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ORIGINAL ARTICLE

Diagnostic performance of choline PET for detection of hyperfunctioning parathyroid glands in hyperparathyroidism: a systematic review and meta-analysis

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Abstract

Purpose Hyperparathyroidism (HPT) is a common endocrine disorder caused by hyperfunctioning parathyroid glands (HP). The correct detection and localization of HP is challenging but crucial, as it may guide surgical treatment, particularly in patients with primary HPT. There is a growing body of data regarding the role of radiolabelled choline positron emission tomography (PET) in this setting. Therefore, we performed a systematic review and meta-analysis of the diagnostic performance of this method in detecting HP in patients with HPT.

Methods This systematic review and meta-analysis was carried out according to PRISMA guidelines. A comprehensive computer literature search of PubMed/MEDLINE, EMBASE and Cochrane Library databases for studies published through May 2018 was performed using the following search algorithm: (a) "choline" or "fluorocholine" or "F-choline" or "C-choline" or "FCH" or "CH" or "FECH" or "FMCH" and (b) "PET" or "positron emission tomography" and (c) "parathyroid" or "hyperparathyroidism". The diagnostic performance of radiolabelled choline PET was expressed as sensitivity and positive predictive value (PPV) on a per-patient and per-lesion basis and as detection rate (DR) on a per-patient basis, with pooled proportion and 95% confidence interval (95% CI) obtained using a random-effects model.

Results Eighteen studies were included in the systematic review. Fourteen articles (517 patients) were selected for the meta-analysis. The meta-analysis provided the following results on a per-patient analysis analysis: sensitivity 95% (95% CI: 92–97%), PPV 97% (95% CI: 95–98%) and DR 91% (95% CI: 87–94%). On a per-lesion analysis, pooled sensitivity and PPV were 92% (95% CI: 88–96) and 92% (95% CI: 89–95%), respectively. No significant heterogeneity was found among the selected studies.

Conclusions Radiolabelled choline PET demonstrated excellent diagnostic performance in detecting HP in patients with HPT. Large multicentre studies and cost-effectiveness analyses are needed to better define the role of this imaging method in this setting.

Keywords PET · Positron emission tomography · Choline · Hyperparathyroidism · Parathyroid

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Introduction

Hyperparathyroidism (HPT) is a common endocrine disorder characterized by an alteration in pathophysiological parathyroid hormone (PTH) secretion due to an independent and abnormal release (primary or tertiary HPT) by hyperfunctioning parathyroid glands (HP) or an alteration in calcium homeostasis that stimulates the excessive production of PTH (secondary HPT) [1–4]. Diagnosis of HPT may be clinical or incidental on biochemical screening [1–4].

HP may occur as single or multifocal lesions and with different histology, such as adenoma, hyperplasia or, more rarely, carcinoma [1–4]. The correct detection and localization of HP is challenging but crucial, as it may guide surgical treatment, particularly in patients with primary HPT who are candidates for parathyroidectomy [5, 6]. Successful localization of HP by morphological or functional imaging, along with rapid intraoperative PTH assay, can enable the use of minimally invasive surgical approaches. Patients with primary HPT in whom localization studies have identified a single HP or unilateral disease are candidates for such focused approaches, instead of the traditional approach of bilateral exploration [5, 6].

Various imaging methods have been used for the detection and localization of HP in patients with HPT, including morphological, functional and hybrid techniques, with no clear consensus on the optimal imaging approach [7–9]. In this setting, neck ultrasonography (US) and parathyroid scintigraphy are established imaging methods, although multi-phase or four-dimensional computed tomography (4D-CT) is an emerging modality [7–9].

Several positron emission tomography (PET) radiotracers evaluating different metabolic pathways have been assessed for the detection of HP in patients with HPT, including ^{11}C-methionine and radiolabelled choline (^{11}C-choline or ^{18}F-choline) [7, 10, 11].

A growing body of literature has examined the role of radiolabelled choline PET, which can be combined with CT (PET/CT) or magnetic resonance imaging (PET/MRI), for the detection of HP in patients with HPT [12, 13]. As a phospholipid analogue, radiolabelled choline is integrated into newly synthesized membranes of proliferating cells, and its uptake is increased by upregulation of choline kinase [14]. Upregulation of phospholipid-dependent choline kinase has been shown to be related to PTH secretion in HP. The increase in phosphatidylcholine turnover in HP is the rationale for using radiolabelled choline PET for HP detection in patients with HPT [7, 10, 13].

Our aim was to perform a systematic review and meta-analysis of the diagnostic performance of radiolabelled choline PET in detecting HP in patients with HPT.

Methods

This study was carried out according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, which describe an evidence-based minimum set of items for reporting in systematic reviews and meta-analyses [15]. In addition, specific suggestions for meta-analyses of studies investigating diagnostic accuracy were followed [16].

Search strategy

Two authors (GT and AP) performed a comprehensive computer literature search of the PubMed/MEDLINE, EMBASE and Cochrane Library databases to identify relevant retrospective or prospective published studies on the diagnostic performance of radiolabelled choline PET in detecting HP in patients with HPT. The search algorithm used was based on a combination of terms, as follows: (a) "choline" or "fluorocholine" or "F-choline" or "C-choline" or "FCH" or "CH" or "FECH" or "FMCH" and (b) "PET" or "positron emission tomography" and (c) "parathyroid" or "hyperparathyroidism". The search was updated through 31 May 2018. No language restriction was applied. To expand the search, references of the retrieved articles were also screened for additional studies.

Study selection

Studies or subsets of studies investigating the diagnostic performance of radiolabelled choline PET in detecting HP in patients with HPT, reporting data on the diagnostic accuracy, were eligible for inclusion in the qualitative analysis (systematic review). The exclusion criteria were as follows: (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 (< 5 patients); (d) articles with insufficient data to reassess the diagnostic performance (such as absence of data about true-positive, true-negative, false-positive or false-negative findings). For the quantitative analysis (meta-analysis), we also excluded studies with possible patient overlap. In the case of possible patient overlap, the most complete article was included in the meta-analysis.

Three researchers (GT, AP, LG) 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 three researchers then independently reviewed the full-text versions of the remaining articles to determine their eligibility for inclusion. Disagreements were resolved in a consensus meeting.

Data extraction

For each potentially eligible study, information was collected concerning basic study characteristics (authors, year of publication, country of origin, study design), patient characteristics (type and number of patients, mean age, sex ratio, mean serum calcium and PTH values) and technical aspects (radiotracer used, hybrid imaging modality, mean injected activity, time interval between radiotracer injection and image acquisition, image analysis). For each study, the number of true-positive, false-positive, true-negative and false-negative findings for radiolabelled choline PET detection of HP were recorded on a per-patient and per-lesion basis.

All foci of radiotracer uptake located behind the thyroid lobes or in the upper mediastinum were considered positive findings for HP at radiolabelled choline PET, with or without a morphological substrate. The combination of histological findings and biochemical resolution of HPT after surgery was our reference standard. The results were judged as true positive only if they were correct with regard to the site (right/left/ectopic) and position of the HP (upper/lower pole of the thyroid lobe, upper/lower part of the mediastinum, or elsewhere). For each study, the following metrics of diagnostic accuracy were obtained: sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV). In addition, the detection rate (DR) was calculated as the ratio of patients with HP detected by radiolabelled choline PET divided by the number of patients undergoing radiolabelled choline PET with sufficient information available.

