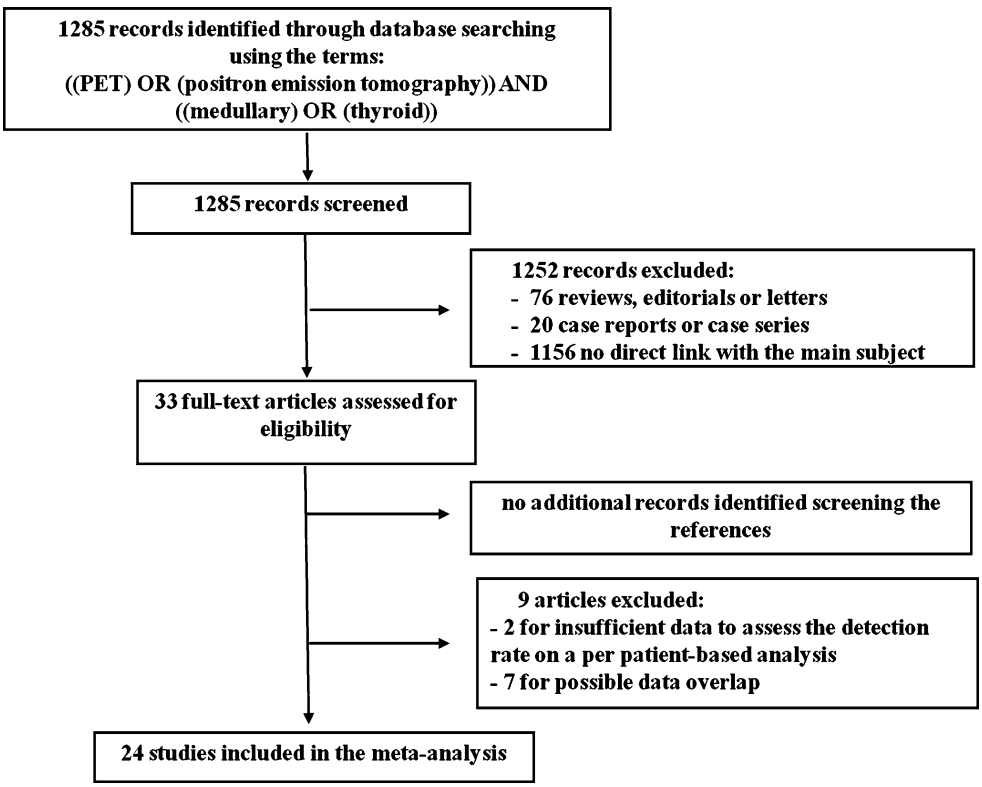

Fig. 1 Flow chart of the search for eligible studies on the diagnostic performance of FDG PET and PET/CT in patients with suspected recurrent/residual MTC

Table 1 Basic study and patient characteristics

Authors	Journal	Year	Country	MTC patients performing ^{18}F-FDG PET or PET/CT	Mean age (years)	Male (%)
Kauhanen et al. [15]	J Nucl Med	2011	Finland	19	52	53
Ozkan et al. [16]	Nucl Med Commun	2011	Turkey	33	50	27
Gómez-Camarero et al. [17]	Rev Esp Med Nucl	2011	Spain	31	56	45
Jang et al. [18]	Endocrine J	2010	Korea	16	51	56
Skoura et al. [19]	Nucl Med Commun	2010	Greece	32 (38 scans)	52	31
Marzola et al. [20]	Eur J Surg Oncol	2010	Italy	18	51	44
Bogsrud et al. [21]	Mol Imaging Biol	2010	USA & Norway	29	50	55
Conry et al. [22]	Eur J Nucl Med Mol Imaging	2010	UK & Singapore	18	54	72
Beheshti et al. [23]	Eur Radiol	2009	Austria	19[b]	59	38
Faggiano et al. [24]	Endocr Relat Cancer	2009	Italy	26	NR	49
Koopmans et al. [25]	J Nucl Med	2008	The Netherlands	17	56	48
Rubello et al. [26]	Eur J Surg Oncol	2008	Italy	19	53	42
Oudoux et al. [6][a]	J Clin Endocrinol Metab	2007	France	33	53	64
Giraudet et al. [27]	J Clin Endocrinol Metab	2007	France	55[b]	56	62
Czepczyński et al. [28]	Eur J Nucl Med Mol Imaging	2007	Poland & Italy	13	50	57
Beuthien-Baumann et al. [29]	Eur J Nucl Med Mol Imaging	2007	Germany	15	56	53
Ong et al. [30]	J Nucl Med	2007	USA	28 (38 scans)	59	64
Iagaru et al. [31]	Mol Imaging Biol	2007	USA	13	48	46
Gotthardt et al. [32]	Eur J Nucl Med Mol Imaging	2006	Germany & The Netherlands	26	45	58
de Groot et al. [33]	Ann Surg Oncol	2004	The Netherlands	26	51	58
Szakáll et al. [34]	J Nucl Med	2002	Hungary	40	48	45
Diehl et al. [55][a]	Eur J Nucl Med	2001	Germany	85 (100 scans)	53	47
Hoegerle et al. [35]	Eur J Nucl Med	2001	Austria	10[b]	57	55
Brandt-Mainz et al. [36]	Eur J Nucl Med	2000	Germany	17	NR	65
Adams et al. [37]	Eur J Nucl Med	1998	Germany	8	49	50
Musholt et al. [38]	Surgery	1997	USA & Germany	10	36	70

