Comparison of SPET/CT, SPET and planar imaging using ^{99m}Tc-MIBI as independent techniques to support minimally invasive parathyroidectomy in primary hyperparathyroidism: A meta-analysis

Wei-Jun Wei* MD,
Chen-Tian Shen* MD,
Hong-Jun Song MD,
Zhong-Ling Qiu MD
And Quan-Yong Luo MD
**These authors contributed equally to this work*

Department of Nuclear Medicine, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, 600 Yishan Road, Shanghai 200233, People's Republic of China

Keywords: SPET/CT -SPET -Planar imaging -Primary hyperparathyroidism- Meta-analysis

Correspondence address:
Quan-Yong Luo,
lqyn@sh163.net.
Zhong-Ling Qiu,
qiuzhongling123@163.com.

Received:
16 April 2015
Accepted revised:
30 June 2015

Abstract

Objective: Successful performance of minimally invasive parathyroidectomy (MIP) is based on the accuracy of preoperative parathyroid localization studies. Despite the various methodologies available, no consensus has been reached so far on the optimal imaging technique. The aim of our meta-analysis was to determine the accuracy of technetium-99m-hexakis methoxyisobutylisonitrile single photon emission tomography/computed tomography (^{99m}Tc-MIBI SPET/CT), SPET and MIBI scintigraphy for the preoperative localization of primary hyperparathyroidism (PHPT) lesions, thus facilitating better management of these patients. **Subjects and Methods**: Publications were screened by a comprehensive computer search of PubMed and EMBASE for 25 years. Data were extracted from included articles and forest plots of sensitivity and positive predictive value were calculated to investigate the diagnostic accuracy of SPET/CT, SPET and MIBI scintigraphy. **Results**: Eighteen articles were included in our study. The sensitivities of SPET/CT, SPET and planar scintigraphy were 84% (95% CI: 78%-90%), 66% (95% CI: 57%-74%) and 63% (95% CI: 51%-74%), respectively. The PPV of the above three imaging modalities were: 95% (95% CI: 92%-98%), 82% (95% CI: 73%-89%) and 90% (95% CI: 96%-99%), respectively. **Conclusion**: Our present meta-analysis showed that using ^{99m}Tc-MIBI, and combining anatomical information of CT and functional abnormalities on SPET, as presented on SPET/CT was by far more sensitive and accurate than SPET or planar scintigraphy in localizing PHPT lesions. We firmly believe that this technique will be the main diagnostic means, to detect PHPT lesions and support minimally invasive parathyroidectomy.

Hell J Nucl Med 2015; 18(2): 127-135 *Epub ahead of print: 19 July 2015* *Published online: 5 August 2015*

Introduction

Primary hyperparathyroidism (PHPT) is characterized, in up to 85% of clinical cases by the autonomous overproduction of parathyroid hormone (PTH), by a solitary parathyroid adenoma. Minimally invasive parathyroidectomy (MIP) in patients with PHPT has recently replaced the conventional bilateral approach because of fewer complication rates and shorter hospitalization time. Precise pre-operative detection and localization of abnormal parathyroid glands is essential for the successful performance of MIP. Currently, numerous imaging modalities are available, such as ultrasound, nuclear medicine imaging, magnetic resonance imaging (MRI) and computed tomography (CT), for the localization of parathyroid lesions.

Coakley et al. (1989) first reported parathyroid imaging using technetium-99m-hexakis2-methoxy-2-methylpropylisonitrile (^{99m}Tc-MIBI). They suggested that ^{99m}Tc may replace thalium-201 for routine preoperative parathyroid localization [1]. Technetium-99m-MIBI scintigraphy and subtraction imaging techniques using thyroid imaging with ^{99m}Tc-pertechnetate or ^{123}I-sodium have since been developed and used in many hospitals for the preoperative localization of diseased parathyroid glands. Several researchers use ^{99m}Tc-MIBI scintigraphy as the technique of choice for parathyroid imaging [2-4]. The addition of SPET to the above methodologies offers high sensitivity and accuracy in localizing abnormal parathyroid glands [5-7]. Recently, the hybrid SPET/CT, is increasingly used because it enables more detailed localization of the involved parathyroid glands. Others, demonstrated that ^{99m}Tc-MIBI SPET/CT had no significant additional clinical value for eutopic parathyroid glands as compared to that of the conventional ^{99m}Tc-MIBI SPET [8], while other researchers showed that ^{99m}Tc-MIBI SPET/CT was superior to ^{99m}Tc-MIBI SPET in preoperative parathyroid imaging [9, 10].

Considering that there is no consensus on the best preoperative imaging protocol for localization of parathyroid adenomas, we performed this systematic meta-analysis and compared, ^{99m}Tc-MIBI SPET/CT, ^{99m}Tc-MIBI SPET and ^{99m}Tc-MIBI planar imaging.

Subjects and Methods

Papers screened

Publications were screened by a comprehensive computer search of PubMed and EMBASE from October 1989 to August 2014. The search strategy was based on the combination of the following keywords: a) ^{99m}Tc-MIBI SPET/CT, b) ^{99m}Tc-MIBI SPET/CT, c) parathyroid adenoma (PA) and PHP, d) sensitivity or diagnostic accuracy of diagnostic value.

Although no language restrictions were imposed initially, the full-text reviews and final analyses were limited to articles published in English. Conference abstracts and letters to the journal were excluded because they contained limited data. Reference lists were manually screened for additional relevant articles. Cross references from selected articles were also used for retrieving relevant studies.

