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Preoperative ^{99m}Tc-sestamibi scintigraphy in patients with primary hyperparathyroidism and concomitant nodular goiter: comparison of SPECT-CT, SPECT, and planar imaging

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Background **Investigations using a hybrid single photon emission computed tomography/computed tomography (SPECT-CT) scanning technique have been carried out in limited studies and have shown mixed results. However, the assessment of this technique for the detection of parathyroid adenoma in patients with a nodular goiter was performed in only one study with a small sample size. The aim of this prospective study was to assess the role of ^{99m}Tc-sestamibi parathyroid SPECT-CT scans for localization of parathyroid adenomas with a concomitant nodular goiter using ^{99m}Tc-methoxyisobutyl isonitrile (MIBI) scintigraphy and to compare it with SPECT and planar imaging.**

Methods **This study was conducted on 48 patients with primary hyperparathyroidism and nodular goiter, who were candidates for parathyroid surgery and had been referred for parathyroid scintigraphy. The patients underwent an early set of planar ^{99m}Tc-MIBI scanning procedures first, followed by SPECT and CT scannings, and finally a delayed set of planar ^{99m}Tc-MIBI scannings. Sensitivity, specificity, negative and positive predictive values, and accuracy were determined on a per-parathyroid-gland basis for each scanning method, as defined by histology and follow-up.**

Results **The surgery was successful in 48 out of 50 patients with primary hyperparathyroidism concomitant with thyroid nodularity, and data were completed for 80 sites in 48 patients. The accuracy of SPECT-CT in correctly identifying a parathyroid adenoma was 85.00, versus 75.00% for SPECT ($P=0.01$, significant). The sensitivity and specificity for SPECT-CT were 77.55 and 96.77%, respectively, versus 67.34 and 87.09%, respectively, for SPECT ($P=0.12$ and 0.12, not significant). There were nine sites that showed better localization on SPECT-CT scans relative to SPECT images, of which five sites were located in the ectopic regions.**

Conclusion **The results of our study indicate that SPECT-CT is more accurate than sestamibi planar imaging and SPECT for the preoperative identification of parathyroid lesions in patients with primary hyperparathyroidism concomitant with thyroid nodularity. Also, we would recommend the use of SPECT-CT for a workup of all patients with ectopic glands who are scheduled for minimally invasive parathyroid surgery.** *Nucl Med Commun* **33:1070–1076** © **2012 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

Bilateral neck exploration as the traditional surgical approach in patients with primary hyperparathyroidism has been replaced recently by limited surgical procedures, such as unilateral neck exploration, minimally invasive parathyroidectomy, and endoscopic surgery, which are feasible only with preoperative localization of a solitary parathyroid adenoma [1].

In addition, the diagnostic imaging methods for parathyroid localization have progressed greatly, allowing identification and localization of obscure and ectopic abnormal parathyroid glands before parathyroid surgery, which increases successful surgical manipulation and decreases the need for reoperation [2].

Most studies demonstrate the superior accuracy of single photon emission computed tomography (SPECT) imaging for the detection and localization of hyperfunctioning parathyroids, as compared with the planar method [3–6], but this was not seen in all previous investigations [7,8]. In addition, there is a wide variety of parathyroid

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scintigraphy protocols: a single set of SPECT images, either early or delayed [4,8]; a dual-phase SPECT [9,10]; a pinhole SPECT [11]; and the planar method.

The integration of computed tomography (CT) with SPECT, either by off-line software fusion [12] or by hybrid SPECT-CT techniques [10,13], has the potential to improve the accuracy of parathyroid scintigraphy [14].

Investigations using hybrid SPECT-CT techniques have been carried out in limited studies and have shown controversial results [10,13]. However, the assessment of this technique in the detection of parathyroid adenoma in patients with a nodular goiter was performed in only one study with a small sample size [15].

The aim of this prospective study was to assess the role of ^{99m}Tc-sestamibi parathyroid SPECT-CT in the localization of parathyroid adenomas with concomitant nodular goiter using ^{99m}Tc-methoxyisobutyl isonitrile (MIBI) scintigraphy and compare it with SPECT and planar imaging [1].