NR not reported

[a] Studies excluded from the analysis for insufficient data to reassess the detection rate of ^{18}F-FDG PET and PET/CT on a per patient-based analysis

[b] Patients evaluated before surgery were excluded from the analysis

Diagnostic performance

The diagnostic performance results of FDG PET or PET/CT in the 24 included studies are presented in Table 3. DR of FDG PET or PET/CT on a per patient-based analysis ranged from 24 to 95 % with pooled estimate of 59 % (95 % CI: 54–63 %). The included studies were heterogeneous in their estimate of DR (*I*-square: 66 %).

Pooled DR of FDG PET or PET/CT was also calculated in patients with serum calcitonin levels $\geq$ 1,000 ng/L (75 %; 95 % CI: 67–81 %), calcitonin levels $<$ 150 ng/L (40 %; 95 % CI: 29–52 %), calcitonin levels $\geq$ 150 ng/L (64 %; 95 % CI: 59–70 %), CEA levels $\leq$ 5 ng/ml (45 %; 95 % CI: 34–57 %), CEA levels $>$ 5 ng/ml (69 %; 95 % CI: 61–76 %), CTDT $>$ 24 months (26 %; 95 % CI: 14–40 %), CTDT $<$ 24 months (67 %; 95 % CI: 52–80 %), CTDT $>$ 12 months (31 %; 95 % CI: 20–44 %), CTDT $<$ 12 months (76 %; 95 % CI: 58–89 %), CEA-DT $>$ 24 months (33 %; 95 % CI: 19–49 %), and CEA-DT $<$ 24 months (91 %; 95 % CI: 59–100 %).

Selecting the studies which performed only hybrid PET/CT scans and excluding those which performed PET scans, DR was 56 % (95 % CI: 50–63 %).

Pooled results are summarized in Table 3 and Fig. 2.

Discussion

The early detection of recurrence represents an important step in the management of patients with MTC [1, 3, 4]. Several studies using FDG PET or PET/CT have reported a wide range of sensitivity and specificity of these imaging

Table 2 Technical aspects of the studies which used ^{18}F-FDG PET and PET/CT for detecting recurrent medullary thyroid carcinoma

Authors	Study design	Device	Injected activity	Time between tracer injection and image acquisition (min)	PET acquisition protocol	Image analysis	Reference standard
Kauhanen et al. [15]	Prospective multicenter	PET/CT	377 (MBq)	60	Static acquisition (3 min per bed position)	Qualitative and semiquantitative	Histology and/or clinical/imaging follow-up
Ozkan et al. [16]	Retrospective single-center	PET/CT	296–370 (MBq)	60	Static acquisition (4 min per bed position)	Qualitative and semiquantitative	Histology and/or clinical/imaging follow-up
Gómez-Camarero et al. [17]	Retrospective single-center	PET and PET/CT	333–434 (MBq)	60	Static acquisition	Qualitative and semiquantitative	Histology and/or clinical/imaging follow-up
Jang et al. [18]	Prospective single-center	PET/CT	370 (MBq)	60	Static acquisition (4 min per bed position)	Qualitative	Histology and/or clinical/imaging follow-up
Skoura et al. [19]	Retrospective single-center	PET/CT	370 (MBq)	60	Static acquisition (4 min per bed position)	Qualitative and semiquantitative	Histology and/or clinical/imaging follow-up
Marzola et al. [20]	NR; multicenter	PET/CT	2.2 (MBq/kg)	60	Static acquisition (3 min per bed position)	Qualitative and semiquantitative	Histology
Bogsrud et al. [21]	Retrospective single-center	PET and PET/CT	740 (MBq)	60–75	Static acquisition (5 min per bed position)	Qualitative	Histology and/or clinical/imaging follow-up
Conry et al. [22]	Retrospective multicenter	PET/CT	195–550 (MBq)	50–75	Static acquisition (1.5/5 min per bed position)	Qualitative and semiquantitative	Histology and/or clinical/imaging follow-up
Beheshti et al. [23]	Prospective single-center	PET/CT	370 (MBq)	60	Static acquisition (4 min per bed position)	Qualitative and semiquantitative	Histology and/or clinical/imaging follow-up
Faggiano et al. [24]	Retrospective multicenter	PET	222–370 (MBq)	60–90	Static acquisition (4 min per bed position)	Qualitative	Histology and/or clinical/imaging follow-up
Koopmans et al. [25]	Prospective single-center	PET	NR	NR	Static acquisition; (5 min per bed position)	Qualitative	Histology and/or clinical/imaging follow-up

