

## Parathyroid adenoma Localization

Shirzad Nasiri<sup>1</sup>, Ahmadsreza Soroush<sup>2</sup>, Amir Pejman Hashemi<sup>3</sup>,  
Anushiravan Hedayat<sup>4</sup>, Kianoush Donboli<sup>5</sup>, Farhad Mehrkhani<sup>6</sup>

*Department of General Surgery, Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran.*

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### Abstract

**Background:** Bilateral neck exploration is the gold standard for parathyroid adenoma localization in primary hyperparathyroidism. But surgeons do not have adequate experience for accurate surgical exploration and new methods are developed for surgery like unilateral exploration and minimally invasive surgery, thus, preoperative localization could reduce time and stress in surgical performance.

**Method:** 80 patients with documented primary hyperparathyroidism and with raised serum calcium and parathyroid hormone (PTH) were selected. The results of ultrasonographic localization for each patient were compared with findings of surgery and 99m technetium sestamibi scintigraphy. Also variables such as preoperative serum calcium, PTH level and adenoma weight were compared between patients who had localized and non-localized adenoma with ultrasonography or Sestamibi scan. The data was compared with student's t-test.

**Results:** In a prospective diagnostic tests accuracy study, 80 patients with primary hyperparathyroidism were enrolled. Ultrasonography images detected enlarged parathyroid glands in 61 of 80 patients (76.3%) with sensitivity of 83.5% and positive predictive value (PPV) of 89.7%. Sestamibi scintigraphy detected adenoma in 63 patients (78.8%) with sensitivity of 85% and PPV of 91.3%. There was no significant difference between ultrasonography and scintigraphy in localization of adenomas. Both ultrasonography and scintigraphy used for determining localization, and they located 73 adenomas (91.3%) with sensitivity of 97.3% and PPV of 93.5%.

**Conclusion:** Ultrasonography as an accurate method for localization of enlarged parathyroid glands in primary hyperparathyroidism, is comparable in overall utility with sestamibi scintigraphy. This study suggests a strategy for initial testing with one method, followed by the alternate imaging test if the first test happens to be negative.

**Keywords:** Primary hyperparathyroidism, Scintigraphy, Ultrasonography, Localization.

### Introduction

The incidence of primary hyperparathyroidism (PHPT) is increasing with rate of 42:100,000 per year. While in women over 60 years of age the average annual incidence rate approaches 190:100,000 per year (1). Whether this gradual rise reflects a true in-

crease in the incidence of PHPT, a greater use of routine testing of serum calcium or an altered referral pattern for surgery is not known. In recent years, minimal invasive parathyroidectomy has challenged the traditional bilateral neck exploration for PHPT and it is suggested that part of the increase is related to the introduction of these less inva-

1. (Corresponding author), Assistant professor of general surgery, Tehran University of Medical Sciences, Tehran, Iran. nasiri@razi.tums.ac.ir

2. MD., Associate professor of general surgery, Tehran University of Medical Sciences, Tehran, Iran. soroush1344@gmail.com

3. MD., Assistant professor of radiology, Tehran University of Medical Sciences, Tehran, Iran. pejman.hashemi@yahoo.com

4. MD, Associate professor of general surgery, Tehran University of Medical Sciences, Tehran, Iran. hedayat@tums.ac.ir

5. MD., Tehran University of Medical Sciences, Tehran, Iran. kia37@yahoo.com

6. MD., Tehran University of Medical Sciences, Tehran, Iran. mehrkhani@yahoo.com

sive techniques for parathyroid surgery (2). The new techniques are believed to offer some distinct advantages over the conventional bilateral approach for the patient. For instance, reducing the rate of early postoperative hypocalcemia, less postoperative pain and smaller scar, and thus there has been a global trend towards the acceptance among endocrine surgeons for these focused approaches (3).