Materials and methods

Participants

This study was conducted on 97 patients with primary hyperparathyroidism who were candidates for parathyroid surgery and had been referred to the nuclear medicine department of Erfan hospital for parathyroid scintigraphy. Endocrine specialists confirmed primary hyperparathyroidism in accordance with their history and laboratory test values [parathyroid hormone (PTH), Ca, P, Cr, and 25-hydroxy-vitamin D3]. The patients were recruited from some clinics and university hospitals in Tehran between May 2009 and August 2010. They underwent early planar ^{99m}Tc-MIBI scanning first, followed by SPECT, CT, and finally a set of delayed planar ^{99m}Tc-MIBI scanning procedures.

Before scintigraphy, all patients underwent a careful physical examination to detect the presence of palpable thyroid nodules, and 50 patients with a nodular goiter were included in this study.

The study complies with the Declaration of Helsinki and was approved by the institutional ethics committee of Shahid Beheshti University of Medical Science; all patients gave their written informed consent.

Imaging protocols

The patients received 740 MBq (20 mCi) of ^{99m}Tc-MIBI by intravenous injection. Anterior planar projections of the neck and chest were acquired 20 and 120 min after the administration, each time for a 10-min duration, using a high-resolution low-energy parallel hole collimator and a large-field-of-view dual-detector camera with a mounted CT scanner (Symbia-T; Siemens Medical Systems, Erlangen, Germany). SPECT images of the same area were obtained immediately after the planar acquisition at 20 min after administration, using 60 frames at 25 s/frame and 3° angles, under a step-and-shoot protocol. The images were compiled into a 128×128 matrix and reconstructed by a two-dimensional ordered-subset expectation maximization iterative method (four subsets and eight iterations). The CT part was acquired at a slice step of 2 mm, a current of 20 mA, and a voltage of 130 kV, after implementation of SPECT.

Image interpretation

Scintigraphic data were interpreted by three nuclear medicine specialists, with differences in judgment resolved by consensus. They read the images while being unaware of any clinical or laboratory information about the patients. Each finding was allocated an anatomic location and scored on a three-point scale of diagnostic impression (1, negative; 2, equivocal; 3, positive) for a parathyroid lesion. A discrete focus of increased MIBI activity in the neck, or focal uptake in the mediastinum, was considered positive for a parathyroid adenoma on scintigraphy. The readers sequentially scored the planar images, the SPECT images, and finally the SPECT/CT images for each patient.

Bilateral or unilateral surgical neck exploration was carried out for each patient by experienced parathyroid surgeons. The choice of the surgical method was made according to preoperative localization findings and/or the surgeon's practice. An attempt to recognize all parathyroid glands was made at the time of surgery, and the location of abnormal parathyroid glands, gross surgical findings, size of excised parathyroid glands, and histopathologic findings were recorded.

Surgical cure was approved by histopathologic verification of the removed abnormal parathyroid tissue, with a decrease in serum calcium and PTH levels to the normal range.

Statistical analysis

The data are presented as mean ± SD. To estimate the statistical parameters for each of the three imaging techniques, scores 1 and 2 were considered negative and score 3 was considered positive. Adenomatous parathyroid glands that showed radiotracer activity on the scans were defined as true-positive findings. Nonparathyroid lesions, especially thyroid nodules or normal parathyroid glands without abnormal radiotracer activity on the scans, were defined as true-negative findings. Activity in a nonparathyroid lesion, especially in a thyroid nodule that showed radiotracer activity on the scans, was defined as a false-positive (FP) finding. A parathyroid lesion confirmed by surgery, which had not been identified by imaging techniques, was defined as a false-negative result. Sensitivity, specificity, negative and positive predictive values, and accuracy were determined on a per-parathyroid-gland basis for each scan method, as defined by histology and follow-up (normal PTH level and calcaemia). The McNemar test was used to compare the statistical parameters of the three

methods: planar, SPECT, and SPECT-CT. A *P*-value of less than 0.05 was considered significant. Statistical analysis was performed using an IBM computer and MedCalc software, version 11.3 (MedCalc Software, Mariakerke, Belgium), and also PASW software, version 18.0 (SPSS Inc., Chicago, Illinois, USA).

Results

The surgery was successful in 48 of 50 patients with primary hyperparathyroidism concomitant with thyroid nodularity, and data were completed for 80 sites in 48 patients. Two patients who underwent unsuccessful surgery had thyroid nodules, and one included a papillary carcinoma. All except one case required only one operation. In total, 49 parathyroid adenomas were detected in 48 cases. Three patients had MEN 1 syndrome. There were 38 cases of multinodular goiter, eight large multinodular goiters (> 100 g), and two patients with nodular goiters upon clinical examination by an expert endocrinologist, with all findings confirmed on CT scans.