Selection of studies

Two reviewers (W-J W and C-T S) independently assessed potentially eligible articles, after reading all abstracts and also any citations for which determination could not be made from the abstract. We then managed to get the full texts of these articles to determine whether they were eligible for the study.

The inclusion criteria were as follows: a) used at least ^{99m}Tc-MIBI SPET/CT to diagnose patients with PHPT or PA; b) at least one of the techniques (SPET/CT, SPET and planar imaging) was relevant for inclusion and related data were amenable to extraction; c) surgical and/or histopathology findings and/or close clinical and imaging follow-up were used as the reference standard; d) the studies were based on per-patient or per-lesion statistics; e) when data or subsets of data were presented in more than one article, the article with more details or the most recent article was selected.

The exclusion criteria were as follows: a) articles which did not include raw data such as case reports, letters, editorials, comments, reviews and meta-analyses; b) articles with secondary or tertiary HPT; c) articles with results of different imaging modalities presented in combination that could not be differentiated for performance assessment of individual modality; d) use of radiopharmaceutical other than ^{99m}Tc-MIBI and publication language other than English; e) articles concerning other cancer types; f) articles focusing on parathyroid surgery and g) studies mainly using other imaging modalities (ultrasound and/or PET/CT).

Quality assessment

The contents of included articles were assessed by two authors (W-J W and C-T S) using the revised Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) [11]. Questions related to the four specific domains-patients selection, index test, reference standard, flow and timing-were set to assess the applicability and risk of bias as follows: a) Patients' selection: The criteria used to select patients with PHPT for the study have been clearly explained. Patients with prior history of neck surgery or with medical history of neoplastic disease in the area of head and neck, or with negative ^{99m}Tc-MIBI scintigraphy were excluded. b) Index test: With the rapid development of medical imaging techniques, it was necessary to specify the detailed parameters of the imaging methodologies used in the research. Explanation of the imaging technique and of the experience of the interpreters as well as the definition of positive and negative findings were explicitly described. c) Reference standard: Surgical and histopathologic findings were considered to be the gold standard for confirming different imaging results. However, reference standard bias existed when different pathologic methods were used to verify the same set of imaging results. On some occasions, confirmation by clinical follow-up was used when histopathologic confirmation couldn't be obtained. We carefully assessed whether these specific patients were closely followed-up or lost to clinical follow-up. Patients lost to follow-up and included in final analysis, could be the potential source of bias. d) Flow and timing: It was also described whether the interpreters of the imaging results were masked to the laboratory, surgical, pathologic results or other imaging findings.

Data extraction and statistical method

Two reviewers independently read the titles and summaries of the papers included in the study and assessed their eligibility. After excluding articles that did not met inclusion criteria illustrated above, the full texts were read and relevant data were extracted from the included studies. The SPET and SPET/CT were limited to techniques using ^{99m}Tc-MIBI with delayed or dual-phase images. Any disagreement was resolved by consensus. The extracted data were recorded on two standardized tables. Specifically, nearly all patients had biochemical confirmation of PHPT before nuclear medicine examinations. Patients with negative imaging results were recommended to have further examinations rather than undergo bilateral neck exploration. Therefore, specificity and negative predictive value (NPV) of most of the studies were not reported. Consequently, pooled proportion of sensitivity and positive predictive value (PPV) of the index tests of included studies were calculated in our meta-analysis, to compare the diagnostic accuracy of the three parathyroid imaging methodologies.

Diagnostic meta-analysis was conducted on StatsDirect2.7.9 (Stats Direct Ltd., UK) using true positive (TP), false positive (FP) and the total number of diseased PT lesions of patients extracted directly or through recalculation. The factor I2 was calculated to quantify heterogeneity between studies. We used an effect model to draw the pooled forest plots of sensitivity and of PPV in the presence of heterogeneity, which was interpreted as low (25%), moderate (50%), and high (75%) [12]. In addition, Funnel plots were drawn to investigate publication bias. The pooled sensitivities and PPV of SPET/CT, SPET and planar imaging were calculated to compare the different diagnostic efficacy of the three imaging modalities.

Results

Literature search and study characteristics

In total of 340 articles were identified from the primary literature search in PubMed and EMBASE. Following the inclusion and exclusion criteria, only 18 were selected as having the diagnostic value of SPET/CT and/or SPET and/or planar imaging. The flow diagrams of the articles of selection process are presented in Figure 1 and the basic features of these studies are shown in Table 1 [9, 10, 13-28].

