Accuracy of Combined Ultrasonography and $Tc^{99}m$ Sestamibi Scintigraphy in Preoperative Localization of Primary Hyperparathyroidism

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Background: Primary hyperparathyroidism remains one of the leading causes of hypercalcemia in the world today. To plan the appropriate surgery with the least morbidity for the patient, preoperative localization of the abnormal parathyroid gland is necessary. $Tc^{99}m$ sestamibi scintigraphy and ultrasonography are the two main modalities for imaging the parathyroid glands.

Patients and methods: This prospective interventional non-randomized non-controlled study was conducted in the Department of General Surgery at Ain Shams University hospitals in the period from April 2013 to October 2016 on thirty patients (7 males and 23 females) with primary hyperparathyroidism. Informed consent was obtained from all patients included in the study.

Results: Out of thirty patients, the combined preoperative ultrasonography and $Tc^{99}m$ sestamibi scintigraphy was accurate in twenty eight patients (93.33%) while they could not identify the pathological gland in two patients (6.66%). Accuracy of ultrasonography alone was 76.66% (23 patients), while accuracy of $T^{99}m$ sestamibi scan alone was 86.66% (26 patients).

Conclusion: The preoperative combination of ultrasonography and $Tc^{99}m$ sestamibi scintigraphy is effective with high accuracy in predicting the location of abnormal parathyroid gland(s) in patients with primary hyperparathyroidism.

Key words: Primary hyperparathyroidism, $Tc^{99}m$ sestamibi scintigraphy, ultrasonography.

Introduction

Hyperparathyroidism is a serious metabolic disorder. The incidence of primary hyperparathyroidism worldwide is about one in 1000 people; it is fairly uncommon actually sort of rare. It occurs in females more than males with average age about 58 years old, but it can occur at any age. The types of hyperparathyroidism are primary, secondary and tertiary.[1]

The majority of patients with parathyroid hormone elevation suffer from single parathyroid adenomas. In a systematic review conducted from 1995 to 2003, it was reported that 88.90% of cases with primary hyperparathyroidism were due to solitary adenomas, whereas 5.74% were multiple gland hyperplasia disease, 4.14% were double adenomas, and 0.74% were parathyroid carcinomas. To plan the appropriate surgery with the least morbidity for the patient, preoperative localization of the abnormal parathyroid gland is necessary.[2]

The treatment of primary hyperparathyroidism is surgical with a high success rate of 90-95%, even if preoperative localization procedures fail to identify the lesion. Recurrent and persistent hyperparathyroidism is usually related to aberrant or ectopically located glands or recurrent hyperplasia. Re-exploration is technically difficult with a higher morbidity and poorer success rate than the initial surgery.[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.[4] Several noninvasive preoperative localization modalities are available, including $Tc^{99}m$ sestamibi scintigraphy, ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI), and thallium-pertechnetate subtraction scanning. Most recently, four-dimensional CT and positron emission tomography (PET-CT) studies have also been used with success for parathyroid localization.[5]

$Tc^{99}m$ sestamibi scintigraphy is the most commonly used radiotracer for imaging the parathyroid glands and has been extensively studied in the setting of hyperparathyroidism.[5]

Ultrasonography and $Tc^{99}m$ sestamibi scintigraphy are the dominant imaging techniques for preoperative localization of hyperparathyroidism. Numerous studies comparing these techniques suggest similar sensitivities and specificities. Localization accuracy is also improved when both studies are obtained preoperatively.[6] A preoperative approach that combines both the anatomic information of ultrasonography and the physiologic information of $Tc^{99}m$ sestamibi scintigraphy has been shown to predict the presence and location of solitary adenomas more accurately than either technique alone.[7]

Over the past decade, the surgical treatment of primary hyperparathyroidism has changed from predominantly a bilateral approach with four gland exploration in all cases to unilateral and focused approaches guided by preoperative imaging showing single adenomas, ultrasonography and $Tc^{99}m$ sestamibi scintigraphy have assumed dominant roles in preoperative localization of solitary adenomas, focused approaches based on concordant findings from both techniques have cure rates equal to that of the traditional approach.[8]

The purpose of this study was to evaluate the accuracy of both ultrasonography and $Tc^{99}m$ sestamibi scintigraphy, together and alone, as techniques for identifying abnormal parathyroid gland(s) in patients with primary hyperparathyroidism.