The study included 33 women and 15 men (mean age: 59.44 ± 11.29; range: 30–85 years).

The mean calcium level was 11.22 ± 0.74 mg/dl (normal range: 9–10.5 mg/dl), phosphor level was 2.73 ± 0.49 mg/dl (normal range: 2.5–4.5 mg/dl), and PTH level was 251.89 ± 405.23 pg/ml (normal range: 15–65 g/ml). The mean size of adenoma was 16.00 ± 9.29 mm.

The location of adenoma as reported in the surgical note was as follows: 13 adenomas in the lower left thyroid lobe, seven adenomas in the left upper thyroid lobe, four adenomas in the right upper thyroid lobe, 17 adenomas in the right lower thyroid lobe, two adenomas in the thyrothymic ligament, four adenomas in the tracheoesophageal groove, one adenoma in the aortopulmonary window, and one adenoma in the thymus.

Furthermore, the precise localization of parathyroid adenoma as seen on SPECT and SPECT-CT findings according to its exact location on surgery was compared. SPECT-CT relative to SPECT showed nine sites with better localization, as follows: three adenomas in the right lower thyroid lobe, one adenoma in the left lower thyroid lobe, one adenoma in the thyrothymic ligament (Fig. 1), three adenomas in the tracheoesophageal groove (Fig. 2), and one adenoma in the thymus.

Both SPECT and SPECT-CT showed good sensitivity and specificity for the diagnosis of parathyroid adenoma (Table 1). The accuracy of planar, SPECT, and SPECT-CT in the diagnosis of parathyroid adenoma was 66.25, 75.00, and 85.00%, respectively.

The accuracy of SPECT-CT in correctly identifying a parathyroid adenoma was 85.00 versus 75.00% for SPECT ($P = 0.01$, significant). The sensitivity and specificity for this attribute were 77.55 and 96.77%, respectively, for SPECT-CT, compared with 67.34 and 87.09%, respectively, for SPECT ($P = 0.12$ and 0.12, not significant) (Table 1).

In addition, SPECT-CT showed higher sensitivity, specificity, and accuracy compared with the planar method ($P = 0.01$, 0.02, and 0.00, respectively) (Table 1). Furthermore, SPECT did not show a statistically significant sensitivity, specificity, or accuracy relative to the planar method ($P = 0.34$, 0.50, and 0.16, respectively).

Discussion

As there is an increasing trend toward unilateral or limited surgical neck explorations for the treatment of primary hyperparathyroidism, preoperative detection and localization investigations have become necessary to distinguish single-gland from multigland disease, to differentiate concomitant thyroid pathology, and also to identify eutopic and ectopic parathyroid lesions [16].

In this context, sestamibi imaging as a widely accepted technique shows the identification of hyperfunctioning parathyroid glands on the basis of their activity. However, there are three main scintigraphic methods, including planar, SPECT, or SPECT-CT, and there is not sufficient evidence for SPECT-CT use in routine practice [14,17].

