## **Original Research Article**

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# Prospective comparison of high resolution ultrasonography with technetium sestamibi scintigraphy and operative findings in detection of abnormally hyper functioning parathyroid gland/glands in primary hyperparathyroidism

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#### **ABSTRACT**

Background: Ultrasonography is cheap, easily available and convenient modality of diagnosis.

**Methods:** We prospectively studied 61 patients with PHPT. Patients preoperatively underwent USG neck and MIBI scan, results were interpreted independently and compaired with intra operative findings.

**Results:** 61 patients who underwent parathyroidectomy for PHPT were studied. Ultrasonography neck showed correct side in 46/51 (90%) and correct site in 32/51 (63%) patients with single parathyroid adenomas. MIBI scan showed correct side and site of parathyroid adenoma in 46/50 (92%) and 43/50 (86%) patients respectively. Patients with double adenomas USG neck showed positive results in all 5 patient with 100% sensitivity where as MIBI scan showed positive results in four out of five patients (80%). 1 patient with four gland hyperplasia USG picked three out of four enlarged glands while as MIBI scan not picked any of the enlarged glands. Operative findings revealed that right lower parathyroid gland was the most common gland involved (54%) followed by left lower (29%), right upper (6.6%), left upper (0%) and multiple / bilateral (9.6%).

**Conclusions:** USG is an affordable, conventional and useful tool in detecting enlarged parathyroid glands in most of the patients with PHPT, but operator dependant. However, when USG can't detect enlarged parathyroid gland 99mTc-MIBI Scan is complimentary to it.

**Keywords:** Hypercalcemia hyperparathyroidism, 99mTc-sestamibi scintigraphy, Parathyroid adenoma, Ultrasonography

## INTRODUCTION

Primary hyperparathyroidism (PHPT) is a common endocrine disorder with increased incidence since the addition of the serum calcium level to the standard base

line investigations or standard chemistry panel.<sup>1</sup> The incidence of PHPT in United States is approximately 22 per 100,000 people.<sup>1</sup> Solitary parathyroid adenoma accounts for approximately 80-85% of these cases, multiple adenomas or hyperplasia in 15% of patients, and

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parathyroid carcinoma in 1% of patients.<sup>2</sup> Surgery is the only definitive treatment recommended for symptomatic and some asymptomatic patients.<sup>3</sup> The main aim of surgery is to remove all the abnormally hyper functioning parathyroid glands and preserve the normal functioning parathyroid glands to achieve normal serum calcium level. Bilateral neck exploration was considered gold standard and all the four parathyroid glands were observed during surgery in patients with PHPT before the introduction of recent advances in imaging technology. Imaging modalities like high resolution ultrasonography (USG), 99mTc-sestamibi scintigraphy (99mTc-MIBI Scan) computerized tomography (CT) and magnetic resonance imaging (MRI) have been developed to localize the abnormal parathyroid glands.

All these imaging modalities have varying success rates with lack of required sensitivity to justify the use of a single imaging modality for routine use before performing definitive surgery. These modalities of diagnosis have made it possible to perform minimal invasive parathyroidectomy.<sup>4</sup>

The success of minimal access surgery has been confirmed by long term objective evidence of cure and complication rate being same or less as that achieved by classic bilateral neck exploration. Preoperative localization also helps to localize the ectopic location of abnormally functioning parathyroid glands and multiple abnormal parathyroid glands in familial hyperparathyroidism (FHPT). It also helps to reduce the operative time, post-operative morbidity and redo surgeries.

In 1979 Edis and Evans first introduced the high resonance USG as a method of diagnosing parathyroid tumors. Subsequently many studies have shown the efficacy of high resolution USG with varying results of sensitivity ranging from 34% to 92% with a false positive rate of 4% to 25%. 5-7 Among the above modalities of diagnosis of abnormally functioning parathyroid glands high resolution USG has the advantage of easily availability, affordability and patient convenience. 8

In 1989 99mTc-MIBI Scan was introduced as a modality for diagnosing abnormally functioning parathyroid glands9. Several studies have confirmed its use for identifying abnormally functioning parathyroid gland with a sensitivity of 71% to 94%. Description Some authors have considered it as a parathyroid imaging technique of choice. Nuclear imaging particularly 99mTc-MIBI Scan is not widely available in comparison to USG which is widely available at an affordable cost and being widely used for location of abnormally functioning parathyroid glands.

In this study we have evaluated the preoperative localization of abnormally hyper functioning parathyroid glands with the high resolution USG and compared it with the 99mTc-MIBI Scan and correlated the imaging

results with the operative findings and histopathological examination in patients with PHPT.