Table 2 continued

Authors	Study design	Device	Injected activity	Time between tracer injection and image acquisition (min)	PET acquisition protocol	Image analysis	Reference standard
Rubello et al. [26]	Prospective multicenter	PET/CT	5.5 (MBq/kg)	60–90	Static acquisition (4 min per bed position)	Qualitative and semiquantitative	Histology
Oudoux et al. [6][a]	Prospective multicenter	PET/CT	310–450 (MBq)	60	Static acquisition	Qualitative and semiquantitative	Histology and/or clinical/imaging follow-up
Giraudet et al. [27]	Prospective single-center	PET/CT	5(MBq/Kg)	60	Static acquisition	Qualitative and semiquantitative	Histology and/or clinical/imaging follow-up
Czepczyński et al. [28]	NR; single-center	PET	NR	NR	NR	NR	NR
Beuthien-Baumann et al. [29]	Retrospective single-center	PET	370 (MBq)	60	Static acquisition	Qualitative	Histology and/or clinical/imaging follow-up
Ong et al. [30]	Retrospective single-center	PET and PET/CT	555 (MBq)	Minimum 45	Static acquisition (4 min per bed position)	Qualitative and semiquantitative	Histology and/or clinical/imaging follow-up
Iagaru et al. [31]	Retrospective single-center	PET and PET/CT	550 (MBq)	45/60	Static acquisition (4/5 min per bed position)	Qualitative	Histology and/or clinical/imaging follow-up
Gotthardt et al. [32]	NR; multicenter	PET	350 (MBq)	60	Static acquisition	Qualitative	Histology and/or clinical/imaging follow-up
de Groot et al. [33]	Prospective single-center	PET	400 (MBq)	90	Static acquisition (5 min per bed position)	Qualitative	Histology and/or clinical/imaging follow-up
Szakáll et al. [34]	Retrospective single-center	PET	5.55 (MBq/Kg)	40	Static acquisition (10 min per bed position)	Qualitative	Histology and/or clinical/imaging follow-up
Diehl et al. [7][a]	Retrospective multicenter	PET	300–500 (MBq)	Minimum 30	Static acquisition	Qualitative	Histology and/or clinical/imaging follow-up
Hoegerle et al. [35]	Prospective single-center	PET	330 (MBq)	90	Static acquisition	Qualitative	Histology and/or clinical/imaging follow-up
Brandt-Mainz et al. [36]	Prospective single-center	PET	350 (MBq)	30	Static acquisition (15–20 min per bed position)	Qualitative	Histology and/or clinical/imaging follow-up

Table 2 continued

Authors	Study design	Device	Injected activity	Time between tracer injection and image acquisition (min)	PET acquisition protocol	Image analysis	Reference standard
Adams et al. [37]	Prospective single-center	PET	374 (MBq)	60	Static acquisition (12–15 min per bed position)	Qualitative	Histology and/or clinical/imaging follow-up
Musholt et al. [38]	NR; single-center	PET	370–555 (MBq)	40	Static acquisition (10 min per bed position)	Qualitative	Histology and/or clinical/imaging follow-up

NR not reported

[a] Studies excluded from the analysis for insufficient data to reassess detection rate of ^{18}F-FDG PET and PET/CT on a per patient-based analysis

techniques in patients with suspected recurrent MTC. However, many of these studies have limited power, analyzing only a relatively small number of patients (Table 1). In order to derive more robust estimates of diagnostic performance of FDG PET and PET/CT, we pooled published studies. A systematic review process was adopted in ascertaining studies; we have attempted to avoid selection bias by including all relevant studies and adopting rigid inclusion criteria in our analysis.