Primary hyperparathyroidism, whether caused by an adenoma or hyperplasia, is surgically curable with a high rate of success (4). When performed by experienced surgeons, traditional surgical therapy-bilateral four-gland exploration is successful in more than 95% of cases (2,3). The development of unilateral and focused surgical approaches over the past decade, however, has made it even more imperative for imaging to accurately locate abnormal parathyroid glands before surgery. With optimized preoperative mapping, the success rate of these less invasive techniques equals that of the traditional bilateral approach (5). For many years, indications for preoperative localization studies in primary neck explorations for PHPT have been regarded unnecessary by many experts. However, others have advocated the use of routine preoperative localization, arguing that, not all surgeons have the full experience for accurate surgical exploration; it can result in a shorter operation time; avoid the need for bilateral neck exploration, and identify rare patients with ectopic parathyroid adenomas (4,6).

The aim of this study was to evaluate sensitivity, positive predictive value (PPV) and usefulness of high-resolution neck ultrasonography (US) and <sup>99m</sup>Tc-sestamibi scintigraphy (SS) as preoperative noninvasive localization procedures in patients with PHPT undergoing parathyroidectomy. We also evaluated factors affecting localization studies in PHPT.

### Methods

In a prospective study from 2005 to 2007, we enrolled patients with primary hyperparathyroidism who underwent parathyroidectomy

based on NIH criteria. Patients undergoing re-exploration for recurrent or persistent PHPT and patients with parathyroid hyperplasia were excluded. We recorded each patient's age, preoperative serum calcium level, preoperative intact parathyroid hormone (PTH) level, preoperative localization findings in SS and US, surgical findings, and parathyroid adenoma weight. We also recorded 24-hours postoperative serum calcium levels. In cases with multiple preoperative laboratory serum determinations, the most recent values were used for analysis. All patients were studied with a single experienced radiologist and operated on by a single experienced surgeon. Surgery was commenced on the side indicated by the scintigram. If the scintigram was negative, the left side was explored first. Bilateral exploration was performed in all patients, attempting to visualize all four parathyroid glands. Decision to terminate the surgery was based on gross morphology in combination with frozen section. All patients stayed overnight in the hospital. The diagnosis for parathyroid adenoma and hyperplasia were established by conventional histologic criteria (19). All of the patients achieved cure from the hyperparathyroidism state and remained normocalcemic in postoperative follow-up.

*Parathyroid scintigraph:* Dual phase scintigraphy scan (SS) was performed with a small field of view gamma camera (209 apex Elscint; General Electric; Milwaukee, WI) with a pinhole collimator. Ten planar anteroposterior images (dynamic acquisition, Matrix 128\*128) were obtained immediately after intravenous injection of 555  $\mu$ Bq <sup>99m</sup>Tc-methoxyisobutylisonitrile, sestamibi (early phase) and 2 hours later (late phase). A static image was taken of the thorax and mediastinum (300 seconds, Matrix 128\*128, parallel collimator) to search for ectopic glands.

*Ultrasonography:* The patients were scanned lying supine position with a pillow beneath the shoulders to slightly hyperextend the neck. Gray-scale imaging was per-

formed with a high-frequency linear transducer (EUB-525 scanner; Hitachi, Japan). The study included longitudinal images extending from the carotid artery to midline and transverse images extending from the hyoid bone superiorly to the thoracic inlet inferiorly. An enlarged parathyroid gland on grey-scale imaging appeared as a hypoechoic or isoechoic (in few cases) nodule posterior or lateral to the thyroid lobe, but separated from it and not adherent to surrounding tissues, or within the thyroid parenchyma. Gray-scale imaging was supplemented by color and power Doppler imaging to look for feeding vessels and vascularity of suspected adenomas shown at initial gray-scale imaging. Color and power Doppler imaging commonly shows a characteristic extra-thyroidal feeding vessel (typically a branch off the inferior thyroidal artery), which enters the parathyroid gland at one of the poles. Internal vascularity is also commonly seen in a peripheral distribution (7,8).

**Analysis:** From 80 enrolled patients, sixty-six (82.5%) were women –the male to female gender distribution was 1:4.7. The mean age was  $48 \pm 14$  years. Adenoma weight ranged from 0.4 to 10 grams (mean  $2.6 \pm 2.2$ ). Table 1 provides more information on patients' demographics, preoperative and postoperative biochemical data, and adenoma weight. Results of imaging studies as determined by the official radiology report were compared with the operative findings.

