Comparison of ^{99m}Tc-MIBI planar scintigraphy, SPET/CT and ultrasonography in detection of parathyroid adenoma in patients with primary hyperparathyroidism

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Abstract

Objective: Primary hyperparathyroidism (PHPT) is a common endocrine disease that is caused by a single adenoma in most of the cases. Surgical management is the mainstay and definitive treatment for parathyroid adenoma (PA). Minimally invasive surgical techniques are as effective as bilateral neck exploration with a lower risk of complications and better cosmetic results in patients with solitary PA. Accurate preoperative localization with imaging modalities is paramount for determining patients candidate for minimally invasive surgery. In this study we aimed to evaluate the diagnostic performance of technetium-99m-methoxyisobutylisonitrile (^{99m}Tc-MIBI) planar scintigraphy (PS), single photon emission tomography/computed tomography (SPET/CT) and ultrasonography (US) in patients with PHPT. **Material and Methods:** Fifty-eight patients with biochemical evidence of PHPT who underwent pre-operative imaging with parathyroid scintigraphy and US for detection and localization of PA and proceeded to surgery were included in the study. All patients underwent dual phase ^{99m}Tc-sesta MIBI parathyroid scintigraphy (early and delayed planar images and delayed SPET/CT). Data analysis was performed to evaluate the sensitivity, specificity, diagnostic accuracy and PPV of planar images, SPET/CT and US alone and combined US and SPET/CT. Histopathology was used as gold standard. **Results:** Sensitivity, specificity, PPV and diagnostic accuracy for detection of PA, 80,4%, 42,8%, 91,1% and 75,8% for PS; 80,4%, 57,7%, 91,1% and 77,5% for delayed SPET/CT; 88,2%, 85,7%, 97,8% and 87,9% for US and 94,1%, 71,4%, 96% and 91,3% for SPET/CT+US. Combined US and SPET/CT has been shown to increase sensitivity and diagnostic accuracy. The overall sensitivity of PS and SPET/CT didn't vary however additional information which is helpful for planning minimally invasive surgery gained from tomographic images. **Conclusion:** The combined use of US and SPET/CT has incremental value in accurately localizing PA over either technique alone. In the preoperative assessment of patients with PHPT combination of imaging methods allows selection of patients who would be suitable for minimally invasive surgery.

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Introduction

Primary hyperparathyroidism (PHPT) is the most common cause of hypercalcemia in the routine clinical setting and characterized by autonomous secretion and excess production of parathyroid hormone (PTH) mostly from a single adenoma (80%-85%), or in rare cases from multiple adenoma, parathyroid gland hyperplasia (5%-15%) or parathyroid carcinoma (<1%) [1]. Surgery is the only definitive treatment [2, 3]. Since PHPT is mostly caused by a single adenoma, resection of the adenoma results in durable cure. There are various methods of surgery and minimally invasive parathyroidectomy (MIP) methods developed recently and reduce the operation related risks and complications, operation duration, postoperative discomfort, and decrease the incision length [3].

In order to choose the candidates for MIP, it is very important to show the surgeon exact localization of the parathyroid adenoma preoperatively with imaging techniques [2, 3]. The imaging modalities used for localization of parathyroid adenomas (PA) are ultrasonography (US), four-dimensional computed tomography (4D CT), magnetic resonance imaging (MRI) and functional imaging techniques such as methoxyisobutylisonitrile (MIBI) scintigraphy and positron emission tomography (PET) [4]. There are pros and cons of each imaging technique and the clinician should consider the local experience, availability, and patient related factors. The most widely used techniques for localization are US and dual phase technetium-99m (^{99m}Tc)-sestamibi scintigraphy.

There are different imaging protocols and various radiotracers that are used during parathyroid scintigraphy such as dual-phase, dual tracer, planar, single photon emission tomography (SPET), SPET/CT imaging [5]. Dual phase ^{99m}Tc-sestamibi scintigraphy is based on the preferential uptake of sestamibi in the mitochondria-rich parathyroid adenoma cells. Technetium-99m-sestamibi has a faster washout from thyroid tissue than from enlarged parathyroid glands, and tracer retention identifies the presence of hyperfunctioning parathyroid tissue. Anterior planar scans are performed at 10-15min postradiotracer administration and following washout (90-120min). Delayed washout in a well-defined area suggests the location of the parathyroid adenoma. During SPET 3 dimensional images are provided instead of planar images which enable the clinician to understand the anatomic localization of the parathyroid lesion. By adding low dose CT with hybrid gamma cameras, SPET/CT is obtained with better resolution and lesion localization [4, 5]. There are reports in the literature with conflicting results evaluating the diagnostic performance and additional benefit of early and delayed planar images on scintigraphy, SPET only and SPET/CT [6-9].