Overall, the studies included in this meta-analysis have shown moderate methodological quality according to QUADAS [5]. The index test and the reference standard were often interpreted without blinding, therefore limiting the methodological quality of the included studies.

We chose to use the DR as measure of diagnostic performance of FDG PET and PET/CT in patients with suspected recurrent MTC in order to homogenize the results of the various studies. In fact, the studies included in our meta-analysis were quite heterogeneous about the definition of false negative and true negative results of these imaging methods; while some studies considered patients with increased calcitonin levels and negative FDG PET and other imaging methods as false negative results, conversely other studies considered the same patients as true negative, thus partially contributing to the wide range of sensitivity and specificity that can be found in the literature. DR overcomes these problems because both false negative and true negative results are considered in the denominator using the DR formula.

In our pooled analysis, we chose to calculate the DR on a per patient-based analysis (instead of a per lesion-based or a per region-based analysis) because most of the authors have adopted this criterion. However, we cannot exclude the potential bias derived from the choice of a per patient-based analysis; nevertheless, only in few studies it would have been possible to reassess the DR on a per lesion- or a per region-based analysis.

Publication bias is a major concern in all forms of pooled analyses, as studies reporting significant findings are more likely to be published than those reporting non-significant results. Indeed, it is not unusual for small-sized early studies to report a positive relationship that subsequent larger studies fail to replicate. We cannot exclude a publication bias in our analysis, but we tried to minimize it selecting only articles that included at least six patients with recurrent/residual MTC.

Evidence-based data from our meta-analysis suggest that FDG PET and PET/CT are associated with a non-optimal DR in the surveillance of MTC patients with rising tumor markers since about 40 % of suspected recurrent MTC cases remain usually unidentified using these imaging methods (pooled DR: 59 %; 95 % CI: 54–63 %). On the other hand, it should be considered that FDG PET and PET/CT are often performed in patients with suspected recurrent MTC after negative conventional imaging studies. Therefore, a DR of 59 %, even if non-optimal, may affect the management of a significant number of patients with recurrent MTC [2].

Possible causes of false negative results of FDG PET and PET/CT should be kept in mind; they could be probably related to small MTC lesions or to the frequent slow growth of this neuroendocrine tumor, both factors affecting the diagnostic accuracy of these imaging methods [3, 4].

Heterogeneity between studies may represent a potential source of bias; the included studies were heterogeneous in their estimates of DR (*I*-square: 66 %). Since systematic reviews bring together studies that are different both clinically and methodologically, heterogeneity in their results is to be expected. For example, heterogeneity is likely to arise through diversity in technical aspects (Table 2), study quality and inclusion criteria.

In order to study the factors which may influence the DR of FDG PET and PET/CT, a sub-analysis considering serum calcitonin, CEA, CTDT, and CEADT values was also performed.

Our sub-analysis confirm that DR of these imaging methods improves in patients with higher serum calcitonin

Table 3 Detection rates of ^{18}F-FDG PET and PET/CT on a per patient-based analysis in the included studies