Correct localization or a true positive (TP) result was defined as identifying an abnormal parathyroid gland during surgery on the same location as reported by the imaging study. Abnormal parathyroid glands that were not identified by imaging technique were considered false negative (FN). Abnormalities reported by imaging that did not correspond to an abnormal parathyroid gland were considered false positive (FP). Sensitivity was calculated as  $TP / (TP + FN)$  and positive predictive value was calculated as  $TP / (TP + FP)$ . We also determined the sensitivity for combined results considering ultrasound and sestamibi as a single test. In this

analysis, the results were considered a TP if either studies correctly localized the abnormal gland. Abnormal parathyroid glands not imaged by either technique were recorded as FN, and all imaged abnormalities that did not correspond to abnormal parathyroid glands for both tests were recorded as FP. The TNs were not recorded in this analysis because of ambiguity of the definition.

All reported data were expressed as mean  $\pm$  SD and comparisons between different groups were performed using Student's t-test, Fischer exact test and chi-square test where appropriate. A p-value of less than 0.05 was considered statistically significant.

## Results

Eighty patients with primary hyperparathyroidism underwent US and SS examination for enlarged and overactive parathyroid glands, including sixty-six women and fourteen men. The mean age  $\pm$  SD was  $48 \pm 14$ . In most recent biochemical test prior to surgery, mean values ( $\pm$ SD) for serum calcium and intact PTH level was  $11.3 \pm 1.4$  mg/dl (range 10-17) and  $451.6 \pm 37.8$  ng/L (range 70-2028) respectively.

Histopathologic findings included 76 (95%) eutopic solitary adenomas, two (2.5%) ectopic adenoma (mediastinal), and two (2.5%) double adenoma. The mean size of removed parathyroid glands was  $14.8 \pm 0.88$  mm (range 4-41mm), and the mean weight of removed glands was  $2.6 \pm 2.2$  gr (range 0.4-15 gr).

The diagnostic accuracy values for SS, US and SS plus US are shown in Table 2. SS was positive in 86.25% of patients and accu-

Table 1. Patients' characteristics and preoperative markers.

Number of patients	80
Age (year's $\pm$ SD)	$48 \pm 14$
Female to male ratio	4.7
Preoperative markers	
Preoperative Calcium (mg/dl)	$11.3 \pm 1.4$
Phosphate (mg/dl)	$2.47 \pm 0.52$
Parathyroid hormone (ng/L)	$451.6 \pm 37.8$
Alkaline phosphatase (IU/l)	$571.75 \pm 137$
Adenoma weight (gr)	$2.6 \pm 2.2$

Table 2. Comparison between SS and US in 80 patients with primary hyperparathyroidism.

Method	positive results	TP	FP	FN	PPV	Sensitivity
US	68(85%)	61(76.3%)	7(8.75%)	12(15%)	89.7%	83.5%
SS	69(86.25%)	63(78.8%)	6(7.5%)	11(13.75%)	91.3%	85%
US and SS	78(97.5%)	73(91.3%)	5(6.25%)	2(2.5%)	93.5%	97.3%

TP: True Positive; FP: False Positive; FN: False Negative; PPV: Positive Predictive Value; SS: Scintigraphy Scan; US: Ultrasonography

Table 3. Serum calcium, serum parathyroid hormone, and weight of parathyroid adenomas in patients with primary hyperparathyroidism results by ultrasonographic localization.

Parameters	Negative Sonogram	Positive Sonogram	p
Serum calcium (mg/dl)	11.6±2	11.1±1.1	N/S
Serum PTH (ng/L)	363.9 ±27.6	480.8±40.5	N/S
Weight of adenomas (gr)	1.9 ±1.3	2.8 ±2.4	N/S

Data shown are in means ± SD. NS,  $p > 0.05$  by Student's t-test

Table 4. Serum calcium, serum parathyroid hormone, and weight of parathyroid adenomas in patients with primary hyperparathyroidism according to results of scintigraphic localization.