Patients and methods

This prospective interventional non-randomized non-controlled study was conducted in the Department of General Surgery at Ain Shams University hospitals in Cairo, Egypt in the period from April 2013 to October 2016 on thirty patients (7 males: 23.3% and 23 female: 76.7%) with primary hyperparathyroidism, all patients with secondary, tertiary, recurrent or persistent hyperparathyroidism were excluded from the study as well as patients unfit for surgery. Informed consent was obtained from all patients included in the study.

All patients were subjected to full history taking, detailed general and local examination, laboratory studies including parathyroid hormone level, serum calcium, serum phosphorus, serum albumin, liver and kidney function tests, complete blood picture and coagulation profile, radiological studies including X-ray survey on skeleton, localization studies in the form of neck ultrasonography and $Tc^{99}m$ sestamibi scintigraphy and vocal cord examination.

Surgical technique: (Figure 1)

The procedure was generally carried out under general endotracheal anesthesia, patients were placed in the neck extension position, with a roll underneath the shoulders, care was taken not to hyperextend the neck, but to allow good exposure for the operation. The arms of the patient were lied alongside the body to allow the surgeon and the assistant to stand on both sides of the neck.

A transverse cervical incision was made and extended through the subcutaneous tissue and platysma muscle to the avascular areolar plane just deep to the platysma muscle. A subplatysmal flap was done in this plane up to the thyroid cartilage level, laterally to the sternocleidomastoid muscles and inferiorly to the sternal notch, using either sharp dissection or electrocautery along with blunt gauze dissection.

The strap muscles were separated in the median raphe and dissected laterally off the thyroid capsule from the thyroid cartilage to the sternal notch. The middle thyroid veins were ligated and divided to allow full mobilization of the thyroid lobes anteromedially. The recurrent laryngeal nerve (RLN) and inferior thyroid artery were identified, in most patients, the RLN lied in the tracheoesophageal groove, less commonly lateral to the trachea, on the right side care was taken to avoid injury to a non-recurrent laryngeal nerve, as this anatomic variant is seen almost exclusively on the right side.

Throughout the procedure, the operative field was kept bloodless as much as possible to prevent discoloring the parathyroid glands, which may impede their identification. Fine bipolar forceps was used to prevent diathermic injury to the RLN. The parathyroid glands are often surrounded by fat, therefore; any lobule of fat at the predilection sites of the parathyroid gland was inspected. Identification of the affected gland(s) was done and was compared with the preoperative studies to ensure that the correct gland was removed, four gland exploration was done for one case that was negative in both neck ultrasonography and Tc99m sestamibi scintigraphy.

After completion of the parathyroidectomy, the operative field was checked thoroughly to achieve meticulous hemostasis, drain may or may not be inserted, the raphe between the strap muscles was re-approximated with absorbable suture, the skin was closed with optimal cosmoses by absorbable sutures.