Quality assessment

The overall quality of the studies included in the systematic review was critically appraised based on the revised Quality Assessment of Diagnostic Accuracy Studies tool (QUADAS-2) [17]. This tool comprises four domains: patient selection, index test, reference standard, and flow and timing. Each domain is assessed in terms of risk of bias, and the first three domains are also assessed in terms of concerns regarding applicability [17].

Statistical analysis

Pooled data on the diagnostic performance of radiolabelled choline PET in detecting HP were obtained on a per-patient and per-lesion basis. A random-effects model was used for statistical pooling of data. Pooled data are presented with 95% confidence intervals (95% CI). Subgroup analyses of study design, patient characteristics and technical aspects were also explored.

Heterogeneity was estimated using the I-square index (I^2), which describes the percentage of variation across studies that is due to heterogeneity rather than chance [18]. Publication bias was assessed through the Egger test [19]. Statistical analyses were performed using StatsDirect 3 software (StatsDirect Ltd., Cambridge, UK).

Results

Literature search

A comprehensive computer literature search of the PubMed/MEDLINE, EMBASE and Cochrane Library databases revealed 91 articles. Upon review of titles and abstracts, 71 articles were excluded, as follows: 38 were not in the field of interest of this review, 10 were reviews, editorials or letters, and 23 were case reports or small case series (< 5 patients). Twenty articles were selected and retrieved in full-text version [20–39]. Subsequently, two full-text articles were excluded from the analysis due to insufficient data to reassess the diagnostic performance of radiolabelled choline PET [20, 21]. No additional studies were found by screening the references of these articles.

Finally, 18 articles including data on the diagnostic performance of radiolabelled choline PET in detecting HP in 671 patients with HPT were eligible for the qualitative analysis (systematic review) [22–39]. The characteristics of the studies included in the systematic review are summarized in Tables 1, 2, 3 and 4.

After reviewing the full-text articles, four articles were excluded from the quantitative analysis (meta-analysis) due to possible patient data overlap [34, 36–38]; thus 14 studies including 517 patients were selected for the meta-analysis [22–33, 35, 39] (Fig. 1).

Qualitative analysis (systematic review)

Basic study and patient characteristics

Using the database search, 18 full-text articles reporting on the diagnostic performance of radiolabelled choline PET in 671 patients with HPT were selected (Table 1) [22–39].

All selected articles were published within the last 5 years. Several countries from Europe, North America and Asia were represented. Half of the studies were retrospective and half were prospective. Most of the articles were single-centre studies (78%).

In 9 out of 18 studies, radiolabelled choline PET was performed in patients with HPT and previous inconclusive US and parathyroid scintigraphy (with planar or tomographic—SPECT and/or SPECT/CT—acquisition, by injection of ^{99m}Tc-MIBI or ^{99m}Tc-tetrofosmin, using dual-phase technique or dual-tracer subtraction imaging), whereas in the remaining studies, radiolabelled choline PET was performed regardless of the result of other imaging methods. Two-thirds of the

Table 1 Basic study and patient characteristics

Authors	Year	Country	Study design	Type of patients evaluated	No. of patients with HPT undergoing PET	Percentage of patients with primary HPT	Age (years)	% Male	Ca^{++} serum values (mmol/l)	PTH serum values (pg/ml)
Grimaldi et al. [22]	2018	France	Prospective bicentric	Patients with primary HPT and inconclusive US and ^{99m}Tc-MIBI scintigraphy (planar ± SPECT/CT), or with suspicion of multiple gland disease, or with persistent/recurrent HPT after previous surgery	27	100%	Median: 58 (22–87)	30%	Median: 2.7 (2.22–3.33)	Median: 102.5 (59–514)
Beheshti et al. [23]	2018	Austria	Prospective bicentric	Patients with primary HPT undergoing both ^{99m}Tc-MIBI/tetrofosmin SPECT/CT and radiolabelled choline PET/CT	100	100%	Mean: 57.4 ± 12.5	21%	Mean: 2.78 ± 0.34	Mean: 196.5 ± 236.4
Fischli et al. [24]	2018	Switzerland	Retrospective single centre	Patients with primary HPT with negative or equivocal US and ^{99m}Tc-MIBI scintigraphy (planar ± SPECT/CT)	39	100%	Mean: 61.9 (41–83)	22%	Median: 2.69 (2.6–2.83)	Median: 137 (104–220)
Huber et al. [25]	2018	Switzerland	Retrospective single centre	Patients with HPT and negative, discordant or equivocal results of US and ^{99m}Tc-tetrofosmin scintigraphy (dual-isotope subtraction planar and SPECT)	26	92%	Median: 60 (24–83)	23%	Median: 2.66 (2.51–3.03)	Median: 110.8 (54.9–257.6)
Parvinian et al. [26]	2018	USA	Retrospective single centre	Patients with suspicious parathyroid adenoma incidentally detected at radiolabelled choline PET/CT performed in men with prostate cancer	13	100%	Mean: 72 ± 7	100%	Mean: 2.6 ± 0.2	Mean: 78 ± 23
Quak et al. [27]	2018	France	Prospective bicentric	Patients with primary HPT and negative or inconclusive US and ^{99m}Tc-MIBI SPECT/CT	25	100%	Mean: 58.9 ± 14.2	40%	Mean: 2.76 ± 0.17	Mean: 94.8 ± 37.4
Rep et al. [28]	2018	Slovenia	Retrospective single centre	Patients with primary HPT undergoing ^{99m}Tc-MIBI scintigraphy (dual isotope subtraction and dual-phase ^{99m}Tc-MIBI SPECT/CT) and radiolabelled choline PET/CT	36	100%	Median: 62 (34–77)	33%	NR	NR
Hocevar et al. [29]	2017	Slovenia	Retrospective single centre	Patients who underwent surgery for primary HPT and with a previously performed radiolabelled choline PET/CT	151	100%	Mean: 61.1 (13–82)	20%	NR	NR
Kluijfhout et al. [30]	2017	Netherlands and USA	Prospective single centre	Patients with primary HPT and negative or discordant US and ^{99m}Tc-MIBI planar scintigraphy ± SPECT/CT	10	100%	Mean: 70.4 (58–82)	10%	Mean: 2.75 (2.6–2.92)	Mean: 86 (48–177)
Taywade et al. [31]	2017	India	Prospective single centre	Patients with primary HPT undergoing both radiolabelled choline PET/CT and 4D-CT	5	100%	Mean: 24.4 (11–38)	60%	NR	Mean: 364.2 (86.29–1021)
Thanseer et al. [32]	2017	India	Prospective single centre	Patients with primary HPT undergoing US, ^{99m}Tc-MIBI planar scintigraphy ± SPECT/CT, and radiolabelled PET/CT	54	100%	Mean: 47.7 ± 14 (19–75)	30%	Mean: 2.97 ± 0.3	Median: 171.5
Kluijfhout et al. [33]	2016	Netherlands	Retrospective multicentre	Patients with HPT and inconclusive US and ^{99m}Tc-MIBI scintigraphy (dual isotope subtraction and dual-phase ^{99m}Tc-MIBI SPECT/CT)	44	98%	Mean: 58.9 (31–80)	11%	NR	NR
Kluijfhout et al. [34]	2015	Netherlands	Retrospective single centre	Patients with primary HPT and negative or inconclusive US and ^{99m}Tc-MIBI SPECT/CT	5	100%	Mean: 61.6 (43–77)	40%	NR	Mean: 175.4
Michaud et al. [35]	2015	France	Retrospective single centre	Patients with HPT and discordant or equivocal US and ^{99m}Tc-MIBI scintigraphy (dual isotope	17	65%	Mean: 52 (25–75)	29%	NR	Mean: 280 (61–1946)