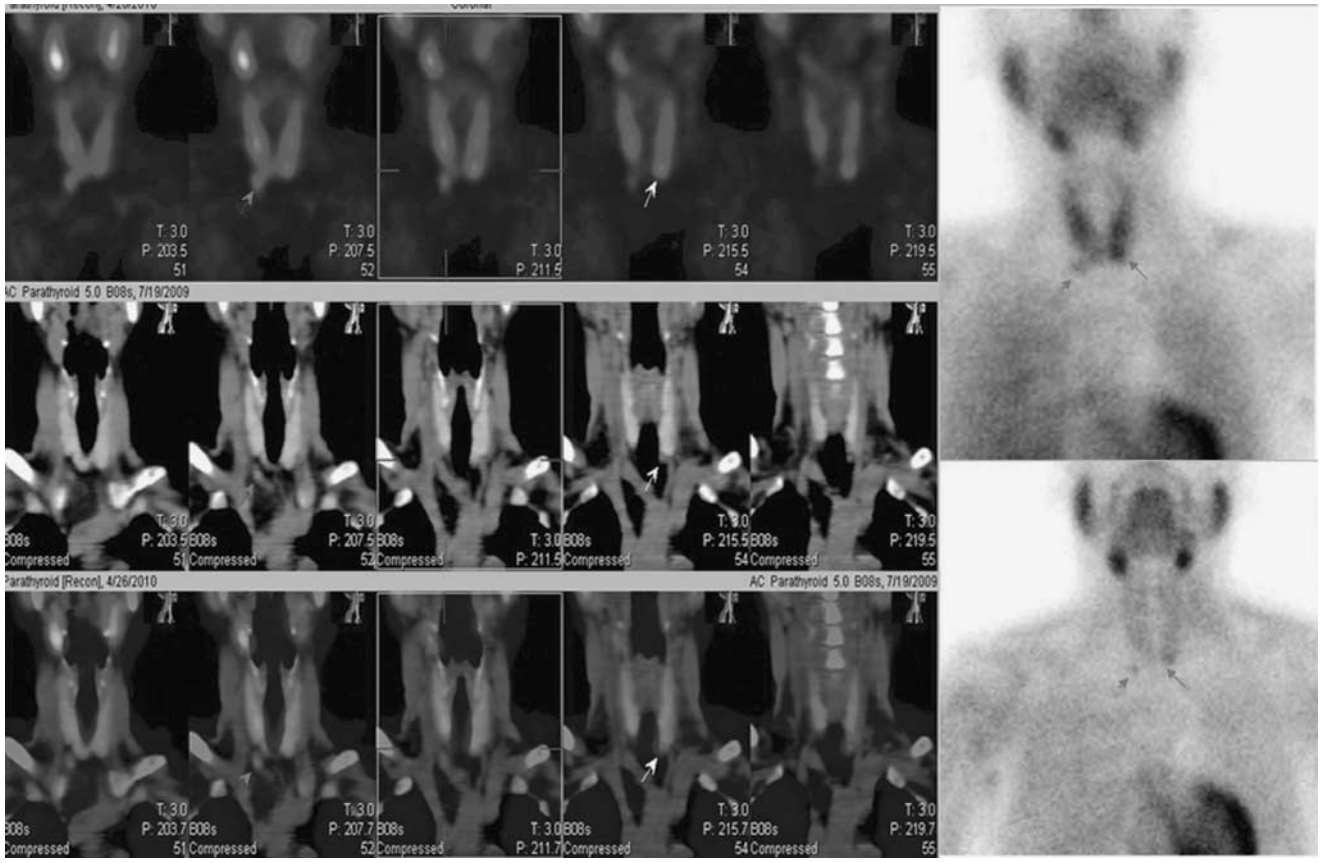
Planar MIBI scintigraphy has typically been the primary imaging technique for preoperative localization of adenomas, with a sensitivity range of 74–87% [18]. Previous studies have demonstrated greater sensitivity using MIBI-SPECT [4,19,20].

Recently, as an alternative approach, hybrid SPECT-CT, which incorporates a SPECT camera with a CT scanner in a single apparatus, has the benefit of sequentially obtaining SPECT and CT projections of the patient in the same position on a single imaging bed [14].

Our present study suggests that the SPECT-CT modality is more accurate than planar and SPECT techniques for parathyroid lesion localization, although the sensitivity and specificity were not statistically significant alone. This improvement in accuracy is mainly because of the ability of SPECT-CT to better characterize SPECT findings on the basis of their congruent CT findings [21]. In some cases, this leads to proper categorization of SPECT findings either as sestamibi-avid nonparathyroid lesions or as artificial findings, thus diminishing FP findings.

In a comprehensive study by Lavely *et al.* [10], the three main image acquisition techniques, planar imaging, SPECT, and SPECT-CT scintigraphy, were applied to 98 patients with primary hyperparathyroidism resulting from single adenomas and were compared with surgical findings. For each patient, planar imaging, SPECT, and SPECT-CT at 15 min and 2 h after sestamibi administration were carried out. Parathyroid localization had a sensitivity of 34% for single-phase early planar views,

Fig. 1



The planar methoxyisobutyl isonitrile scintigraphy of a 34-year-old patient with primary hyperparathyroidism and concomitant multinodular goiter at 20 min (upper right) and 120 min (bottom right) showing positive activity in the right lower lobe of the thyroid and equivocal activity in the left lower lobe of the thyroid (arrows). The single photon emission computed tomography (SPECT) views (upper row) show localization of parathyroid adenomas in the lower right and left thyroid lobes (arrows). The hybrid SPECT/computed tomography (CT) images on the lower row also show the precise localization of the parathyroid adenoma in the left lower thyroid and also the thyrothymic ligament (arrows). The center row is a CT image of the same patient. During surgery, an 8-mm-diameter adenoma in the thyrothymic ligament and a 9-mm adenoma in the left lower thyroid lobe were excised.