From what has been summarized in Table 1, we can see that 4 studies were from USA, 2 from Italy, 2 from Austria and 1 study from each of the following countries UK, China, Slovenia, Turkey, Japan, Iran, Korea, France, Canada and Switzerland. Of the eighteen included publications, 6 studies were prospective while the remaining twelve studies were retrospective. Eighteen of the above studies provided diagnostic proof of SPET/CT, by acquiring fusion information 1.5-2h after injection [13, 15, 17, 18, 20-22, 25, 26], after early phase image [14, 16, 24], or after dual phase images of the radiopharmaceutical [9, 19, 23]. Regarding the 9 studies which assessed the clinical utility of ^{99m}Tc-MIBI scintigraphy, all groups except one used dual phase

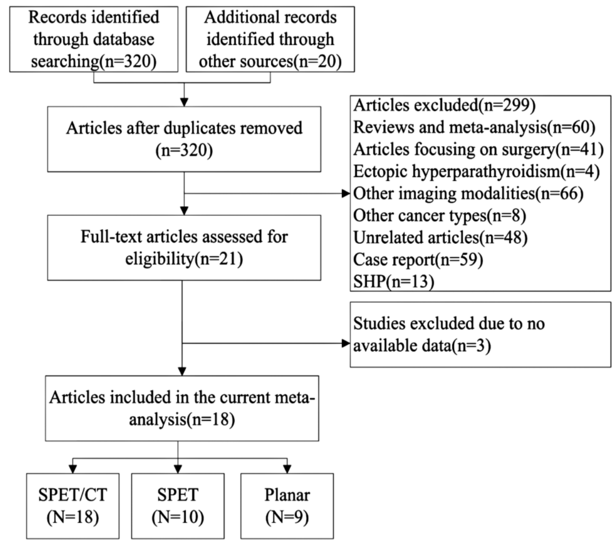

Figure 1. Flow chart showing the process of study selection.

planar imaging protocols [9, 14-17, 21, 26, 28]. Tokmak et al. (2014) showed the diagnostic efficacy of SPET/CT combined with conventional planar scintigraphy in the detection and localization of hyper-functioning parathyroid glands, in 154 patients who had neck surgery with definitive histology reports. In this study ectopic adenoma accounted for 1.19% of all 168 lesions [9]. Prommegger et al. (2009) showed that Technetium-99m-MIBI SPET/CT image fusion exactly localized 6 of the 8 ectopic glands [23]. Other researchers assessed the clinical utility of SPET-CT in subjects with endocrine and neuroendocrine tumors compared to SPET and found that 32 of the 48 included subjects underwent ^{99m}Tc-MIBI scans [19]. As we mainly emphased on the clinical utility of SPET/CT in localizing PA, we solely extracted the data related to HPT from studies that evaluated the diagnostic utility of the three imaging modalities on a per-patient basis and on a per-lesion basis [15, 17]. The imaging acquiring protocols and the detailed information of the included 18 studies are showed in Table 2.

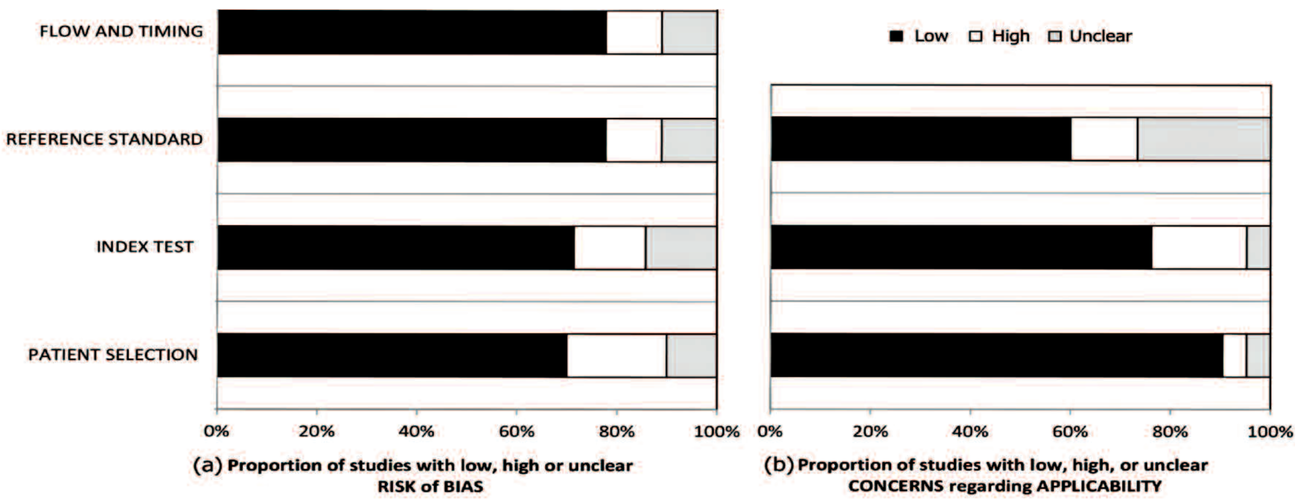

Figure 2. a) Proportion of studies with low, high, or unclear risk of bias; b) Proportion of studies with low or unclear concerns regarding applicability.