Table 1 (continued)

Authors	Year	Country	Study design	Type of patients evaluated	No. of patients with HPT undergoing PET	Percentage of patients with primary HPT	Age (years)	% Male	Ca^{++} serum values (mmol/l)	PTH serum values (pg/ml)
				subtraction and dual-phase ^{99m}Tc-MIBI planar scintigraphy)						
Rep et al. [36]	2015	Slovenia	Retrospective single centre	Patients with primary HPT undergoing radiolabelled choline PET/CT in addition to US and ^{99m}Tc-MIBI SPECT/CT	43	100%	Mean: 59.6 ± 11 (36–77)	19%	Mean: 2.8 (2.6–4.1)	Mean: 311.5 (70.6–2022)
Lezaic et al. [37]	2014	Slovenia	Prospective single centre	Patients with primary HPT undergoing both radiolabelled choline PET/CT and ^{99m}Tc-MIBI scintigraphy (dual isotope subtraction and dual-phase ^{99m}Tc-MIBI SPECT/CT)	24	100%	NR (42–77)	17%	Mean: 2.68 (2.41–2.83)	Mean: 83.5 (67.4–357)
Michaud et al. [38]	2014	France	Prospective single centre	Patients with HPT and discordant or equivocal US and ^{99m}Tc-MIBI scintigraphy (dual isotope subtraction and dual-phase ^{99m}Tc-MIBI planar scintigraphy)	12	67%	Mean: 51.6	33%	NR	Mean: 304.8 (70–1946)
Orevi et al. [39]	2014	Israel	Prospective single centre	Patients with HPT undergoing both ^{99m}Tc-MIBI scintigraphy (dual isotope subtraction and dual-phase ^{99m}Tc-MIBI planar ± SPECT/CT) and radiolabelled choline PET/CT	40	50%	Mean: 55 (21–72)	35%	Mean: 2.8 (2.4–3.11)	Mean: 149.5 (33.8–496)

NR not reported, *HPT* hyperparathyroidism, Ca^{++} calcium, *PTH* parathyroid hormone, *US* ultrasonography, ^{99m} *Tc-MIBI* technetium-99 m methoxy-isobutyl-isonitrile, *SPECT* single-photon emission computed tomography, *CT* computed tomography, *4D-CT* four-dimensional computed tomography

studies included patients with primary HPT only, while a mixed patient population with different types of HPT scheduled for surgery was included in the rest of the studies. Most of radiolabelled choline PET scans were performed before primary surgery in patients with primary HPT, whereas few patients underwent radiolabelled choline PET after unsuccessful primary surgery [22, 27, 32, 33, 39]. The mean patient age ranged from 24 to 72 years, and the mean percentage of male patients was approximately 30%. The mean calcium serum levels ranged from 2.6 to 2.97 mmol/l, and mean PTH serum levels from 78 to 364.2 pg/ml.

Technical aspects

Heterogeneous technical aspects were found among the included studies (Table 2). The radiotracer used was ^{18}F-choline in 16 studies (89%) [22–25, 27–38] and ^{11}C-choline in two studies (11%) [26, 39]. The most common hybrid imaging modality was PET/CT, which was performed using low-dose CT acquisition in most of the studies [22, 23, 26–29, 31–39], while contrast-enhanced CT combined with PET imaging was used in one study only [24]. Hybrid PET/MRI was performed in only two studies [25, 30]. The reported mean injected activity of radiolabelled choline ranged from 100 to 370 MBq (in absolute values) and from 1.5 to 3.2 MBq/kg. The time interval between radiotracer injection and image acquisition varied considerably among studies, ranging from 0 to 120 min after injection.

The PET/CT or PET/MRI acquisition included the head and neck region and the mediastinum. PET image analysis was performed using qualitative (visual) analysis in all studies, with additional semi-quantitative analysis via calculation of the maximal standardized uptake values (SUV_{max}) in two-thirds of the studies (Table 2).

Main findings

Data on sensitivity, specificity, PPV, NPV and DR from each study are listed in Table 3. Overall, radiolabelled choline PET demonstrated high diagnostic performance in detecting HP in patients with HPT across all studies included in the systematic reviews [22–39], both in patients with HPT undergoing primary surgery [22–39] and in those evaluated after unsuccessful primary surgery [22, 27, 32, 33, 39].

Several articles demonstrated that radiolabelled choline PET may be useful in the pre-surgical detection and localization of HP in patients with HPT and with negative, equivocal or discordant US and parathyroid scintigraphy findings [22, 24, 25, 27, 30, 33–35, 38]. In their pilot studies on patients with both primary and secondary HPT, Michaud et al. showed that localization of HP can be achieved by ^{18}F-choline PET/CT with good accuracy [35, 38]. A retrospective multicentre study by Kluijfhout et al. in 44 patients with HPT (most with primary HPT) showed excellent diagnostic performance of ^{18}F-choline PET/CT in patients with HPT and inconclusive conventional imaging [33]. In the prospective APACH1 study, including 25 patients with primary HPT and negative or inconclusive conventional imaging, pre-surgical ^{18}F-choline PET/CT demonstrated high sensitivity (90.5% in per-patient and 91.3% in per-lesion analysis) and high PPV (86.4% in per-patient and 87.5% in per-lesion analysis) in detecting HP, and bilateral cervical exploration was able to be avoided in the majority (75%) of patients with primary HPT who underwent ^{18}F-choline PET/CT [27]. The recent retrospective study by Huber et al., which included 26 patients with HPT and negative or conflicting US and scintigraphy findings, demonstrated that both ^{18}F-choline PET/CT and PET/MRI were able to detect HP (overall DR of 96%) [25]. In the retrospective study by Fischli et al., HP were identified correctly by ^{18}F-choline PET/CT in 21/23 (91%) patients with primary HPT and negative conventional imaging [24]. Finally, in the recent prospective study by Grimaldi et al., ^{18}F-choline PET/CT was able to detect HP in 24/27 (89%) patients with primary HPT and negative conventional imaging [22].

In studies comparing radiolabelled choline PET with ^{99m}Tc-MIBI/tetrofosmin parathyroid scintigraphy (performed with planar or tomographic acquisition—SPECT or SPECT/CT—with a dual-phase technique or dual-tracer subtraction imaging) for the detection of HP, the diagnostic performance of radiolabelled choline PET was higher than that of parathyroid scintigraphy (higher sensitivity and comparable specificity), with quicker and easier acquisition [23, 28, 32, 37, 39]. The pilot study by Lezaic et al. in 24 patients with primary HPT reported sensitivity and specificity of 92 and 100%, respectively, for localization of HP with ^{18}F-choline PET/CT, in contrast to 49 and 100%, 46 and 100%, and 44 and 100% for ^{99m}Tc-MIBI SPECT/CT, ^{99m}Tc-MIBI/pertechnetate subtraction imaging and ^{99m}Tc-MIBI dual-phase imaging, respectively [37]. In the prospective study by Thanseer et al., including 54 patients with primary HPT, patient-based sensitivity and PPV were 100 and 96.3%, respectively, for ^{18}F-choline PET/CT, and 80.7 and 97.6%, respectively, for ^{99m}Tc-MIBI scintigraphy (with or without SPECT/CT); on a per-lesion basis, sensitivity and PPV were 100 and 92.8%, respectively, for ^{18}F-choline PET/CT, and 76.4 and 97.7%, respectively, for ^{99m}Tc-MIBI scintigraphy (with or without SPECT/CT) [32]. A recent prospective study by Beheshti et al. in 82 patients with primary HPT demonstrated 93% detection of HP for ^{18}F-choline PET/CT and 61% for ^{99m}Tc-MIBI/tetrofosmin SPECT/CT in per-patient-based analysis. Lesion-based analysis revealed sensitivity, specificity, PPV, NPV and overall accuracy of 93.7, 96.0, 90.2, 97.4 and 95.3%, respectively, for ^{18}F-choline PET/CT, with corresponding values of 60.8, 98.5, 94.1, 86.3 and 87.7% for ^{99m}Tc-MIBI/tetrofosmin SPECT/CT [23]. Overall, based on literature data, radiolabelled choline PET/CT was able to detect HP in a high