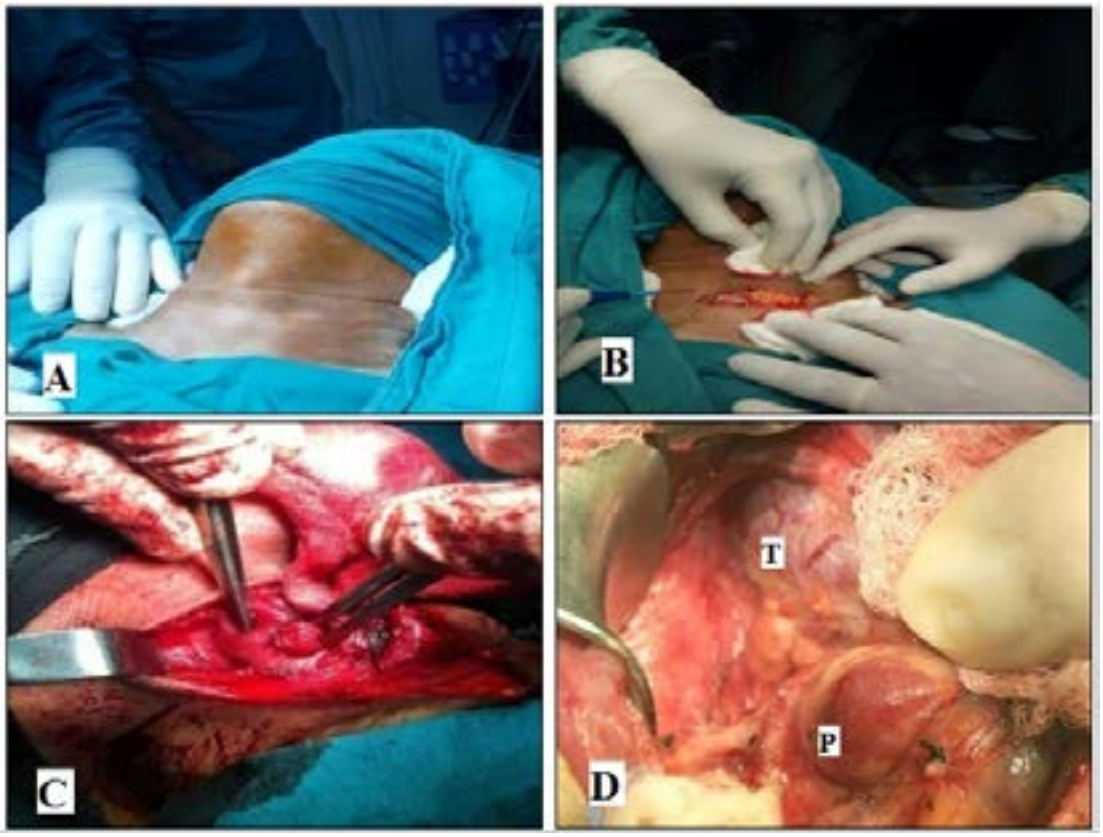

Fig 1A: Positioning of the patient, B: Neck incision, C: Dissection, D: Identification of the parathyroid gland (T= thyroid gland, P= parathyroid gland).

Postoperative assessment:

- Vocal cords assessment
- Measurement of serum calcium and parathyroid hormone level
- Relative efficacy of the preoperative localization studies had been prospectively evaluated and correlated with the intraoperative findings
- Histopathological examination of the removed gland(s)

Statistical methodology:

Data were coded and entered using the statistical package SPSS (Statistical Package for the Social Science) version 23.

Data was summarized using mean, minimum and maximum in quantitative data and using frequency (count) and relative frequency (percentage) for categorical data.

Results:

In this prospective interventional study, we had thirty patients with primary hyperparathyroidism which was localized preoperatively by neck ultrasonography and $Tc^{99}m$ sestamibi scintigraphy.

Patients' demographics: (Table 1)

Our study consisted of thirty patients: 7 males (23.3%) and 23 females (76.7%) with primary hyperparathyroidism.

The age varied between 23 years and 70 years with mean age 47.03 years (maximum was 70 & minimum was 23). Age was not a significant indicator for accuracy of pre-operative localization.