Parameters	Negative Scintigram	Positive Scintigram	p
Serum calcium (mg/dl)	11.6±2	11.1±1.1	N/S
Serum PTH (ng/L)	247.6 ±29.5	506.6±38.2	0.001
Weight of adenomas	2.4 ±2.2	2.7 ±2.2	N/S

Data shown are means ± SD. NS,  $p > 0.05$  by Student's t-test

rately localized the pathology in 78.8% according to surgery; including 62 of 76 patients with solitary eutopic parathyroid adenomas (81.5%), one patient with ectopic (mediastinal) adenoma and none of double adenomas. SS had a false positive rate of 7.5%, false negative rate of 13.75%, sensitivity of 85 % and PPV equal to 91.3%.

US was positive in 85% of patients and preoperatively localized the pathology in 76.3% of patients according to surgery; including 60 of 76 patients with solitary eutopic parathyroid adenomas (79%), one patient with double adenomas, but none of the patients with ectopic (mediastinal) adenoma. US had a false positive rate of 8.75%, false negative rate of 15%, sensitivity of 83.5% and PPV of 89.7%.

Combination of the two techniques yielded sensitivity of 97.3% and PPV of 93.5%. However, when each technique was separately interpreted to specify the glands at which side were affected (left or right), US and SS reached sensitivity and positive pre-

dictive values of 84.6% and 97% vs. 87% and 97.1% respectively. There were a statistically significant difference between the diagnostic accuracy of US, SS and "US plus SS" as shown via comparison between two proportion version 8. The combination of SS and US enhanced sensitivity when compared with either technique alone.

In order to determine which factors may interfere in the accuracy of US and SS, we compared preoperative serum calcium level, serum intact PTH level and parathyroid adenoma weight between those patients in which US and SS correctly localized the adenoma vs. those undetected. According to US results, the two groups had no significant difference in the factors mentioned (Table 3), whereas there was a significant difference in the mean intact preoperative PTH level of correctly localized vs. undetected patients examined by SS ( $506.6 \pm 38.2$  vs.  $247.6 \pm 29.5$   $p$ -value = 0.001). Other parameters between the two groups were of no statistical significance (Table 4).

## Discussion

The average size of a normal parathyroid gland is  $5 \times 3 \times 1$  mm; normal glands weigh between 40 and 50 mg. They are thus infrequently identified at imaging. Adenomas, on the other hand, are considerably larger, and have a mean mass of greater than 10 times of the normal parathyroid gland, and are thus often identified at cross-sectional imaging (9). Ultrasonography and  $^{99m}\text{Tc}$ -sestamibi scintigraphy were the dominant imaging techniques for preoperative localization of parathyroid adenomas. Numerous studies comparing these techniques suggest similar sensitivities and specificities for solitary adenoma detection (10,11). Localization accuracy is also improved when both studies are obtained preoperatively (12). Reported sensitivities for the detection of solitary parathyroid adenomas with preoperative ultrasonography range from 72% to 89% in recent large series (23). A meta-analysis performed by Ruda et al (21), encompassing 54 studies performed between 1995 and 2003 using ultrasonography for preoperative localization in primary hyperparathyroidism calculated ultrasonographic sensitivity for the detection of solitary adenoma, hyperplasia, and double adenoma to be 79% (95% confidence interval 77–80%), 35% (95% confidence interval, 30–40%), and 16% (95% confidence interval, 4–28%), respectively.

Sestamibi with  $^{99m}\text{Tc}$  is the most commonly used radiotracer for imaging the hyperfunctioning parathyroid glands and has been extensively studied in the setting of primary hyperparathyroidism. Sestamibi is taken up by both the thyroid and parathyroid glands, but adenomatous and hyperplastic parathyroid tissue shows more avid uptake of the radiotracer and often retains the radiotracer longer than adjacent thyroid tissue. Thus, initial planar images obtained shortly after the administration of radiotracer will show both thyroid and parathyroid tissue (12,13). Asymmetric foci of increased radiotracer uptake on early images can be seen, representing abnormal parathyroid tissue superimposed on the normal thyroid (14). Delayed images, obtained approximately 2

hours after radiotracer administration, are acquired to look for foci of retained radiotracer characteristic of hyperfunctioning parathyroid tissue (15,16).