Table 2 Technical aspects of radiolabelled choline PET in the included studies

Authors	Radiotracer	Hybrid imaging modality	Mean injected activity	Time interval between radiotracer injection and image acquisition	Image analysis
Grimaldi et al. [22]	^{18}F-choline	PET/CT (low-dose CT)	100 MBq	30 min	Visual and semi-quantitative (SUV_{max})
Beheshti et al. [23]	^{18}F-choline	PET/CT (low-dose CT in most patients)	3.2 MBq/kg	60 min and optional 100–120 min	Visual and semi-quantitative (SUV_{max})
Fischli et al. [24]	^{18}F-choline	PET/CT (contrast-enhanced CT)	160 MBq	45 min	Visual
Huber et al. [25]	^{18}F-choline	PET/CT or PET/MRI	151 MBq	NR	Visual
Parvinian et al. [26]	^{11}C-choline	PET/CT (low-dose CT)	NR	NR	Visual and semi-quantitative (SUV_{max})
Quak et al. [27]	^{18}F-choline	PET/CT (low-dose CT)	1.5 MBq/kg	60 min	Visual and semi-quantitative (SUV_{max})
Rep et al. [28]	^{18}F-choline	PET/CT (low-dose CT)	100 MBq	5 min and 60 min	Visual
Hocevar et al. [29]	^{18}F-choline	PET/CT (low-dose CT)	100 MBq	5 min and 60 min	Visual
Kluijfhout et al. [30]	^{18}F-choline	PET/MRI	188 MBq	0 (dynamic imaging for 40 min)	Visual and semi-quantitative (SUV_{max})
Taywade et al. [31]	^{18}F-choline	PET/CT (low-dose CT)	185 MBq	60 min	Visual and semi-quantitative (SUV_{max})
Thanseer et al. [32]	^{18}F-choline	PET/CT (low-dose CT)	150–185 MBq	10–15 min and 60 min	Visual and semi-quantitative (SUV_{max})
Kluijfhout et al. [33]	^{18}F-choline	PET/CT (low-dose CT)	2 MBq/kg	30 min	Visual and semi-quantitative (SUV_{max})
Kluijfhout et al. [34]	^{18}F-choline	PET/CT (low-dose CT)	2 MBq/kg	30 min	Visual and semi-quantitative (SUV_{max})
Michaud et al. [35]	^{18}F-choline	PET/CT (low-dose CT)	3 MBq/kg	0 (dynamic imaging for 10 min followed by a static acquisition)	Visual and semi-quantitative (SUV_{max})
Rep et al. [36]	^{18}F-choline	PET/CT (low-dose CT)	100 MBq	5 min, 60 min and 120 min	Visual and semi-quantitative (SUV_{max})
Lezaic et al. [37]	^{18}F-choline	PET/CT (low-dose CT)	100 MBq	5 min and 60 min	Visual
Michaud et al. [38]	^{18}F-choline	PET/CT (low-dose CT)	3 MBq/kg	0 (dynamic imaging for 10 min followed by static acquisition)	Visual
Orevi et al. [39]	^{11}C-choline	PET/CT (low-dose CT)	370 MBq	NR	Visual and semi-quantitative (SUV_{max})

NR not reported, *MBq* megabecquerel, SUV_{max} maximal standardized uptake value, *PET/CT* positron emission tomography/computed tomography, *PET/MRI* positron emission tomography/magnetic resonance imaging

Table 3 Diagnostic accuracy of radiolabelled choline PET in detecting hyperfunctioning parathyroid glands in patients with hyperparathyroidism using the combination of histological findings and biochemical resolution of HPT after surgery as reference standard

Authors	Patients analysed according to the reference standard (% of all HPT patients undergoing PET)	True positive	False positive	True negative	False negative	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Detection rate[a]
Grimaldi et al. [22][b]	21 (78%)	17 (p) 22 (l)	1 (p) 4 (l)	NA (p) 43 (l)	3 (p) 7 (l)	85% (p) 76% (l)	NA (p) 91% (l)	94% (p) 85% (l)	NA (p) 86% (l)	24/27 (89%)
Beheshti et al. [23][b]	82 (82%)	76 (p) 74 (l)	0 (p) 8 (l)	3 (p) 190 (l)	3 (p) 5 (l)	96% (p) 94% (l)	100% (p) 96% (l)	100% (p) 90% (l)	50% (p) 97% (l)	76/82 (93%)
Fischli et al. [24][b]	23 (59%)	21 (p) 21 (l)	1 (p) 1 (l)	NA (p) 4 (l)	1 (p) 3 (l)	95% (p) 87% (l)	NA (p) 80% (l)	95% (p) 95% (l)	NA (p) 57% (l)	21/23 (91%)
Huber et al. [25][b]	26 (100%)	25 (p) 27 (l)	0 (p) 0 (l)	NA	1 (p) 1 (l)	96% (p) 96% (l)	NA	100% (p) 100% (l)	NA	25/26 (96%)
Parvinian et al. [26][b]	8 (62%)	8 (p) 8 (l)	0 (p) 0 (l)	NA	0 (p) 0 (l)	100% (p) 100% (l)	NA	100% (p) 100% (l)	NA	13/13 (100%)
Quak et al. [27][b]	24 (96%)	19 (p) 21 (l)	3 (p) 3 (l)	NA	2 (p) 2 (l)	90% (p) 91% (l)	NA	86% (p) 87% (l)	NA	19/25 (76%)
Rep et al. [28][c]	36 (100%)	39 (l)	1 (l)	103 (l)	1 (l)	97% (l)	99% (l)	97% (l)	99% (l)	NA
Hocevar et al. [29][d]	151 (100%)	144 (p)	4 (p)	1 (p)	2 (p)	99% (p)	20% (p)	97% (p)	33% (p)	144/151 (95%)
Kluijfhout et al. [30][b]	10 (100%)	9 (p) 10 (l)	0 (p) 0 (l)	NA	1 (p) 4 (l)	90% (p) 71% (l)	NA	100% (p) 100% (l)	NA	9/10 (90%)
Taywade et al. [31][b]	5 (100%)	5 (p) 7 (l)	0 (p) 0 (l)	NA	0 (p) 0 (l)	100% (p) 100% (l)	NA	100% (p) 100% (l)	NA	5/5 (100%)
Thanseer et al. [32][b]	54 (100%)	52 (p) 52 (l)	2 (p) 4 (l)	NA	0 (p) 0 (l)	100% (p) 100% (l)	NA	96% (p) 93% (l)	NA	52/54 (96%)
Kluijfhout et al. [33][b]	33 (75%)	30 (p) 33 (l)	1 (p) 2 (l)	NA	2 (p) 2 (l)	94% (p) 94% (l)	NA	97% (p) 94% (l)	NA	34/44 (77%)
Kluijfhout et al. [34][e]	5 (100%)	4 (p) 4 (l)	0 (p) 0 (l)	NA	1 (p) 1 (l)	80% (p) 80% (l)	NA	100% (p) 100% (l)	NA	4/5 (80%)
Michaud et al. [35][b]	17 (100%)	15 (p) 23 (l)	1 (p) 4 (l)	NA (p) 5 (l)	1 (p) 1 (l)	94% (p) 96% (l)	NA (p) 56% (l)	94% (p) 85% (l)	NA (p) 83% (l)	15/17 (88%)
Rep et al. [36][e]	43 (100%)	NA	NA	NA	NA	95%	98%	97%	97%	NA
Lezaic et al. [37][e]	24 (100%)	23 (p) 36 (l)	0 (p) 0 (l)	NA	1 (p) 3 (l)	96% (p) 92% (l)	NA	100% (p) 100% (l)	NA	23/24 (96%)
Michaud et al. [38][e]	12 (100%)	11 (p) 17 (l)	0 (p) 1 (l)	NA	1 (p) 2 (l)	92% (p) 89% (l)	NA	100% (p) 94% (l)	NA	11/12 (92%)
Orevi et al. [39][b]	27 (68%)	25 (p) 25 (l)	0 (p) 2 (l)	NA	2 (p) 2 (l)	93% (p) 93% (l)	NA	100% (p) 93% (l)	NA	37/40 (93%)