45% for single-phase delayed planar views, 57% for dual-phase planar images, 54% for single-phase early SPECT, 54% for single-phase delayed SPECT, and 62% for dual-phase SPECT, which increased to 73% sensitivity for dual-phase studies with early SPECT-CT. They recommended using early SPECT-CT accompanied by any delayed (2 h) imaging method or dual-phase acquisition as a routine practice.

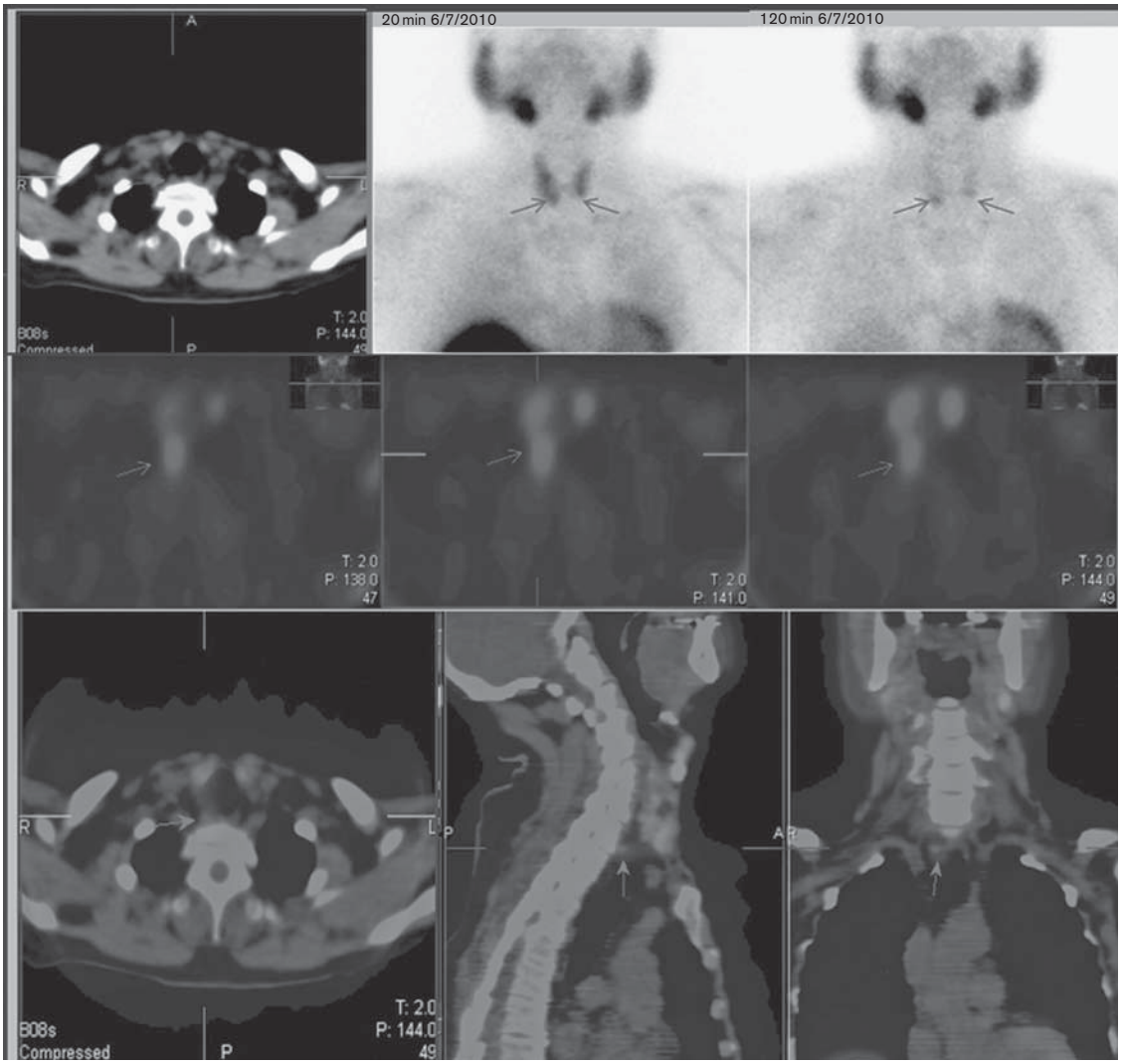
In our study, the dual-phase planar sensitivity was 59.18%, with an accuracy of 65.47%, which is similar to the investigation by Lavely *et al.* [10]. The sensitivity for single-phase early SPECT was 67.34%, which is more than the above and may be a result of testing a different population.