Table 1. Basic study and patients characteristics

Author	Year	Country	Study design	Cause	No. of patients	Age (years)	Sex (M/F)	Median Serum calcium (mg/dL)	Median Serum PTH (ng/L)	Gold standard
Lavely	2007	USA	Prospective	PA	98	60 (28-94)	30/68	NR	NR	Surgery
Serra	2006	Italy	Retrospective	PA, PH, Ca	16	51 (35-80)	5/11	10.64	708	»
Patel	2009	UK	»	PA, MA, MGH	63	59 (10-86)	21/42	2.83mmol/L	36pmol/L	»
Qiu	2014	China	»	PA, Ca, PH	244	57 (7-86)	50/194	2.67ng/mL	293.80ng/mL	Surgery & pathology
Lezaic	2014	Slovenia	Prospective	PA, PH	24	42-77	4/20	2.68mol/L	8.8pmol/L (83.5 pg/mL)	», follow-up
Tokmak	2014	Turkey	Retrospective	PA, Ca, PH	154	54 (15-86)	30/124	11.13mg/dL	434.17pg/mL	Surgery
Hayakawa	2014	Japan	»	PA, PH, MEN1	15	63 (32-83)	3/12	NR	208pg/mL	Surgery & pathology
Prommegge	2009	Austria	»	pHPT	116	59 (14-85)	36/80	NR	NR	Intraoperative finding
Shafiei	2012	Iran	Prospective	PHP, NG, MEN1	48	59 (30-85)	15/33	11.22mg/dL	251.89pg/mL	Histology & follow-up
Kim	2012	Korea	»	PA, PH, SHP	31	60 (35-78)	10/21	NR	NR	Surgery
Bural	2012	USA	Retrospective	PA, PH	32	NR	NR	NR	NR	Pathology & follow-up
Ciappuccini	2012	France	»	PA, Ca	94	61 (18-85)	21/73	2.75mmol/L	121pg/mL	Surgery & pathology findings
Pata*	2011	Italy	»	PA, NG	27	55 (18-80)	5/22	11.7mg/dL	154pg/mL	Intraopera-tive findings
Pata*	2011	Italy	»	PA, NG	28	57 (22-83)	7/21	11.5mg/dL	142pg/mL	»
Profanter	2003	Austria	Prospective	PHP, SHP	24	60 (29-79)	4/20	NR	NR	»
Sharma*	2006	USA	Retrospective	MGH, PA	138	49.5	NR	11.8mg/dL	165pg/mL	Intraopera-tive parathyroid pathology
Sharma*	2006	USA	»	MGH, PA	165	52.2	NR	11.7mg/dL	179pg/mL	»
Sharma*	2006	USA	»	MGH, PA	180	55.8	NR	11.7mg/dL	147g/mL	»
Harris	2007	Canada	»	PA, MGH	23	66 (26-80)	9/14	2.85mmol/L	22.4pmol/L	Intraopera-tive findings
Neumann	2008	USA	Prospective	PA, PH	61	59 (18-85)	18/43	11.0mg/dL	114pg/mL	Surgery & pathology findings
Öksüz	2010	Switzerland	Retrospective	PHP, SHP	60	51 (22-80)	16/44	NR	NR	»

NG: nodular goiter; MGD: multiple gland disease; PA: Parathyroid adenoma; Ca: carcinoma; PH: parathyroid hyperplasia; MA: multiple adenomas; MGH: multiglandular hyperplasia; MEN1: multiple endocrine neoplasia type 1; NG: nodular goiter;:*

Table 2*. Imaging protocols and diagnostic performance of three image modalities*

Author	Dose(MBq)	Image	Acquisition protocol	Sensitivity %
Lavely	925-1110	Planar SPET SPET/CT Planar	Dual phase, Anterior/RAO/LAO, 128×128 matrix 25s/3°, 60 views, dual-head SPET/CT; 2.5mA, 140kV, 10mm slices, 256×256 matrix for CT Dual phase, Anterior, 128×128 matrix	56.5 61.5 72.0 60.0
Serra	370	SPET SPET/CT	25s/3°, 120 views, dual-head SPET/CT, 128×128 matrix; 2.5mA, 140kV, 5mm slices, 256×256 matrix for CT	100 100
Patel	800	SPET/CT	128×128matrix for SPET; 2.5mA, 140 kV, 10mm slices, 256×256 matrix for CT	89.8
Qiu	555	SPET/CT Planar	128×128matrix for SPET; 80mA, 5-mm slices, B70 kernel filter for CT Dual phase, 128×128 matrix, zoom level 2.5	73.7 44
Lezaic	600	SPET/CT	Dual-head gamma camera, 128×128 matrix, 32views, 20s/frame, Dual-head camera for SPET; 25mAs, 130kV for CT	48.7
Tokmak	925-1110	Planar SPET/CT Planar	Dual phase, Anterior/RAO/LAO, 128×128 matrix 128 stops, 20s/stop for early, 30s/stop for delayed, 128×128 matrix Anterior planar images	87.5 97.6 54.5
Hayakawa	600	SPET SPET/CT	Dual-head gamma camera, Infinia Hawkeye 4, GE Healthcare for SPET; Low-dose, four-slices for CT	54.5 54.5
Prommegger	370	SPET SPET/CT	NR 16 row MD-CT, 1.25mm and 2.5mm for CT	63.4 88.7
Shafiei	740	Planar SPET SPET/CT	Anterior planar image, Dual-detector camera, 60 frames, 25s/3°, 128×128 matrix for SPECT; 30mA, 130kV, 2mm slices for CT	59.18 67.34 77.55
Kim	555	Planar SPET SPET/CT	NR Hawkeye 4 instrument, GE Healthcare,128×128 matrix for SPECT; 5.0 mm slices, 140kV, 2.5mA, 512×512 matrix for CT	67.6 76.5 100
Bural	1110	SPET SPET/CT	128×128 matrix, 30 s/stop, 64 stops, 128 projections for SPET; 140kV for CT	68.8 96.8
Ciappuccini	740	SPET/CT	Double-head camera, 128×128 matrix, 64 projections for SPET; 60mA, 5mm slices for CT	91.7
Pata	740	SPET SPET/CT SPET	64×64 matrix, 120 frames, 20s/3° for SPET; 140kv, 2.5 mA, 10mm slices, 256×256 matrix for CT CT MIBI image fusion;	61.1 86.7 31.0
Profanter	370	SPET/CT Planar SPET	1.25mm and 2.5mm slices for CT NR	93.0 62.2
Sharma	703-925		Hawkeye; General Electric Medical Systems NR	84.7
Harris	700	SPET/CT SPET/CT	60 projections, 30s/6°, 128×128 matrix for SPET; 5-10mm slices, 140kV, 2.5mA for CT	73.9
Neumann	1191	SPET/CT	Dual detectors, 60 steps, 25 s/3°, 128×128matrix for SPET; 130kV 100mA, 5mm slices for CT	70.0
Öksüz	400	Planar SPET/CT	Anterior planar images, 256×256 matrix 120 projections, 20s/3°, 128×128 matrix	76.0 97.0