Table 1: Patients' demographics

			Number	Percentage
Sex	Male		7	23.3%
	Female		23	76.7%
Age	Mean	47.03	Minimum	Maximum
	47.03	11.44	23.00	70.00

Thirteen patients (43.33%) presented by bony aches, five patients (16.66%) by pathological fractures, 6 patients (20%) with renal stones, five patients (16.66%) by muscles weakness and one patient (3.33%) was discovered accidentally **(Table 2).**

Table 2: Different clinical presentations

		Percent-age	Percent-age
Clinical Presentation	Accidental	1	3.33%
	Renal stones	6	20%
	Bony aches	13	43.33%
	Pathological fractures	5	16.66%
	Muscle weakness	5	16.66%

All patients included in this study had elevated parathyroid hormone level and calcium level. The mean preoperative calcium level was 10.91 mg/dl (normal range for total calcium 8.5-10.5 mg/dl) (maximum was 13.5 mg/dl & minimum was 8.6 mg/dl). The mean preoperative parathyroid hormone level was 1589.8 pg/ml (maximum was 3200 pg/ml & minium was 822.6 pg/ml) (normal 10-71 pg/ml). Pre-operative parathyroid Ultrasonography was negative in five patients (16.66%), while identified abnormal gland in 25 patients (83.33%) (Left inferior gland in 6 patients, left superior gland in 2 patients, Right inferior gland in 12 patients and Right superior gland in 5 patients).

Pre-operative $Tc^{99}m$ sestamibi scintigraphy was negative in three patients (10%), while identified abnormal gland in 27 patients (90%) (Left inferior gland in 7 patients, Left superior gland in 3 patients, Right inferior gland in 11 patients and Right superior gland in 6 patients) **(Table 3).**

Table 3: Preoperative localization

Gland site	Preoperative ultrasonography		Preoperative $Tc^{99}m$ sestamibi scintigraphy	
	Number	Percentage	Number	Percentage
Left inferior	6	20.00%	7	23.33%
Left superior	2	6.66%	3	10.00%
Right inferior	12	40.00%	11	36.66%
Right superior	5	16.66%	6	20.00%
Negative	5	16.66%	3	10.00%

Operative findings:

According to the intraoperative findings, 29 patients (96.66%) were subjected for single gland resection and one patient (3.33%) needed unilateral clearance **(Table 4).**

Table 4: Intraoperative pathological glands' site finding

	Number	Percentage
Left inferior	7	23.33%
Left superior	4	10.00%
Right inferior	11	36.66%
Right superior	7	23.33%
Right inferior+ Right superior	1	3.33%

Regarding intraoperative complications, 28 patients (93.33%) didn't have any intraoperative complication. Only two patients had intraoperative bleeding, one due to slipped ligature of the middle thyroid vein which was controlled immediately by religation and the other one due to bleeding from the thyroid gland capsule during medial mobilization and was controlled by electrocautery diathermy.

The mean operative time was 76 minutes with minimum time 60 minutes and maximum 115 minutes.

Postoperative findings:

Regarding postoperative pathological examination of the resected gland(s), the results were single adenoma in 28 patients (93.33%), single adenomatous hyperplasia in one patient (3.33%) and double adenomas on the same side (right inferior and right superior glands) in one patient (3.33%).

As regarding postoperative calcium and parathyroid hormone levels, postoperative parathyroid hormone level decreased in all patients with mean level 49.87 pg/ml (Maximum was 110 pg/ml & minium was 22 pg/ml). Postoperative calcium level also decreased in all patients with mean level 7.72 mg/dl (maximum was 8.9 mg/dl & minimum was 5 mg/dl). Postoperative hypocalcemia was corrected by intravenous calcium infusion that needed hospital stay for 2-7 days before discharge on oral calcium **(Table 5).**

Table 5: Comparison between preoperative and postoperative parathyroid hormone and calcium levels showing significant correction of their levels (p value <0.001)

	Preoperative				Postoperative				
	Mean	SD	Mini-mum	Maxi-mum	Mean	SD	Mini-mum	Maxi-mum	P value
PTH	1589.8	711.65	822.6	3200	49.78	17.44	22.00	110.00	<0.001
Calcium	10.91	1.07	8.60	13.50	7.72	0.83	5.00	8.90	<0.001

Accuracy of preoperative localization studies:

The preoperative localization studies has been prospectively evaluated and correlated with the intraoperative findings, pathological examination of the removed gland(s) and postoperative calcium and parathyroid hormone levels. The combined preoperative ultrasonography and $Tc^{99}m$ sestamibi scintigraphy was accurate in 28 patients (93.33%) while they could not identify the pathological gland(s) in two patient (6.66%). Accuracy of ultrasonography alone was 76.66% (23 patients), while accuracy of $Tc^{99}m$ sestamibi scintigraphy alone was 86.66% (26 patients) **(Table 6).**

Table 6: Accuracy of preoperative localization studies

		Number	Percentage
Both are accurate		21	70%
Accurate ultrasonography alone		2	6.66%
Accurate $Tc^{99}m$ sestamibi scintigraphy alone		5	16.66%
Both are inaccurate		2	6.66%
Accuracy of ultrasonography alone	Accurate	23	76.66%
	Inaccurate	7	23.33%
Accuracy of $Tc^{99}m$ sestamibi scintigraphy alone	Accurate	26	86.66%
	Inaccurate	4	13.33%
Accuracy of combined ultrasonography and $Tc^{99}m$ sestamibi scintigraphy	Accurate	28	93.33%
	Inaccurate	2	6.66%

Discussion

This prospective study was conducted to delineate the accuracy of combined ultrasonography and $Tc^{99}m$ sestamibi scintigraphy in preoperative localization of the abnormal gland(s) in primary hyperparathyroidism and in turn will be reflected on the technique of surgery, the duration of hospital stay, hospital cost and patient's satisfaction. This study showed that the accuracy of combined ultrasonography and $Tc^{99}m$ sestamibi scintigraphy in preoperative localization of primary hyperparathyroidism was 93.33% while ultrasonography alone was accurate in about 76.66% and $Tc^{99}m$ sestamibi scintigraphy alone in 86.66% of patients.

Patel et al., 2010[9] found that the identification of adenomas relies on accurate interpretation of radiographic studies. Ultrasonography successfully identifies a solitary adenoma in 61%-92% of patients, and when combined with $Tc^{99}m$ sestamibi scintigraphy has been found to have greater than 90% sensitivity. Ultrasonography has a lower false positive rate than sestamibi scan (6% versus 29%) as well as a higher sensitivity for identifying single gland disease.

Solorzano et al., 2005,[10] who advocate preoperative ultrasonography as the only preoperative location test, found that ultrasonography and $Tc^{99}m$ sestamibi scintigraphy each correctly predicted uniglandular disease in 77% of patients, but this increased to 90% when both techniques were combined.

In opinion of Grant et al., 2008,[8] identification of solitary adenomas relies on accurate imaging studies, ultrasonography when combined with $Tc^{99}m$ sestamibi scintigraphy has been found to have accuracy greater than 93% while ultrasound alone was less than 80% and $Tc^{99}m$ sestamibi scintigraphy alone was 85%.

Cameron et al., 2013[11] found that preoperative accurate localization occurred significantly more often for ultrasonography than $Tc^{99}m$ sestamibi scintigraphy and when combined the accuracy is greater than 93%. For ultrasonography, accurate localization was found in patients with larger or heavier adenomas and those with adenomas located inferiorly.

Prasannan et al., 2007[12] found that Ultrasonography & $Tc^{99}m$ sestamibi scintigraphy scan are the most commonly employed techniques in preoperative identification of parathyroid adenomas. Early reports claimed >90% sensitivity rate for parathyroid adenoma detection using ultrasonography when combined with $Tc^{99}m$ sestamibi scintigraphy.

De Feo et al., 2008[13] observed that the overall sensitivity of combined ultrasonography and $Tc^{99}m$ sestamibi scintigraphy was 96% and showed that the combination of ultrasonography and $Tc^{99}m$ sestamibi scintigraphy had high accuracy results. In fact, with $Tc^{99}m$ sestamibi scintigraphy, it is possible to characterize nodules that were not characterized at ultrasonography and to detect ectopic glands, whereas with ultrasonography, it is possible to detect lesions that may have been overlooked at $Tc^{99}m$ sestamibi scintigraphy due to their small dimensions, low metabolic activity, and/or the presence of necrotic or cystic areas.