Ultrasonography is the primary imaging modality for PA localization and is noninvasive, widely available with low cost [2]. However, it is subjective and diagnostic success depends on the experience of the operator and effected by the presence of thyroid nodules and diameter of the adenoma. Ectopic localization of the PA is also a challenging factor that decreases the sensitivity of US. There are plenty of reports in the literature depicting increased diagnostic accuracy and sensitivity when combining scintigraphy with US [10-13].

In this study, we aimed to determine and compare the diagnostic accuracy of dual early and late phase scintigraphy, ultrasound, SPET/CT and SPET/US combination in patients who underwent MIP.

Subjects, Material and Methods

Patient Selection

Fifty-eight patients who had biochemically proven PHPT and had US and dual phase ^{99m}Tc-MIBI parathyroid scintigraphy and underwent surgery after imaging were enrolled in this study. Their data was evaluated retrospectively. The preoperative Ca, P and PTH levels and post-operative histopathology results were recorded.

Scintigraphy imaging protocol

Early acquisition was performed at 15 minutes after intravenous injection of 740MBq ^{99m}Tc-MIBI. Planar images of the neck and chest were obtained in a 256x256 matrix, with a 20% energy window centered at 140keV photopeak using a dual-head SPET/CT system (GE Infinia Hawkeye 4, GE Healthcare, Buckinghamshire, UK) equipped with low-energy high-resolution parallel-hole collimators. Delayed planar imaging was performed at 2 hours and SPET/CT was performed immediately after acquisition of planar images. Single photon emission tomography images were acquired in a 128x128 matrix with a step and shoot protocol of 25 seconds per frame for a total of 64 frames. Reconstruction of the SPET was performed using an iterative reconstruction algorithm (two iterations and 10 subsets) both with and without CT-based attenuation correction and a Butterworth postprocessing filter (cut-off frequency 0.48 cycles/cm, order 10). The CT component of the imaging was acquired immediately after the SPET acquisition with the parameters included a slice step of 10 mm in helical mode, a current of 2.5mA and a voltage of 140kV.

Scintigraphy imaging analysis

Scintigraphy images were evaluated by two experienced nuclear medicine specialists. First they evaluated the early and delayed phase images. Then they combined dual phase images with SPET/CT. And in the last phase all imaging results (US, dual phase scintigraphy and SPET/CT) were combined and reevaluated. Focal areas of radiotracer involvement were considered as positive for parathyroid adenoma.

Ultrasonographic imaging

An Esaote Colour Doppler system (Model 796FDII; MAG Technology Co. Ltd., Yung-Ho City, Taipei, Taiwan) with a superficial probe (Model LA523 13e4, 5.5e12.5MHz) was used for US. The procedure was applied to patients in the supine position with their necks hyperextended and skin coated with acoustic material. During B-mode US, parathyroid lesion features, such as size, volume, neck location, echogenicity were recorded.

Statistical analysis

We used SPSS software (version 16.0, SPSS, Inc, Chicago, IL, USA) for data collection and analysis. Descriptive statistics are presented as means±standard deviation (SD) and medians (minimum-maximum) for continuous variables and as percentages (%) for categorical variables. We accepted the histopathology gold standard and calculated the sensitivity, specifity, positive predictive value and diagnostic accuracy of planar imaging, SPET/CT and SPET/CT+US. The correlation of results of imaging tests, histopathology reports with preoperative PTH and Ca levels were evaluated with Mann Whitney U Test.

Results

Fifty eight out of 130 PHPT patients who underwent surgery and had final histopathology report were enrolled. Fifty (86.2%) of 58 were female and 8 (13.8%) were male. The mean age of the patients was 5612.9 (25-80). The results of the DPS, SPET/CT, SPET/CT+US and US results were analyzed and compared with the histopathology results in order to see if the correct lesion could be localized. Histopathologic examination revealed single parathyroid adenoma in 51 (87.9%) of 58 patients and parathyroid hyperplasia in 3(5.1%), and no lesion could be found in remaining 4 cases.

None of the imaging techniques was positive in 3 cases of parathyroid hyperplasia. In 41 (80.3%) of 51 patients with parathyroid adenoma planar DPS and SPET/CT detected the right lesion successfully. Ultrasonography detected the lesion in 45 of 51 parathyroid adenomas (88%) whereas number of parathyroid adenomas that could be localized increased to 48 (94%) when US and SPET/CT findings were combined. Among all imaging protocols in patients with histopathological proven PA, the ones with successful PA localization preoperatively had higher serum Ca and PTH levels compared with patients with negative imaging (Table 1).