HPT hyperparathyroidism, *NA* not available, *(p)* patient-based analysis, *(l)* lesion-based analysis

[a] Calculated as the ratio of patients with hyperfunctioning parathyroid glands detected by radiolabelled choline PET divided by the number of patients undergoing radiolabelled choline PET with sufficient information available

[b] Included in the meta-analysis

[c] Included in the lesion-based meta-analysis only

[d] Included in the patient-based meta-analysis only

[e] Excluded from the meta-analysis for possible data overlap

Table 4 Quality assessment of the studies included in the systematic review according to the QUADAS-2 tool [17]

Authors	Patient selection		Index test		Reference standard		Flow and timing
	Risk of bias	Applicability concerns	Risk of bias	Applicability concerns	Risk of bias	Applicability concerns	Risk of bias
Grimaldi et al. [22]	Unclear	Low	Low	Low	Low	Low	High
Beheshti et al. [23]	Low	Low	Low	Low	Low	Low	High
Fischli et al. [24]	Unclear	Low	Unclear	Low	Low	Low	High
Huber et al. [25]	Unclear	Low	Unclear	Low	Low	Low	Low
Parvinian et al. [26]	High	Unclear	Unclear	Unclear	Unclear	Unclear	High
Quak et al. [27]	Unclear	Low	Low	Low	Low	Low	Unclear
Rep et al. [28]	Low	Low	Unclear	Low	Low	Low	Low
Hocevar et al. [29]	Low	Low	Unclear	Low	Low	Low	Low
Kluijfhout et al. [30]	Unclear	Low	Low	Low	Low	Low	Low
Taywade et al. [31]	Low	Low	Low	Low	Low	Low	Low
Thanseer et al. [32]	Low	Low	Low	Low	Low	Low	Low
Kluijfhout et al. [33]	Unclear	Low	Unclear	Low	Low	Low	High
Kluijfhout et al. [34]	Unclear	Low	Unclear	Low	Low	Low	Low
Michaud et al. [35]	Unclear	Low	Unclear	Low	Low	Low	Low
Rep et al. [36]	Low	Low	Unclear	Low	Low	Low	Low
Lezaic et al. [37]	Low	Low	Low	Low	Low	Low	Low
Michaud et al. [38]	Unclear	Low	Low	Low	Low	Low	Low
Orevi et al. [39]	Low	Low	Low	Low	Low	Low	High

percentage (72–91%) of patients in whom ^{99m}Tc-MIBI SPECT/CT was negative or inconclusive [23, 24, 27, 34].

With respect to radiation exposure, the mean effective dose of radiolabelled choline PET (ranging from 2.5 to 3.8 mSv) was lower than that of parathyroid scintigraphy performed with different techniques [27, 28]. The addition of low-dose CT imaging for the hybrid approach yielded minimal further radiation exposure (0.8 mSv) [28], whereas there is no additional radiation exposure for MRI combined with PET imaging [25, 30]. On the other hand, the costs for radiolabelled choline PET are higher than those for scintigraphy, with lower availability [25].

Regarding the comparison between radiolabelled choline PET and morphological imaging techniques, radiolabelled choline PET demonstrated clearly superior diagnostic performance versus US in the detection of HP [32]. In the prospective study by Thanseer et al., including 54 patients with primary HPT, patient-based sensitivity and PPV were 100 and 96.3%, respectively, for ^{18}F-choline PET/CT, and 69.3 and 87.1%, respectively, for US; on a per-lesion basis, sensitivity and PPV were 100 and 92.8%, respectively, for ^{18}F-choline PET/CT, and 69.3 and 87.1%, respectively, for US [32].

In the pilot study by Kluijfhout et al. investigating the role of radiolabelled choline PET/MRI in detecting HP in patients with primary HPT, the diagnostic performance of the PET component was superior to that of MRI; MRI alone showed true-positive lesions in only 5/10 patients and a false-positive lesion in one patient, whereas ^{18}F-choline PET allowed correct localization of HP in 9/10 cases (90% sensitivity), with no false-positive results (100% PPV) [30].

Only the pilot study by Taywade et al., which included five patients with primary HPT, demonstrated 100% concordance between ^{18}F-choline PET/CT and 4D-CT in detecting HP, with a DR of 100% [31].

With regard to the correlation between radiolabelled choline PET findings and biological parameters, no statistically significant correlation was found between HP weight and size and the findings on imaging [22, 39]. In some studies, mean calcium and PTH serum levels were higher in patients with positive versus negative radiolabelled choline PET, but no statistically significant differences were found between groups [23, 33]. Overall, studies investigating a possible correlation between radiolabelled choline uptake and PTH or calcium serum values reported discordant findings [21, 35, 39].

In the comparison of radiolabelled choline uptake between the HP and thyroid, the thyroid gland showed mild to moderate physiological tracer uptake on radiolabelled choline PET, but this did not affect the interpretation of abnormal parathyroid lesions [23]. The mean HP SUV_{max} was significantly higher than the mean thyroid SUV_{max} [26, 27, 30, 33–36].

In two studies, parathyroid adenomas positive at radiolabelled choline PET had higher SUV_{max} values than hyperplastic parathyroid glands, but the difference was not statistically significant [23, 35].