A preoperative approach that combines both the anatomic information of sonography and the physiologic information of scintigraphy has been shown to predict the presence and location of solitary adenomas more accurately than either technique alone (17,18). Lumachi (et al), retrospectively reviewed preoperative sonography and  $^{99m}\text{Tc}$ -sestamibi findings in patients with proven solitary adenomas and found a combined sensitivity of 95% versus 80% for sonography and 87% for scintigraphy alone. Sonography has the advantage of being more specific regarding the site of an adenoma in relation to the thyroid gland (19). Scintigraphy clearly has an advantage in the detection of ectopic glands, particularly in the mediastinum (20). Given that the operation of choice for both multiglandular disease and double adenomas is a traditional bilateral approach, some endocrine surgeons have advocated that equivocal, negative, or discordant results on both preoperative studies warrant a nonselective approach because a high proportion of these patients will have multifocal disease (21,22).

Our current large study of 80 unselected patients, confirms the validity of US for preoperative localization of parathyroid adenomas in patients with PHPT. Ultrasonography provided positive imaging results in 85% of these patients. The reliability of positive ultrasonographic imaging was high with 89.7% positive predictive value based on correlation with surgical findings. Overall, US correctly predicted the surgical findings in 76.3% of patients in which enlarged parathyroid glands were found at surgery. The sensitivity of US was 83.5% in this study. The ability of ultrasonography to correctly localize enlarged parathyroid glands in primary hyperparathyroidism ranged from 44–87% (5–7), with the most recent studies reporting sensitivity of 67–87% in patients without prior parathyroid surgery (5,6). Previously reported positive predictive values of

89-97% are also in concordance with the present results (8). It is likely that the reported accuracy of US for preoperative localization of enlarged parathyroid glands is highly dependent on the skill and experience of the examiner (5).

In the current study, we compared dual phase parathyroid scintigraphy with ultrasonography. The significant positive result reported by SS (86.25%) as well correctly predicting the surgical findings in 78.8% of patients with PHPT, signifies the importance of utilizing SS as well. The results however were not significantly higher than the corresponding value for US, (85% positive result, and predicting the surgical findings in 76.3% of patients). The sensitivity and positive predictive value were similar for US and SS based on correlation with surgical findings (83.5%, 89.7% vs. 85%, 91.3%).

Among previous reports that have directly compared US and SS in patients undergoing initial parathyroid surgery, Mazzeo et al (1996) (13) and De feo et al (2000) (6) reported that the two methods were similar in their ability to correctly predict the surgical findings, while Casas et al (1993) (14) and Lumachi et al (2000) (1) found that the SS imaging was superior. In a large study encompassing US in 449 patients and SS in 700 of these patients, Cha Puis et al (1996) (15) found that the US provides better results.

We also determined whether the patients with more severe hypercalcemia, higher PTH levels, and larger abnormal parathyroid glands are more likely to have positive tests. The parameters in patients with localized adenomas detected by US and SS were compared with those undetected by localization studies. The only significant difference between the groups was mean intact preoperative PTH level which was higher in patients that their adenoma was detected by SS.

Taken together with the present study, it appears that there is a little overall difference between the ability of ultrasonography and scintigraphy to correctly localize abnormal glands in patients without prior surgery for PHPT.

## Conclusion

No statistically significant difference was evident for sensitivity and positive predictive values between ultrasonography and sestamibi scintigraphy for localization of pathologic parathyroid glands in patients with primary hyperparathyroidism. However, the study shows that the combination of SS and US enhances sensitivity and positive predictive value compared to either single technique. This is consistent with previous reports showing combined the two methods provides superior sensitivity (1,6,16).

In fact, SS and US can complement each other when both methods are applied. While SS provides functional information on nodules, US yields anatomic details (17). Unlike US, SS can visualize adenomas inferior to the thyroid in sonographically silent regions (18). Since surgical removal of adenomas is the only safe and final treatment of PHPT, both techniques give directions to the surgeon and may reduce operating stress and duration.

Overall, we suggest using US as the primary technique and reserving SS for cases with negative US results. The combination of both techniques is recommended if the surgeon is planning to perform unilateral neck exploration or minimally invasive surgery.

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