Other studies have shown similar sensitivities with more remarkable specificity for SPECT-CT in localizing parathyroid adenomas. In comparing SPECT with SPECT-CT images of 61 patients with primary hyperparathyroidism, although the sensitivities of SPECT (71%) and SPECT-CT (70%) were the same ($P = 0.779$), the specificity of SPECT-CT (96%) was considerably greater than that of SPECT alone (48%; $P = 0.006$) [14]. In another investigation on 116 patients with a single adenoma, sensitivity for SPECT-CT was 88% and that for SPECT was 59%. Specificity for SPECT-CT was 99% and that for SPECT was 95% [22]. Both studies demonstrated that SPECT-CT fusion was superior to SPECT images alone in the identification of parathyroid adenomas.

In a report on 28 patients undergoing reoperative surgery for a 'missed' parathyroid gland, SPECT-CT was able to predict the exact location of the abnormal gland in 86% of patients, whereas sestamibi-SPECT was successful in only 43% of cases ($P < 0.004$) [23].

Further investigations demonstrated that hybrid SPECT-CT imaging is often helpful in the detection and localization of ectopic parathyroid adenomas [24].

Fig. 2



The planar methoxyisobutyl isonitrile scintigraphy of a 61-year-old patient with primary hyperparathyroidism and concomitant multinodular goiter at 20 min (center column of the upper row) and 120 min (right column of the upper row) showing positive activity in the right lower lobe of the thyroid and equivocal activity in the left lower lobe of the thyroid (arrows). The single photon emission computed tomography (SPECT) views (middle row) show localization of the parathyroid adenoma in the posterior of the lower right lobe of the thyroid (arrow). The hybrid SPECT/computed tomography (CT) images on the lower row show the precise localization of the parathyroid adenoma on the right side of the tracheoesophageal groove (arrow). The left column of the upper row is a CT image of the same patient. During surgery, an 8.5-mm-diameter adenoma on the right side of the tracheoesophageal groove was excised. The left lower activity on planar views was a thyroid nodule.

Table 1 The accuracy of different scintigraphy procedures in parathyroid adenoma diagnosis

	True positive	False positive	True negative	False negative	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Planar	29	7	24	20	59.18	77.41	80.55	54.54	66.25
SPECT	33	4	27	16	67.34	87.09	89.18	62.79	75.00
SPECT-CT	38	1	30	11	77.55	96.77	97.43	73.17	85.00

NPV, negative predictive value; PPV, positive predictive value; SPECT-CT, single photon emission computed tomography/computed tomography.

Another study, with participant characteristics similar to those of ours, compared SPECT-CT with SPECT in 33 subgroups of patients with multinodular goiters and primary hyperparathyroidism. After cervical ultrasounds, all 33 patients underwent sestamibi planar scintigraphy, but SPECT or SPECT-CT was also performed on 18 or 15 patients, respectively [15]. SPECT-CT showed higher sensitivity compared with SPECT (87.5 vs. 55.6%;

$P = 0.0001$) and also higher positive predictive value (87.5 vs. 62.5%; $P = 0.0022$) for correct detection of parathyroid adenoma; although the specificity of SPECT-CT was greater than of SPECT, it was not significant (95.5 and 88.5%, respectively). They recommended that SPECT-CT be routinely performed for patients with primary hyperparathyroidism and multinodular goiter. Our study showed a nonsignificant increase in the sensitivity and specificity of SPECT-CT relative to SPECT and a significant difference in accuracy, which may have been because of a larger sample size in our patient numbers.

Furthermore, Neumann *et al.* [14] compared the diagnostic accuracy of ^{99m}Tc-sestamibi/^{123}I subtraction SPECT with SPECT-CT for the identification of abnormal parathyroid glands in patients with primary hyperparathyroidism and showed only higher specificity of SPECT-CT relative to SPECT. The sensitivities of SPECT and SPECT-CT were similar (71 vs. 70%; $P > 0.05$). The specificity of SPECT-CT was considerably greater than that of SPECT (96 vs. 48%; $P < 0.05$) [14].