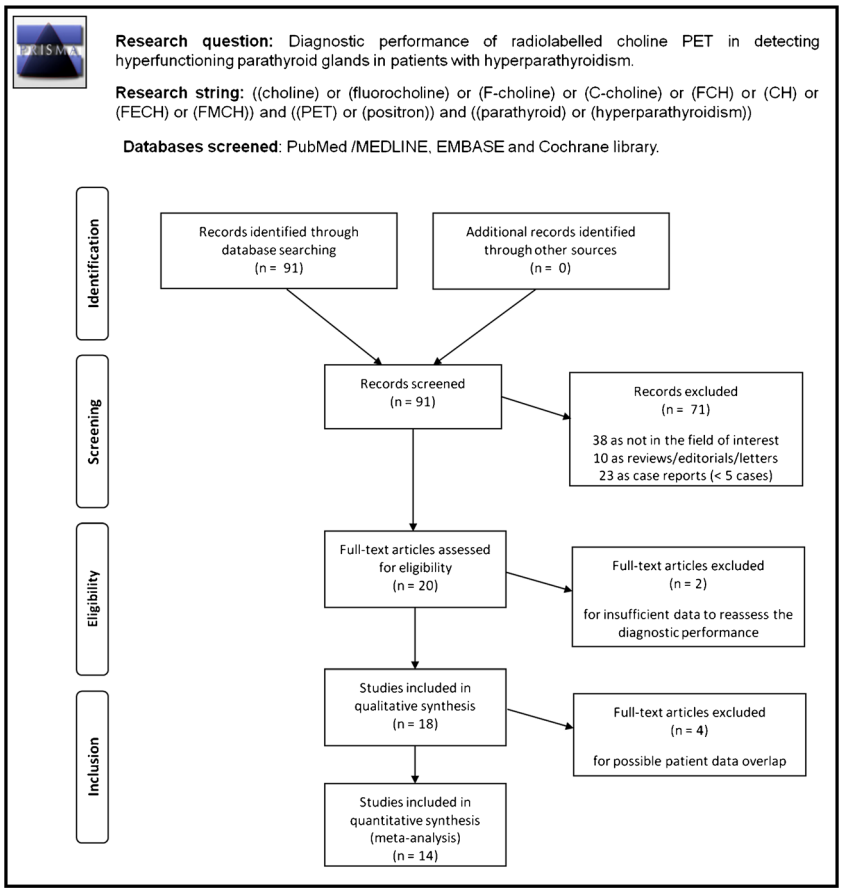

Fig. 1 Flow chart of the search for eligible studies on the diagnostic performance of radiolabelled choline PET in detecting hyperfunctioning parathyroid glands in patients with hyperparathyroidism

Optimal timing reported for radiolabelled choline PET acquisition differed among studies. Lezaic et al. performed ^{18}F-choline PET at 5 and 60 min after radiotracer injection, and found that HP were visible at both imaging times, with better lesion-to-background and lesion-to-thyroid contrast on delayed imaging [37]. A study by the same group reported better diagnostic accuracy for ^{18}F-choline PET performed at 60 and 120 min compared to early acquisition at 5 min after radiotracer injection [36]. Conversely, Michaud et al. reported that all detected HP were identified on early radiolabelled choline PET images [35, 38]. However, the majority of HP demonstrated increased uptake from early to delayed phase [21, 32, 36], whereas the thyroid gland and inflammatory lesions usually showed decreased uptake from early to delayed phase [21].

With regard to interobserver agreement using ^{18}F-choline PET/CT for the detection of HP, Quak et al. reported a kappa statistic of 0.79 (95% CI: 0.63–0.90) [27]; this value indicates that study results will not necessarily be reproducible in daily routine.

The prevalence of HP incidentally detected by radiolabelled choline PET in patients undergoing this type of imaging for other purposes (i.e. oncological evaluation of choline-avid tumours) is quite low (about 0.4%), as reported in the retrospective study by Parvinian et al. [26].

Quantitative analysis (meta-analysis)

Fourteen studies including 517 patients were selected for the meta-analysis of the diagnostic performance of radiolabelled choline PET [22–33, 35, 39]. Thirteen studies were available for the patient-based pooled analysis [22–27, 35, 39], and thirteen articles were available for the lesion-based pooled analysis [22–28, 30–33, 35, 39]. The combination of histological findings and biochemical resolution of HPT after surgery was used as reference standard. For each study, the following metrics of diagnostic accuracy were obtained: DR (on per-patient analysis only), sensitivity, specificity, PPV and NPV (Table 3). Because of the low number of articles with true-negative findings, pooled specificity and pooled NPV were not calculated. Diagnostic performance of radiolabelled choline PET was therefore expressed as pooled sensitivity and pooled PPV in per-patient and per-lesion analysis, and pooled DR on a per-patient basis (Figs. 2, 3 and 4).

The sensitivity of radiolabelled choline PET in detecting HP in patients with HPT on a per-patient and per-lesion basis ranged from 85 to 100% and from 71 to 100%, respectively, with a pooled estimate of 95% (95% CI: 92–97%) and 92% (95% CI: 88–96%), respectively (Fig. 2). The heterogeneity among studies was moderate (I^2 of 27% for per-patient and

49% for per-lesion analysis). Publication bias was detected by the Egger test ($p < 0.05$).

The PPV of radiolabelled choline PET in detecting HP in patients with HPT on a per-patient and per-lesion basis ranged from 86 to 100% and from 85 to 100%, respectively, with a pooled estimate of 97% (95% CI: 95–98%) and 92% (95% CI: 89–95%), respectively (Fig. 3). The heterogeneity among studies was not significant (I^2 of 7% for per-patient and 2% for per-lesion analysis). Publication bias was not detected by the Egger test ($p = 0.1$).

The DR of HP using radiolabelled choline PET on a per-patient basis ranged from 76 to 100%, with a pooled estimate of 91% (95% CI: 87–94%) (Fig. 4). The heterogeneity among studies was moderate ($I^2 = 42\%$). Publication bias was not detected by the Egger test ($p = 0.09$).

No significant difference in the diagnostic performance of radiolabelled choline PET was found between prospective and retrospective studies in a subgroup analysis by study design type.

Subgroup analysis by patient type showed lower diagnostic performance in patients with inconclusive US and parathyroid scintigraphy (pooled DR = 85%, 95% CI: 79–90%) than in patients evaluated regardless of the results of other imaging modalities (pooled DR = 94%, 95% CI: 92–96%).

A subgroup analysis that included only articles focusing on patients with primary HPT ($n = 390$) demonstrated pooled sensitivity of 96% (95% CI: 92–98%) and 91% (95% CI: 84–97%), and pooled PPV of 96% (95% CI: 94–98%) and 92% (95% CI: 88–95%), for radiolabelled choline PET on a per-patient and per-lesion basis, respectively. Pooled DR in per-patient analysis was 92% (95% CI: 88–95%). The diagnostic performance of radiolabelled choline PET was similar between patients with primary HPT and those with different types of HPT.

Subgroup analyses based on the type of radiotracer and hybrid imaging modality used were not performed due to the limited number of studies using ^{11}C-choline (vs ^{18}F-choline) and PET/MRI (vs PET/CT).

Discussion

Several recent studies using radiolabelled choline PET for the detection of HP in patients with HPT have reported varying levels of diagnostic performance. However, most of these studies have limited power because of the relatively small numbers of patients enrolled. In order to obtain more robust estimates in this setting, we have pooled the published studies. A systematic review process was adopted to identify eligible studies, and the quality of the studies was assessed using the QUADAS-2 tool (Table 4) [17]. In addition, a random-effects model was used for quantitative analysis [16].

The findings of our systematic review and meta-analysis indicate that radiolabelled choline PET/CT or PET/MRI achieves excellent diagnostic performance in detecting HP, with high sensitivity, PPV and DR [22–39]. Nevertheless, some false-negative and false-positive results should be taken into account. False-negative findings at radiolabelled choline PET may be related to the small size or pathological characteristics of HP, including a low number of adenoma-like cells corresponding to low functional status or a fairly low number of oxyphilic cells. Intrathyroidal HP may also cause false-negative results due to the masking effect of thyroid uptake [22–39]. False-positive findings may be related to thyroid gland uptake, thyroid nodules, faint uptake in normal parathyroid glands, and uptake in normal, reactive or metastatic lymph nodes [22–39].