When we consider the surgery and histopathology result as the gold standard for determining the PA, sensitivity of DPS, SPET/CT, US and US+SPET/CT were 80,4%, 80,4%, 88,2% and 94,1%, respectively. Specifity of the tests were calculated as 80,4%, 80,4%, 88,2% and 94,1%.The highest calculated specifity was for US which was 85.7%. Diagnostic accuracy was 75.8% for DPS, 77.6 % for SPET/CT, 87.9% for US and the highest accuracy was calculated for combined US+SPET/CT as 91.4%. The diagnostic performances of imaging modalities are listed on Table 2. The strongest correlation between the imaging result and histopathology was observed in combination of US+SPET/CT (r:0.619, P<0,001) (Table 3).

Table 1. *Correlation of preoperative serum Ca and PTH with different imaging results.*

		PTH pg/mL		Ca (mg/dL)	
		Median (min-max)	P	Mean SD	P
Dual phase planar	PA (-)	103(73-1292)	0,056	11,34±1,71	0,852
	PA (+)	187 (69-2219)		11,03±1,00	
SPET/BT	PA (-)	113 (69-1292)	0,061	11,08±1,53	0,393
	PA (+)	188 (70-2219)		11,11±1,07	
US	PA (-)	146 (73-157)	0,81	10,68±0,63	0,182
	PA (+)	178 (69-2219)		11,21±1,27	
US +SPET/CT	PA (-)	133 (73-1292)	0,191	11,12±2,00	0,207
	PA (+)	178 (69-2219)		11,10±1,03	
Histopathology	PA (-)	117 (73-148)	0,049*	10,34±0,64	0,024*
	PA (+)	187 (69-2219)		11,21±1,20	

Table 2. *Sensitivity, Specifity, PPV, NPV and Accuracy of each and combined imaging technique.*

	Sensitivity	Specifity	PPV	NPV	Accuracy	TP	TN	FP	FN
Dual phase planar imaging	80,4%	42,8%	91,1%	23,8%	75,8%	41	3	4	10
SPET/CT	80,4%	57,1%	93,2%	28,5%	77,6%	41	4	3	10
US	88,2%	85,7%	97,8%	50%	87,9%	45	6	1	6
SPET/CT +US	94,1%	71,4%	96%	62,5%	91,4%	48	5	2	3

Table 3. *The best compatibility with histopathology could be provided with combination of US and SPET/CT which was 61.9% and positive correlation was statistically significant *P<0,05 ; **P<0,001*

		Planar	SPET/BT	US	US+SPET/CT
Histopathology	r	0,182	0,286*	0,595**	0,619**
	P	0,172	0,030	0,000	0,000

Discussion

Primary hyperparathyroidism is caused by inappropriate overproduction of PTH from the parathyroid glands and a common endocrinologic disease [1]. The gold-standard surgical management of PHPT is bilateral neck exploration (BNE) and identification of all 4 parathyroid glands. For single adenomas that are localized preoperatively, MIP are appropriate since they need a smaller incision and outcomes are similar to more extensive surgeries in regard to lower cost, shorter hospital stay, reduced patient discomfort [14, 15]. Imaging techniques, including ultrasound, sestamibi scans, and 4D-CT scans, have made identification of single parathyroid adenomas possible. However there is no widely accepted standard imaging algorithm for preoperative localization of PA. In this study we aimed to determine the best localization protocol for PA.

Most widely used imaging techniques in PHPT are US and DPS. Ultrasonography is the first one preferred for anatomic localization [4]. The operator can easily detect the enlarged parathyroid gland during examination. It is safe since carries no radiation, is cheap, easily accessible and well tolerated by the patients. However coexisting nodular disease, deep tracheal/esophageal or mediastinal localization decrease the sensitivity of US [8, 19-21]. The sensitivity of US for localizing PA changes between 64%-94,4% in different reports [4, 8, 12, 16, 17]. In our study sensitivity of US was found relatively higher (88.2%) which maybe explained by the experience of the endocrinologists working in a high volume tertiary center.

The most common radiotracer used in parathyroid imaging is ^{99m}Tc-sestamibi. There are different protocols for ^{99m}Tc-sestamibi parathyroid scintigraphy. In dual phase protocol which was evaluated in this study, early and late phase planar images are provided and parathyroid adenoma is discriminated from thyroid lesions by relatively late and slow clearance of the radiotracer [5]. Images can be obtained with pinhole, planar, SPET or SPET/CT. In this study we evaluated the results of dual phase early and delayed planar imaging and delayed SPET/CT. There are previous studies in the literature comparing with those different protocols but a standard imaging technique couldn't be defined yet [6, 7, 9, 11, 22-25].

In hybrid devices a low dose CT can be applied to SPET protocol and SPET/CT is obtained. Previous reports demonstrated that addition of SPET/CT to planar imaging increase the rate of detection of the PA [6, 7].