Hajioff et al., 2008[14] in their published systematic review, reported that the sensitivities for ultrasonography and $Tc^{99}m$ sestamibi scintigraphy were 78.55% and 88.44% respectively, for solitary adenomas and suggested that $Tc^{99}m$ sestamibi scintigraphy is the preferred method to image the parathyroid glands, with a higher sensitivity and specificity than ultrasonography. However, when $Tc^{99}m$ sestamibi scintigraphy fails to reveal an enlarged gland in a patient with hyperparathyroidism, ultrasonography is a reliable alternative and greatly improves the likelihood in finding the adenoma, especially in patients in whom multiple glands are involved. It has been demonstrated that the sensitivity of the combined imaging tests was greater than if both tests are applied alone.

In a study conducted at Mount Sinai Hospital in New York City, by Roni et al., 2008,[15] the parathyroid adenoma was found in 98% of the time with unilateral neck exploration when both ultrasonography and $Tc^{99}m$ sestamibi scintigraphy were employed, This strongly suggests that $Tc^{99}m$ sestamibi scintigraphy and ultrasonography should be considered the first line imaging methods for patients with primary hyperparathyroidism.

Yip et al., 2009[16] categorized $Tc^{99}m$ sestamibi scintigraphy on a scale of 0-3 (0-negative, 1-possible, 2-probable, 3-definite adenoma) and found that a higher score on $Tc^{99}m$ sestamibi scintigraphy correlated with a higher likelihood of single adenoma and that the score correlated linearly with the study's positive predictive value. Conversely, a negative $Tc^{99}m$ sestamibi scintigraphy more often was associated with multigland disease, leading the authors to conclude that negative $Tc^{99}m$ sestamibi scintigraphy more often results in surgical failure and that "expert surgeons must use validated adjuncts" to $Tc^{99}m$ sestamibi scintigraphy to avoid a failed operation.

Lumachi et al., 2009[17] retrospectively reviewed preoperative ultrasonography and $Tc^{99}m$ sestamibi scintigraphy findings in patients with proven hyperparathyroidism and found a combined sensitivity of 95% versus 80% for ultrasonography and 87% for $Tc^{99}m$ sestamibi scintigraphy alone.

Siperstein et al., 2008[18] predicted 79% surgical success in their prospective study combining both techniques versus 74% for ultrasonography and 68% for $Tc^{99}m$ sestamibi scintigraphy alone.

Summary and Conclusion:

The difficulty of parathyroid surgery lies not only in reduced size and delicate location of glands among important nerves and vessels, but also in distinguishing an adenoma from hyperplasia, a distinction that can be difficult not only intraoperatively, but sometimes also histolopathologically.

Imaging is not for diagnosis as calcium and parathyroid hormone plasma levels establish the diagnosis of hyperparathyroidism, imaging is a localization technique for abnormal parathyroid gland(s) and does not identify normal parathyroid glands, which are too small (20-50 mg) to be seen. The success of surgery for primary hyperparathyroidism depends on accurate preoperative localization of parathyroid adenomas. Successful parathyroidectomy depends on the recognition and excision of all hyperfunctioning parathyroid glands. Preoperative localization is essential for the safety and efficacy of surgery, particularly in the present era of minimally invasive surgery.

The aim of this study was to detect the importance of combination of ultrasonography and $Tc^{99}m$ sestamibi scintigraphy in the preoperative localization of patients with primary hyperparathyroidism to increase the adoption of minimally invasive parathyroidectomy techniques. The combined ultrasonography and $Tc^{99}m$ sestamibi scintigraphy accuracy in the preoperative localization of patients

with hyperparathyroidism is 93.33%, therefore, we recommend the combination of preoperative ultrasonography and $Tc^{99}m$ sestamibi scintigraphy in predicting the location of pathological parathyroid gland(s) in patients with primary hyperparathyroidism.

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