As most of the patients in the included studies had primary HPT (Table 1), we can state that based on our pooled analysis, radiolabelled choline PET exhibits high diagnostic performance in detecting HP in patients with primary HPT and negative, equivocal or discordant US and parathyroid scintigraphy findings [22, 24, 27, 30]. Smaller HP were better identified on radiolabelled choline PET/CT or PET/MRI compared to conventional imaging modalities, suggesting that lesion size is an important factor contributing to the good diagnostic performance of PET/CT or PET/MRI, which can be attributed to their superior spatial resolution [25].

Currently, parathyroid scintigraphy with ^{99m}Tc-MIBI is the most commonly used functional imaging modality for detecting HP in patients with HPT. The addition of tomographic acquisition (SPECT or SPECT/CT) to planar imaging can improve the DR [40]. Notably, while a direct comparison could not be performed, we found that the pooled DR for radiolabelled choline PET in patients with primary HPT (DR = 92%, 95% CI: 88–95%) was higher than that reported in the literature for ^{99m}Tc-MIBI SPECT/CT performed in the same type of patients (DR = 88%, 95% CI: 84–92%) [40]. Overall, compared to the different parathyroid scintigraphy techniques, radiolabelled choline PET protocols provide better accuracy, clearer images due to better lesion-to-background contrast, faster acquisition and lower radiation exposure [23, 28, 32, 37, 39].

Radiolabelled choline PET demonstrated superior diagnostic performance versus US in detecting HP [32], but with obviously higher costs and radiation exposure and lower availability; US, however, is a highly operator-dependent technique.

A pilot study reported similar diagnostic performance between radiolabelled choline PET and 4D-CT in detecting HP, but further comparative studies are needed [31]. A recent meta-analysis found that the pooled sensitivity of CT for the detection and localization of HP was dependent on the number of contrast phases used, and reached as high as 80% [41], which is lower than the pooled sensitivity of radiolabelled

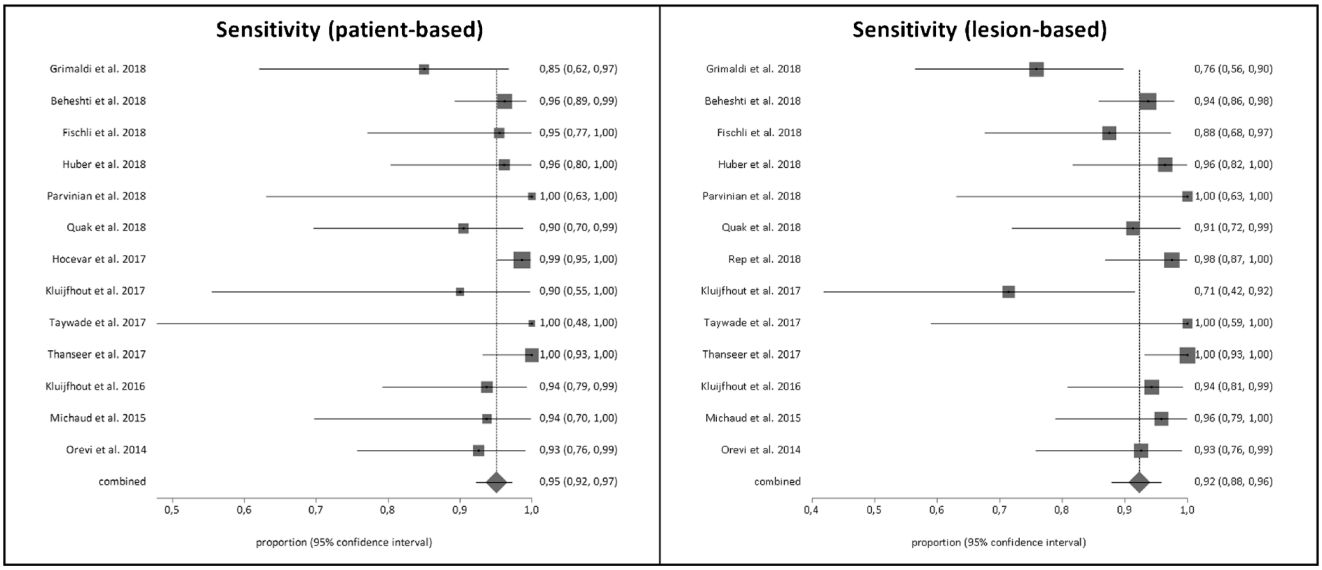

Fig. 2 Plots of individual studies and pooled sensitivity of radiolabelled choline PET for the detection of hyperfunctioning parathyroid glands on a per-patient and per lesion basis, including 95% confidence intervals (95% CI). The size of the squares indicates the weight of each study

choline PET (92%). Moreover, radiation exposure is higher with the use of 4D-CT [7].

To date, no studies have compared radiolabelled choline to the radiolabelled amino acid ^{11}C-methionine as PET radiotracers for detecting HP. However, a previous meta-analysis of ^{11}C-methionine PET reported per-lesion sensitivity and PPV of 77 and 98%, respectively [10]. In our meta-analysis, we found higher per-lesion sensitivity (92%) and lower PPV (92%) compared to the same values reported for ^{11}C-methionine PET. We should also take into account that the short half-life of ^{11}C hampers the wide use of ^{11}C-methionine, which is limited to centres with an on-site cyclotron [11].

Heterogeneity among studies represents a potential source of bias in meta-analysis. This heterogeneity is likely to arise through baseline differences among patient samples (Table 1), diverse methodological aspects (Table 2), and differences in study quality (Table 4). However, we failed to detect significant heterogeneity among the studies in our pooled analysis ($I^2 < 50\%$). No statistically significant differences were found in the diagnostic performance of radiolabelled choline PET based on study design (prospective vs retrospective). Likewise, diagnostic performance was similar between patients with primary HPT and those with different types of HPT. However, a lower DR was found for HPT patients with inconclusive US and parathyroid scintigraphy (pooled DR = 85%, 95% CI: 79–90%) compared to HPT patients evaluated regardless of the results of other imaging modalities (pooled DR = 94%, 95% CI: 92–96%), which was likely due to

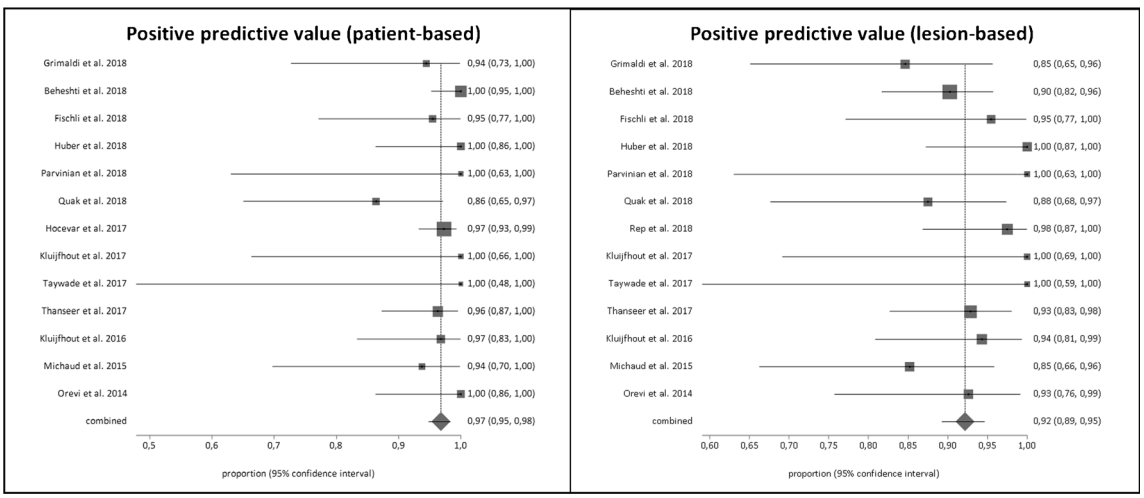

Fig. 3 Plots of individual studies and pooled positive predictive value of radiolabelled choline PET for the detection of hyperfunctioning parathyroid glands on a per-patient and per-lesion basis, including 95% confidence intervals (95% CI). The size of the squares indicates the weight of each study