RAO: right anterior oblique; LAO: left anterior oblique; NR: not reported

Quality assessments and meta-analysis

The qualities of the 18 studies were methodologically assessed using QUADAS-2 [11]. The guidelines used to quality assessment have been explained above. As a whole, the qualities of the included studies were satisfactory, eligible and results are shown in a bar chart of QUADAS-2, in Figure 2.

For the three different imaging modalities, results from these 18 studies were not statistically homogeneous and we found significant heterogeneity in sensitivity and PPV data (I^2=88.2%/74.6%/86.5% for sensitivity and I^2=83.5%/74.8%/92.9% for PPV, respectively). Funnel plots of the included studies are presented in Figure 3.

For the diagnostic value of SPET/CT, the pooled sensitivity and PPV were, 84% (95% confidence interval: 78%-90%) and 95% (95% confidence interval: 92%-98%), respectively. For the diagnostic efficacy of SPET, the pooled sensitivity and PPV were 66% (95% confidence interval: (57%-74%) and 82% (95% confidence interval: 73%-89%), respectively. For the diagnostic utility of planar scintigraphy, the pooled sensitivity and PPV were 63% (95% confidence interval: 51%-74%) and 90% (95% confidence interval: 96%-99%), respectively.

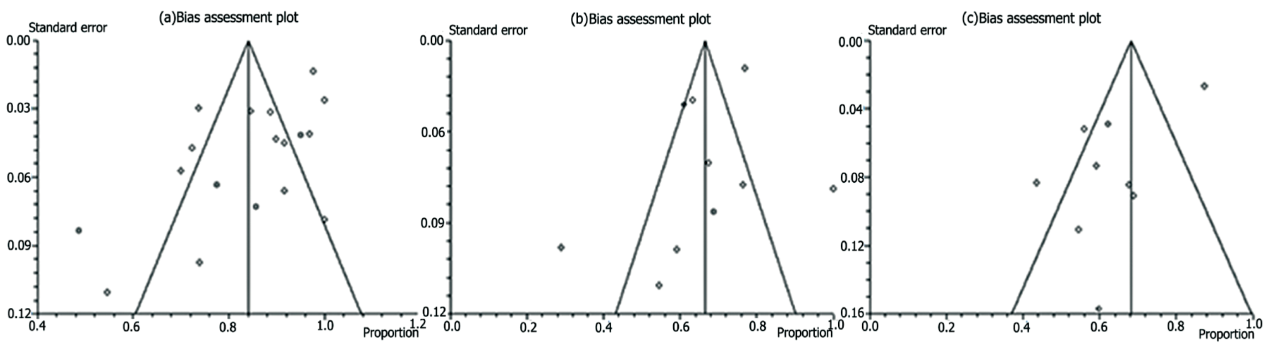

Figure 3. (a) Publication bias assessment of the included studies for SPET/CT, (b) SPET and (c) planar imaging. Two of the three Figures also demonstrate significant heterogeneity between the included studies (Figures 3. b and c). Therefore, the random-effect model was used to calculate the pool estimates in our study.

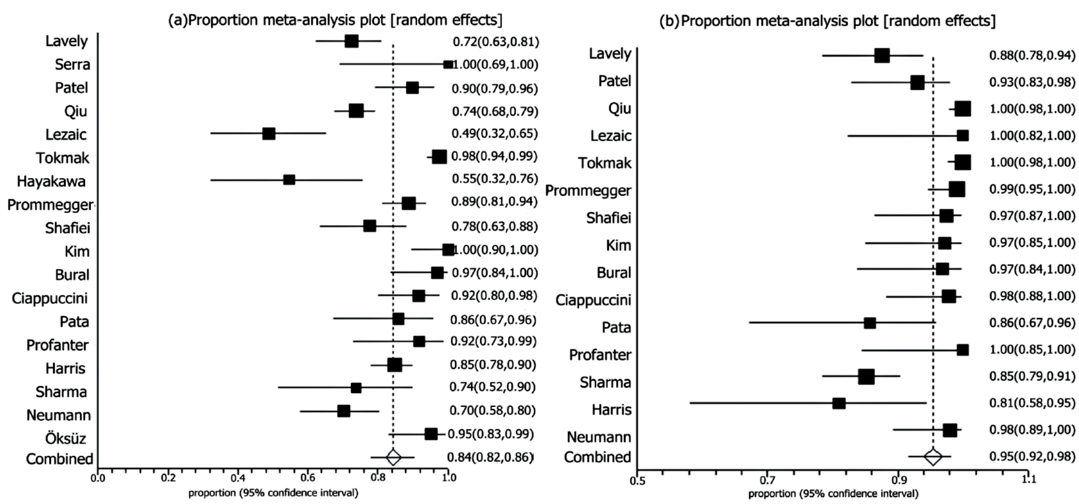

Figure 4. The pooled sensitivity a) and PPV b) of SPET/CT.