In contrast, Gayed *et al.* [13] performed a comparison study on 32 patients and concluded that SPECT-CT did not provide remarkable additional clinical information to conventional SPECT for parathyroid imaging, except in locating ectopic parathyroid glands; in addition, omitting the CT component of the SPECT-CT acquisition would save time and reduce radiation exposure and expense [13].

In the current investigation, we detected nine adenomas with better localization, including four eutopic and five ectopic adenomas, in addition to better accuracy, which could mainly be explained as a result of using a different population sample. The localization was compared with adjacent organs such as the thyroid gland, trachea, esophagus, and great vessel. Similarly, in our investigation, SPECT-CT showed more lesions in all eutopic adenomas, except in the left upper thyroid region and five ectopic regions. The ability of SPECT-CT to detect ectopic adenomas seems to be its major advantage.

Furthermore, when there is an abnormal activity in the lower level of the thyroid in planar images, SPECT-CT may help to distinguish a descended superior parathyroid adenoma from an inferior parathyroid adenoma, which cannot be differentiated on planar images [25]. It is the most important point for surgeons so that they can properly resect the adenoma. In the present study, ectopic adenomas were found in eight of the 48 patients (16.66%). This relatively high number of ectopic lesions, compared with the 8–11% in the literature [26], may be due to the initial referral bias of participants and could, in part, be the reason for the noteworthy benefit provided by SPECT-CT in the current study [1].

More investigations concluded that SPECT-CT improves the ability to localize abnormal parathyroid glands, rather than planar scintigraphy or SPECT alone. This valuable role of SPECT-CT in general oncologic patients, including those with parathyroid adenomas, is due to the acquisition of both functional and anatomic images from SPECT and CT, which has been demonstrated to be synergistic as against complementary [27]. Because of challenges in the acquisition of SPECT-CT and the potential increase in patient radiation doses [22,24], the benefits of its improved accuracy need to be evaluated by future confirmatory imaging studies.

The accuracy of the studies in the detection of parathyroid adenomas may be adversely affected by some factors. In a study to assess the parameters that predicted an accurate scan using a multivariate logistic regression model, it was observed that a higher percentage of oxyphil cells ($P = 0.03$), heavier gland ($P = 0.03$), female sex ($P = 0.04$), and gland location in the lower position ($P = 0.04$) were associated [28]. Another study showed that a positive ^{99m}Tc-MIBI scan is most associated with adenoma size and ionized calcium level [29], which will be demonstrated later [14].

It also suggested that the accuracy of ^{99m}Tc-MIBI-SPECT in the identification of residual hyperactive glands is considerably lower before reoperative parathyroidectomy for persistent hyperparathyroidism than before initial surgery [30].

In addition, other studies demonstrated that failure of sestamibi scans was more common in cases of primary hyperparathyroidism with multinodular goiter [31]. Furthermore, patients with hypovitaminosis D are more likely to reveal positive results on a sestamibi scan [32].

In brief, our study demonstrated a potentially higher accuracy for SPECT-CT compared with planar and SPECT scintigraphic procedures. Particularly, SPECT-CT may decrease FP results attributable to thyroid nodules and false-negative results attributed to adenoma of a cystic nature or associated with concomitant thyroid nodules, which may go unidentified by scintigraphy. It also showed that SPECT-CT was able to validate the inconclusive findings of SPECT or planar images.

Finally, it should be mentioned that, although the findings of this study are encouraging, they must be considered as groundwork because of the relatively small sample size of our patient series. Hence, further well-designed studies of patients with primary hyperparathyroidism, both with and without previous neck surgery, as well as with and without thyroid nodularity, should be implemented to confirm these findings.

Conclusion

The results of our study indicate that SPECT-CT is more accurate than sestamibi planar and SPECT for the preoperative identification of parathyroid lesions in patients with primary hyperparathyroidism concomitant

with thyroid nodularity. Also, we would recommend the use of SPECT-CT for the workup of all patients with ectopic glands who are scheduled for minimally invasive parathyroid surgery. However, a larger study should be conducted to assess the clinical procedures, cost-effectiveness, and exposure rate of SPECT-CT relative to SPECT.

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Conflicts of interest

There are no conflicts of interest.

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