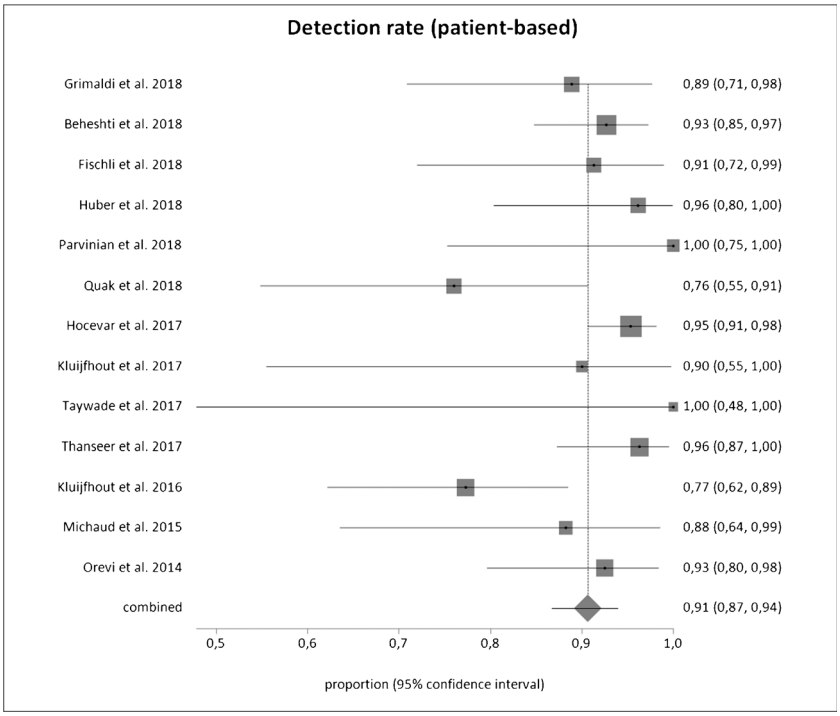

Fig. 4 Plots of individual studies and pooled rate of detection of hyperfunctioning parathyroid glands by radiolabelled choline PET on a per-patient basis, including 95% confidence intervals (95% CI). The size of the squares indicates the weight of each study

selection bias in the first group of patients. Unfortunately, the lack of sufficient data prevented us from performing subgroup analyses based on the type of HP (adenomas vs hyperplastic glands) and their location (eutopic vs ectopic). Nevertheless, good diagnostic accuracy was reported in all these settings across studies [22–39].

Subgroup analysis by type of radiotracer (^{18}F-choline vs ^{11}C-choline) and hybrid imaging modality (PET/MRI vs PET/CT) was also not performed due to the limited available data. Nonetheless, we did not expect a significant difference in diagnostic performance between ^{18}F-choline and ^{11}C-choline, although the longer half-life of ^{18}F (110 vs 20 min, respectively) makes it more suitable for clinical imaging and obviates the need for an on-site cyclotron [14].

No studies to date have compared the diagnostic accuracy of radiolabelled choline PET/MRI and PET/CT for the detection of HP. However, PET/MRI is probably the more appropriate, owing to the lower radiation exposure and higher soft-tissue contrast, which potentially allows for a more precise anatomical correlation of PET findings [25, 30]. Furthermore, MRI as an anatomical component of hybrid PET imaging is considered more useful than CT for differentiating HP from thyroid nodules [7].

Theoretically, the diagnostic performance of radiolabelled choline PET could be influenced by the choice of PET acquisition time, but the findings regarding optimal timing reported in the studies examined were conflicting [35–38]. A recent study described three patterns of HP uptake at radiolabelled choline PET (early washout, stable uptake and late increase), suggesting the importance of both early and delayed PET acquisition [20].

Publication bias is a major concern in all meta-analyses, as studies reporting significant positive findings are more likely to be published than those reporting negative results. Indeed, it is not unusual for small early studies to report positive findings that subsequent larger studies fail to replicate. In our meta-analysis, we found significant publication bias with respect to the calculation of the sensitivity of radiolabelled choline PET, but not the calculation of PPV or DR.

In a clinical setting characterized by an extremely high pretest probability of a positive finding, careful validation of the results is extremely important. This is underscored by the fact that the clinical relevance of parathyroid imaging is largely defined by the avoidance of exploratory surgery, which is dependent on the accuracy of pre-surgical HP localization. A possible limitation of our meta-analysis is the discrepancy between the high sensitivity and PPV of radiolabelled choline PET and the number of bilateral cervical exploration procedures that were avoided in patients with HPT. For example, despite the high per-lesion sensitivity and PPV of radiolabelled choline PET/CT reported in the APACH1 study (91.3 and 87.5%, respectively), bilateral cervical exploration was avoided in only 75% of patients with primary HPT [27]. This indicates that HP localization in terms of predicting the affected site of the neck was incorrect in some cases which were rated true positive when calculating sensitivity and PPV.

Another limitation of our analysis is our inability to calculate pooled specificity and NPV due to the limited number of articles reporting true-negative findings. Furthermore, it is

unclear whether the utility of radiolabelled choline PET varies based on the types of imaging techniques that have been performed previously.

Diagnostic accuracy of a test is not a measure of clinical effectiveness, and improved accuracy does not necessarily result in improved patient outcomes. Overall, our systematic review and meta-analysis showed excellent diagnostic performance for radiolabelled choline PET in detecting HP in patients with HPT, but to date there is no clear consensus on the optimal imaging modality for the detection and localization of HP. In the absence of studies comparing the diagnostic performance of different promising techniques (e.g. radiolabelled choline PET vs 4D-CT or radiolabelled choline PET vs ^{11}C-methionine PET), the preference of one technique over another may be based on local availability and the absence of contraindications.

Large prospective multicentre studies evaluating other parameters beyond the diagnostic accuracy of radiolabelled choline PET (e.g. the clinical impact or change in therapy and management based on PET findings) could be useful to better define the role of this imaging technique in patients with HPT. Cost-effectiveness analyses of radiolabelled choline PET/CT or PET/MRI compared to other imaging methods are also needed. These analyses should take into account several parameters, including diagnostic performance, radiation exposure and the costs of different imaging modalities. Despite the higher costs of radiolabelled choline PET/CT or PET/MRI compared with other imaging modalities for HP detection, the higher DR achievable could facilitate focused surgical exploration, shorten surgical times, and eventually reduce overall costs related to the management of patients with HPT.

Conclusions

Radiolabelled choline PET demonstrated excellent diagnostic performance in the detection of HP in patients with HPT. Because of the heterogeneity among methodologies in the published literature, it is not possible to reach definitive conclusions regarding the routine use of radiolabelled choline PET/CT or PET/MRI in patients with HPT. Further prospective studies, along with cost-effectiveness analyses, are therefore warranted.

Compliance with ethical standards

Conflict of interest The authors declare that they have no financial or non-financial competing interests.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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