Authors	Detection rate													
	All patients included		Only PET/CT studies		Calcitonin ≥ 1000 ng/L		Calcitonin < 150 ng/L		Calcitonin ≥ 150 ng/L		CEA ≤ 5 ng/ml		CEA > 5 ng/ml	
Kauhanen et al. [14]	10/19	53 %	10/19	53 %	6/6	100 %	0/5	0	10/14	71 %	2/8	25 %	8/11	73%
Ozkan et al. [15]	13/33	39 %	13/33	39 %	3/5	60 %	2/5	40 %	11/28	39 %	NC	NC	NC	NC
Gómez-Camarero et al. [16]	16/31	52 %	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC
Jang et al. [17]	10/16	63 %	10/16	63 %	3/3	100 %	1/6	17 %	9/10	90 %	4/9	44 %	5/6	83 %
Skoura et al. [18]	17/38	45 %	17/38	45 %	8/10	80 %	3/13	23 %	14/25	56 %	NC	NC	NC	NC
Marzola et al. [19]	11/18	61 %	11/18	61 %	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC
Bogsrud et al. [20]	13/29	45 %	NC	NC	11/19	58 %	0/3	0	13/25	52 %	3/8	38 %	8/16	50 %
Conry et al. [21]	14/18	78 %	14/18	78 %	4/4	100 %	5/7	71%	9/9	100 %	NC	NC	NC	NC
Beheshti et al. [22]	10/19	53 %	10/19	53 %	3/6	50 %	2/2	100 %	8/17	47 %	7/13	54 %	3/6	50 %
Faggiano et al. [23]	13/26	50 %	NC	NC	5/7	71 %	2/9	22 %	11/17	65 %	NC	NC	NC	NC
Koopmans et al. [24]	4/17	24 %	NC	NC	3/8	38 %	1/5	20 %	3/12	25 %	1/6	17 %	3/11	27 %
Rubello et al. [25]	15/19	79 %	15/19	79 %	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC
Giraudet et al. [26]	32/55	58 %	32/55	58 %	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC
Czepczyński et al. [27]	7/13	54 %	NC	NC	4/8	50 %	0/0	NC	7/13	54 %	3/4	75 %	4/9	44 %
Beuthien-Baumann et al. [28]	7/15	47 %	NC	NC	0/0	NC	2/6	33 %	5/9	56 %	1/4	25 %	3/7	43 %
Ong et al. [29]	23/38	61 %	NC	NC	21/27	78 %	0/1	0	23/37	62 %	2/7	29 %	11/14	79 %
Iagaru et al. [30]	6/13	46 %	NC	NC	5/9	56 %	0/3	0	6/10	60 %	NC	NC	NC	NC
Gotthardt et al. [31]	19/26	73 %	NC	NC	14/16	88 %	0/0	0	15/18	83 %	3/4	75 %	12/14	86 %
de Groot et al. [32]	13/26	50 %	NC	NC	9/12	75 %	2/10	20 %	11/16	69 %	2/8	25 %	11/18	61 %
Szakáll et al. [33]	38/40	95 %	NC	NC	15/15	100 %	10/12	83 %	28/28	1005	9/11	82 %	29/29	100 %
Hoegerle et al. [34]	6/10	60 %	NC	NC	4/5	80 %	0/0	0	6/10	60 %	0/0	0	6/10	60 %
Brandt-Mainz et al. [35]	13/17	76 %	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC
Adams et al. [36]	7/8	88 %	NC	NC	6/7	86 %	0/0	0	7/8	88 %	0/0	0	7/8	88 %
Musholt et al. [37]	8/10	80 %	NC	NC	5/6	83 %	0/0	0	7/9	78 %	NC	NC	NC	NC
Pooled results		59 %		56 %		75 %		40 %		64 %		45 %		69 %
95 % Confidence interval		54–63 %		50–63 %		67–81 %		29–52 %		59–70 %		34–57 %		61–76 %
Heterogeneity (*I*-square test)		66 %		45 %		48 %		61 %		72 %		39 %		72 %