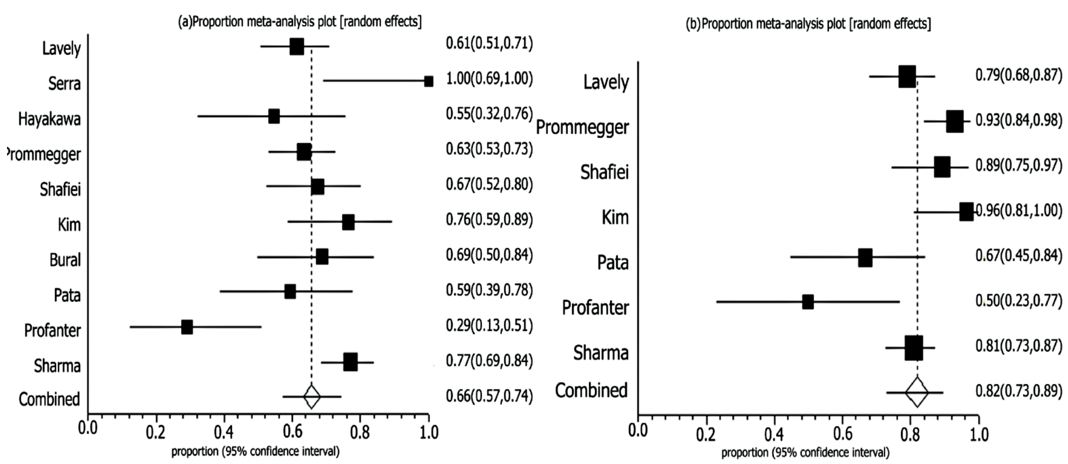

Figure 5. The pooled sensitivity a) and PPV b) of SPET.

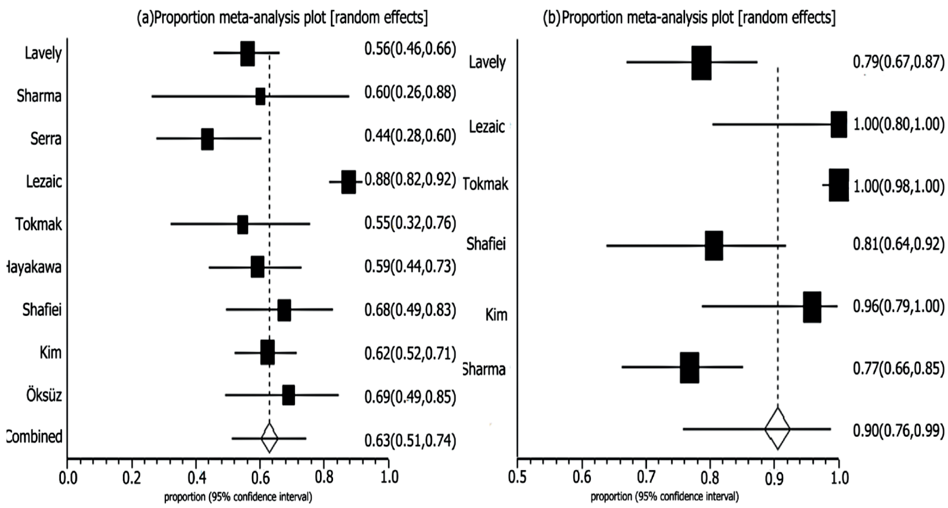

Figure 6. The pooled sensitivity a) and PPV b) of SPET.

Discussion

The management of PHPT has dramatically developed over the past few decades from performing a conventional limited diagnostic evaluation, to bilateral neck exploration (BNE) with both laboratory and radiographic evaluation followed by MIP. Precise preoperative localization is essential for the successful performance of MIP. Despite various methodologies that are available for preoperative localization of parathyroid lesions, there are few papers directly comparing the different methods and even fewer supporting the superiority of one over another. To our best knowledge, this is the first meta-analysis that systematically evaluated the diagnostic value of three nuclear medicine techniques for the detection of parathyroid disease.

Planar^{99m}Tc-MIBI scintigraphy has typically been widely-used for preoperative localization of parathyroid adenomas. However, false-positive results due to uptake by thyroid adenomas, multinodular goiter scintigraphy or metastatic medullary cancer, as well as metastatic lung cancer have been reported. Although neck ultrasound examination has an acceptable sensitivity for identifying adenomas located close to or within the thyroid gland, this is an operator-dependent technique, with limited practical use when detecting intrathyroidal parathyroid lesions, deeply located lesions, ectopic or especially mediastinal parathyroid lesions. In addition, SPET compared to planar scintigraphy has increased sensitivity and accuracy in diagnosing parathyroid diseases [29, 30], however, the degree of anatomic details they provided, is limited. In our meta-analysis we concluded that SPET had similar diagnostic efficacy with that of planar imaging.