According to Lavely et al. (2007), compared 19 combination of early and late phase planar images with 98 planar SPET or SPET/CT images in different anatomic localizations and found that early phase SPET/CT with one of late phase imaging (planar, SPET or SPET/CT) has the highest sensitivity (>70%). In the same report sensitivity of combination early phase SPET with any late phase imaging was 61%-66% and early planar with delayed imaging combination was 56%-64%. In our Instuition's protocol we prefer late SPET images since early images can cause false positivity caused by concomitant thyroid nodules which is common in our country since it is a mild iodine deficiency area. In our study conducted with 58 patients sensitivity, specifity, positive predictive value (PPV) and diagnostic accuracy for DPS were 80,4%, 42,8% and 91,1%, 75,8%; for planar+delayed SPET/CT were 80,4%, 57,1%, 93,2%, and 77,6%, respectively. In our study addition of SPET/CT to DPS didn't increase the sensitivity whereas specifity and PPV were higher than DPS alone. Single photon emission tomography/CT didn't serve a sensitivity advantage but provided a better anatomic localization for the surgeon. Wong et al. (2015) reported a metanalysis of 24 studies with 1276 patients and the sensitivities of SPET/CT, SPET alone and planar imaging were detected as 86%, 74% and 70%, respectively. Study protocols in that metanalysis were heterogenous and included studies with early, late or combined protocols. In one of the studies included in the metanalysis sensitivity of SPET/CT was 28%, in the other studies it was between 71%-98%. In that metanalysis it was highlighted that hybrid SPET/CT cameras used for parathyroid scintigraphy could be broadly considered as 'early'-generation cameras, such as the GE Hawkeye (General Electric Medical System, Milwaukee, Wisconsin, USA) and Millenium (General Electric Medical Systems, Carrollton, Texas, USA), which use a very low exposure of 2.5mAs, producing nondiagnostic quality axial slices for localization alone, and 'later'-generation ameras such as the Symbia T series (Siemens Medical Systems, Erlangen, Germany) and GE Discovery (General Electric Healthcare, Milwaukee, Wisconsin, USA), which have CT acquisition parameters with slightly higher exposure (in mAs) that allows multiplanar reformats, potentially with advantages for visualization of an adenoma on the CT portion [7]. In our study the gamma camera had early generation very low dose CT with low quality of images (GE Infinia Hawkeye 4, GE Healthcare, Buckinghamshire, UK) which can partly explain relatively low additional value of SPET/CT to sensitivity when combined with planar images. However additional anatomic information increased the specifity and the accuracy of the test. In the clinical setting SPET/CT provides an advantage of better anatomic visualization of the lesion by the surgeons [5, 7-8]. In our study there wasn't any ectopically located adenoma but it is reported that SPET/CT can detect ectopic adenomas which are located in inferior, mediastinal, retrotracheal or posterior planes, better [7, 26]. In another metanalysis by Treglia et al. (2016) including 23 studies and 1236 patients, with PA, the pooled detection rate of ^{99m}Tc-MIBI SPET/CT in the preoperative planning of patients with PHPT was 88% (95% CI=84% to 92%) [28].

Combined ultrasound and parathyroid scintigraphy have been shown to increase the overall sensitivity for localization of solitary parathyroid adenomas, up to 95% [12, 29-32]. In our study best diagnostic procedure was combination of SPET CT and US which localized the PA in 48 of 51 (94%) patients with proven histopathology. Combination of those two imaging modalities were found to be superior than each one alone. Our study results are similar to Patel et al. (2010), who found the sensitivity of combined US and SPET/CT 95% and accuracy 91% for the preoperative localization of solitary parathyroid adenomas. In our study US was false positive in 6 patients in whom SPECT/CT could detect the right lesion. Ultrasonography could detect 9 of 10 PA in which SPET/CT resulted false negative. Those findings demonstrate that two techniques complete each other and can be used as each other's alternative. Ultrasonography can detect PA which are small, not rich in oxyphilic cells, with rapid MIBI washout that can't be visualized with scintigraphy. Comorbid thyroid diseases lower the diagnostic accuracy of both tests.

In our study, the PA with positive SPET/CT results had statistically insignificant higher Ca and PTH levels compared to imaging negative adenomas. We can explain the weak correlation due to better retention of ^{99m}Tc-MIBI in mitochondria rich oxyphilic cells compared with chief cells. There are conflicting results in the literature about correlation of MIBI SPET/CT positivity and serum Ca, PTH levels [23, 27, 33-35]. In our study this correlation was only significant for histopathologically proven PA.

Limitations of our study were its retrospective design and low number of patients. We couldn't evaluate the effect and additional value of imaging studies in the surgical approach of surgeons because of the retrospective nature. Since we enrolled only operated patients with PHPT, we couldn't make a comment on patients with negative imaging.

In conclusion, the combined use of US and SPET/CT has incremental value in accurately localizing PA over either technique alone. In the preoperative assessment of patients with PHPT combination of imaging methods allows selection of patients who would be suitable for minimally invasive surgery.

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