NC not calculable

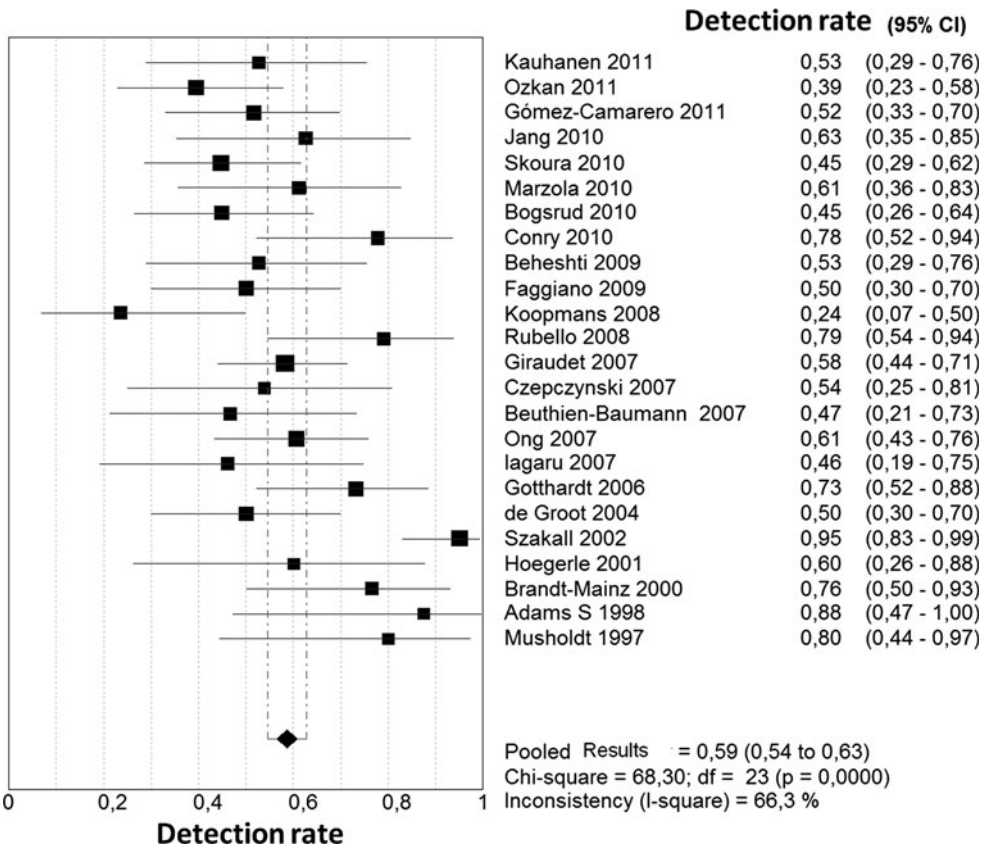

Fig. 2 Plot of individual studies and pooled detection rate of FDG PET and PET/CT in patients with suspected recurrent/residual MTC including 95 % confidence intervals. The *size of the squares* indicates the weight of each study

and CEA levels; in fact DR was 75 % (95 % CI: 67–81 %) in patients with calcitonin values ≥ 1,000 ng/L and 69 % (95 % CI: 61–76 %) in patients with CEA values >5 ng/ml (Table 3). These findings suggest that FDG PET and PET/CT could be very useful imaging methods in patients with advanced disease.

Also, our sub-analysis confirm that DR of FDG PET and PET/CT improves in patients with lower CTDT or CEADT, confirming the usefulness of these imaging methods in patients with aggressive disease (with high glucose consumption and high FDG uptake) compared to those with indolent course of the disease (with low glucose consumption and low FDG uptake). Nevertheless, CTDT and CEADT were calculated only in five [15, 18, 21, 23, 25] and three included studies [15, 23, 25], respectively; therefore other studies are necessary in order to correlate FDG PET or PET/CT findings to CTDT and CEADT in patients with recurrent MTC.

Hybrid PET/CT imaging is usually superior in terms of sensitivity and specificity compared to PET alone for tumor imaging; therefore, we performed a sub-analysis excluding the studies performing PET imaging alone, in order to demonstrate a possible superiority of hybrid PET/CT imaging in terms of DR. Surprisingly, a significant advantage of FDG PET/CT compared to FDG PET regarding the DR in patients with recurrent MTC was not found; in fact, excluding the studies performing FDG PET, the DR was only 56 % (95 % CI: 50–63 %). Therefore, the non-optimal DR value of FDG PET and PET/CT imaging in patients with recurrent/residual MTC could be more influenced by tumor characteristics (small lesions, slow growth) rather than by technical aspects.

Other PET radiopharmaceuticals seem to show promising results in the imaging of recurrent MTC, overcoming the limits of FDG PET and PET/CT. For instance, some studies reported that PET and PET/CT performed with F-DOPA have a higher sensitivity compared to FDG PET and PET/CT in this setting [15, 20, 23, 25, 29, 35, 39]; nevertheless, it should be considered that these functional imaging methods may have a complementary role in diagnosing recurrent MTC; in particular, FDG is very useful to detect recurrence in MTC patients with more aggressive disease and increased CEA levels compared to F-DOPA. Other radiopharmaceuticals, as Gallium-68 somatostatin analogs that bind to somatostatin receptors, are also being evaluated for this indication [22, 40–42].

Conclusions

In patients with suspected recurrent MTC FDG PET and PET/CT are associated with a non-optimal DR since about

40 % of suspected residual/recurrent MTC cases remain usually unidentified. FDG PET and PET/CT could modify the patient management in a certain number of recurrent MTC, even if DR is non-optimal, because these methods are often performed in patients with suspected recurrent MTC after negative conventional imaging studies. DR of FDG PET and PET/CT increases in MTC patients with higher calcitonin and CEA values and lower CTDT and CEADT values, suggesting that these imaging methods could be very useful in patients with more aggressive disease. Hence, these imaging techniques should not be considered as first-line diagnostic imaging methods in patients with suspected recurrent MTC, but could be very helpful in detecting tumor recurrence in those MTC patients in whom a more aggressive disease is suspected.

Conflict of interest None.

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