Our meta-analysis also suggested that SPET/CT had a superior diagnostic efficacy in detecting and localizing diseased parathyroid glands when compared with SPET and planar imaging (with sensitivity of 84% and PPV of 95%). This improvement in accuracy is mainly because hybrid SPET/CT offers the possibility of attenuation correction and co-registration of functional and anatomical information. In addition, for patients who have distorted neck anatomy, due to previous neck surgery or have multiglandular disease, or nodular thyroid disease, SPET/CT is obviously advantageous and improves the detections of PA. Ectopic superior parathyroid glands may be located either above the superior thyroid pole, below the inferior thyroid artery, or in the retropharyngeal, retrotracheal or retroesophageal space. Ectopic inferior parathyroids are most frequently found in the anterior mediastinum and 30% of ectopic parathyroids are associated with thymus gland [31]. Less frequently, ectopic sites are anterio-superior mediastinal, intrathyroidal, within the thyrothymic ligament or rarely submandibular [32]. Ectopic parathyroid tumors and unrecognized multiglandular parathyroid disease are major causes of clinical surgical failure. It is always difficult to differentiate ectopic PA from lymph nodes, thyroid or thymus tissue on conventional CT or MRI. Fortunately, by providing detailed anatomic information, SPET/CT contributed much to the precise localization and the detection of both eutopic and ectopic PA. In another study SPET/CT not only improved localization but also facilitated the surgical approach of all 10 ectopic lower adenomas [33]. By using combined transmission and emission SPET/X-rays-CT imaging in 4 patients, other researchers accurately localized mediastinal parathyroid tumors. Thus morbidity, radiation exposure time and costs were reduced [34].

There are several limitations of our study. First, the selective publication bias is an important concern in meta-analytic reviews of the literature, because papers reporting positive imaging findings are more likely to be published. Asymmetric funnel plot has long been associated with publication bias. It has been reported that English language bias and methodological bias are the two main sources of publication bias [35]. Considering the insufficient number of studies for SPET and planar imaging in our current paper and the asymmetric funnel plots (Figures 3 b and c), the small cohort of patients for the two nuclear medicine techniques limited our work's eligibility and may have caused heterogeneity. Second, our meta-analysis was limited by the fact that primary patients' data of some of the included studies were not available so some data had to be extrapolated from graphs or tables, possibly resulting in some error, particularly in pooled analyses. However, the relatively large number of patients in our meta-analysis for the last 25 years strengthened the eligibility of our work.

In conclusion, based on the statistical results of this meta-analysis we showed that ^{99m}Tc-MIBI SPET/CT is advantageous over SPET or planar imaging in diagnosing useful anatomic and metabolic information, in patients with PHPT.

The authors declare that they have no conflicts of interest.

Bibliography

1. Coakley AJ, Kettle AG, Wells CP et al. ^{99m}Tc MIBI-a new agent for parathyroid imaging. *Nucl Med Commun* 1989; 10: 791-4.
2. Hindie E, Melliere D, Simon D et al. PHPT: is technetium 99m-MIBI/iodine-123 subtraction scanning the best procedure to locate enlarged glands before surgery? *J Clin Endocrinol Metab* 1995; 80:302-7.
3. Casas AT, Burke GJ, Sathyanarayana et al. Prospective comparison of technetium-99m-MIBI/iodine-123 radionuclide scan versus high-resolution ultrasonography for the preoperative localization of abnormal parathyroid glands in patients with previously unoperated PHPT. *Am J Surg* 1993; 166: 369-73.
4. Johnston LB, Carroll MJ, Britton KE et al.The accuracy of parathyroid gland localization in PHPT using MIBI radionuclide imaging. *J Clin Endocrinol Metab*1996; 81: 346-52.
5. Lorberboym M, Minski I, Macadziob S et al. Incremental diagnostic value of preoperative ^{99m}Tc-MIBI SPET in patients with a parathyroid adenoma. *J Nucl Med* 2003; 44: 904-8.
6. Billotey C, Sarfati E, AurengoA et al. Advantages of SPET in technetium-99m-MIBI parathyroid scintigraphy. *J Nucl Med* 1996; 37: 1773-8.
7. Staudenherz A, Abela C, Niederle B et al. Comparison and histopathological correlation of three parathyroid imaging methods in a population with a high prevalence of concomitant thyroid diseases. *Eur J Nucl Med* 1997; 24: 143-9.
8. Gayed IW, Kim EE, Broussard WF et al. The value of ^{99m}Tc-MIBI SPET/CT over conventional SPET in the evaluation of parathyroid adenomas or hyperplasia. *J Nucl Med* 2005; 46: 248-52.
9. Tokmak H, Demirkol MO, Alagol F et al. Clinical impact of SPET-CT in the diagnosis and surgical management of hyper-parathyroidism. *Int J Clin Exp Med* 2014; 7: 1028-34.
10. Profanter C, Wetscher GJ, Gabriel M et al. CT-MIBI image fusion: a new preoperative localization technique for primary, recurrent, and persistent hyperparathyroidism. *Surgery* 2004; 135: 157-62.
11. Whiting PF, Rutjes AW, Westwood ME et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med* 2011; 155: 529-36.
12. Moher D, Liberati A, Tetzlaff J et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Int J Surg* 2010; 8: 336-41.
13. Qiu ZL, Wu B, Shen CT et al. Dual-phase Tc-MIBI scintigraphy with delayed neck and thorax SPET/CT and bone scintigraphy in patients with PHPT: correlation with clinical or pathological variables. *Ann Nucl Med* 2014; 10.1007/s12149-014-0876-z
14 Lezaic L, Rep S, Sever MJ et al. ^{18}F-Fluorocholine PET/CT for localization of hyperfunctioning parathyroid tissue in PHPT: a pilot study. *Eur J Nucl Med Mol Imaging* 2014; 41: 2083-9.
15. Hayakawa N, Nakamoto Y, Kurihara K et al. A comparison between ^{11}C-methionine PET/CT and MIBI SPET/CT for localization of parathyroid adenomas/hyperplasia. *Nucl Med Commun* 2014; 10.1097.
16. Shafiei B, Hoseinzadeh S, Fotouhi F et al. Preoperative^{99m}Tc- MIBI scintigraphy in patients with PHPT and concomitant nodular goiter: comparison of SPET-CT, SPET, and planar imaging. *Nucl Med Commun* 2012; 33: 1070-6.
17. Kim YI, Jung YH, Hwang KT et al. Efficacy of ^{99m}Tc-MIBI SPET/CT for minimally invasive parathyroidectomy: comparative study with ^{99m}Tc-MIBI scintigraphy, SPET, US and CT. *Ann Nucl Med* 2012; 26: 804-10.
18. Ciappuccini R, Morera J, Pascal P et al. Dual-phase ^{99m}Tc MIBI scintigraphy with neck and thorax SPET/CT in PHPT: a single-institution experience. *Clin Nucl Med* 2012; 37: 223-8.
19. Bural GG, Muthukrishnan A, Oborski MJ et al. Improved Benefit of SPET/CT Compared to SPET Alone for the Accurate Localization of Endocrine and Neuroendocrine Tumors. *Mol Imaging Radionucl Ther* 2012; 21: 91-6.
20. Pata G, Casella C, Magri GC et al. Financial and clinical implications of low-energy CT combined with ^{99m}Technetium-MIBI SPET for PHPT. *Ann Surg Oncol* 2011; 18: 2555-63.
21. Oksuz MO, Dittmann H, Wicke C et al. Accuracy of parathyroid imaging: a comparison of planar scintigraphy, SPET, SPET-CT, and C-11 methionine PET for the detection of parathyroid adenomas and glandular hyperplasia. *Diagn Interv Radiol* 2011; 17: 297-307.
22. Patel CN, Salahudeen HM, Lansdown M et al. Clinical utility of ultra sound and ^{99m}Tc MIBI SPET/CT for preoperative localization of parathyroid adenoma in patients with PHPT. *Clin Radiol* 2010; 65: 278-87.
23. Prommegger R, Wimmer G, Profanter C et al. Virtual neck exploration: a new method for localizing abnormal parathyroid glands. *Ann Surg* 2009; 250: 761-5.
24. Neumann DR, Obuchowski NA, Difilippo FP. Preoperative ^{123}I/^{99m}Tc-MIBI subtraction SPET and SPET/CT in PHPT. *J Nucl Med* 2008; 49: 2012-7.
25. Harris L, Yoo J, DriedgerA et al. Accuracy of technetium-99m SPET-CT hybrid images in predicting the precise intraoperative anatomical location of parathyroid adenomas. *Head Neck* 2008; 30: 509-17.
26. Lavely WC, Goetze S, Friedman KP et al. Comparison of SPET/CT, SPET, and planar imaging with single- and dual-phase ^{99m}Tc-MIBI parathyroid scintigraphy. *J Nucl Med* 2007: 48: 1084-9.
27. Sharma J, Mazzaglia P, Milas M et al. Radionuclide imaging for hyperparathyroidism (HPT): which is the best technetium-99m MIBI modality? *Surgery* 2006; 140: 856-63; discussion 863-55.
28. Serra A, Bolasco P, Satta L et al. Role of SPET/CT in the preoperative assessment of hyperparathyroid patients. *Radiol Med* 2006; 111: 999-1008.
29. Gallowitsch HJ, Mikosch P, Kresnik E et al. Comparison between ^{99m}Tc-tetrofosmin/pertechnetatesubtraction scintigraphy and ^{99m}Tc-tetrofosmin SPET for preoperative localization of parathyroid adenoma in an endemic goiter area. *Invest Radiol* 2000; 35: 453-9.
30. Slater A, Gleeson FV. Increased sensitivity and confidence of SPET over planar imaging in dual-phase MIBI for parathyroid adenoma detection.*Clin Nucl Med* 2005; 30: 1-3.
31. Noussios G, Anagnostis P, Natsis K. Ectopic parathyroid glands and their anatomical, clinical and surgical implications. *Exp Clin Endocrinol Diabetes* 2012; 120 : 604-10.

32. Phitayakorn R, McHenry CR. Incidence and location of ectopic abnormal parathyroid glands. *Am J Surg* 2006; 191: 418-23.
33. Krausz Y, Bettman L, Guralnik L et al.Technetium-99m-MIBI SPET/CT in PHPT. *World J Surg* 2006; 30 :76-83.
34. Kaczirek K, Prager G, Kienast O et al. Combined transmission and ^{99m}Tc-MIBI emission tomography for localization of mediastinal parathyroid glands. *Nuklearmedizin* 2003; 42: 220-3.
35. Egger M, Zellweger-Zahner T, Schneider M et al. Language bias in randomised controlled trials published in English and German. *Lancet* 1997; 350: 326-9.

A pelican nest on an electric pole often seen in greek villages.