#### **METHODS**

We prospectively studied 61 consecutive patients with PHPT who underwent parathyroidectomy at our institute Sher-I-Kashmir Institute of Medical Sciences (SKIMS) from June 2010 to May 2015. PHPT was defined as the persistent serum calcium level more than the upper normal limit of 10.5 mg/dl (excluding the other causes of hypercalcemia), elevated levels of intact parathyroid hormone (iPTH) and characteristic radiographic features of PHPT. All patients with the above features of PHPT underwent high frequency USG neck and 99mTc-MIBI Scan for the location of abnormally functioning parathyroid gland/glands before undergoing surgery. The position of the abnormal parathyroid glands was defined in relation with the right and left thyroid lobes with isthmus as the dividing land mark and the location of each parathyroid gland (right superior, right inferior, left superior and left inferior) was recorded.

## Ultrasonography

The USG of neck was performed by a single experienced radiologist by using high resolution transducer. The USG examiner was unaware about the results of other investigations like 99mTc-MIBI Scan. USG neck was performed with the patient in spine position and neck extended. First whole of the thyroid gland was evaluated followed by the central neck compartment from clavicles to submandibular glands on both sides respectively. The parathyroid gland was identified by its oval shape, hypoechogenicity and encapsulation. The size of the abnormal parathyroid gland was measured by taking two largest dimensions.

## Technetium (99mTc) sestamibi scintigraphy

For Sestamibi Scintigraphy after taking proper consent 99mTc-Sestamibi was introduced intravenously and the images were taken after 15 minutes (early thyroid scan), 90 minutes and 2.5 hours (delayed parathyroid scan). A focal area of increased tracer in the thyroid area and surrounding area or any ectopic location which shows a progressive intensity over time or a fixed uptake that persisted in the delayed phase was considered as positive scan image. The examiner was unaware about the results of other investigations like USG neck.

#### Surgery

All the patients were operated by a single surgeon (one of the authors). The classical bilateral neck exploration was performed and all the parathyroid glands were examined. The success of the operation was defined by the eucalcemia at 6 months after surgery and normalization of iPTH.

#### **RESULTS**

61 patients who underwent parathyroidectomy from June 2010 to May 2015 were studied. Out of these 61 patients. 9 were males and 52 were females. The male-to-female ratio was 1:5.7. Age of the subjects ranged from 16 to 70 years with a mean of 44.72±12.46 years (median, 45). Most of the study subjects in our study had classical of primary hyperparathyroidism symptom nephrolithiasis being the most common single manifestation (46%). Other common presentations included bone pain (43%), abdominal pain (39%), constipation (26%), polyurea (12%), fractures (5%), and headache (7%). Only three (5%) of our study subjects were asymptomatic. Fifty five (90%) patients had single parathyroid adenoma, five (8%) had double parathyroid adenoma and one (1.6%) had hyperplasia. Preoperative and post-operative serum calcium, phosphate and iPTH profile are shown in Table 1. Histopathological findings are shown in Table 2.

In case of single adenoma all the parathyroid glands were examined at the time of neck exploration. The abnormal parathyroid gland was excised and out of the three normal looking parathyroid glands one was randomly biopsied. Fifty five single adenomas and five double adenomas had chief cells on histopathology while as the one with four gland disease had hyperplasia on histopathology.

Ultrasonography neck showed correct side in 46 (90%) out of 51 patients and correct site in only 32 (63%) out of 51 patients with positive predictive value of 95.7% and 96.9% for correct side and site respectively. Accuracy for side and site was 86.3% and 62.7% respectively (Table 3). There was a significant difference in weight of adenomas between the patients with positive and negative ultrasonographic results. Patients with positive ultrasonographic results had more weight of adenomas as compared to those with negative ultrasonographic results. There was no significant difference in serum calcium, phosphate and iPTH between patients with positive or negative ultrasonographic results. The smallest parathyroid gland picked up by USG in our study was 1.4 grams.

The sensitivity of MIBI scan for correct side and site of parathyroid adenoma was 46/50 (92%) and 43/50 (86%) respectively with positive predictive value of 96% and 97% for correct side and site of parathyroid adenoma. The accuracy of MIBI scan for correct side and site was 89% and 84% respectively (Table 3). When both USG neck and MIBI scan were combined the results of sensitivity, positive predictive value and accuracy improved (Table 2).

In case of patients with double adenomas USG neck showed positive results in all five patients with 100% side and site sensitivity whereas MIBI scan showed positive results in four out of five patients (80%). Side

and site accuracy of MIBI scan was 100% in four out of five patients and was negative in one patient in whom USG showed few cysts in the bilateral thyroid lobes. One patient with four gland hyperplasia on histopathology USG was able to detect three out of four enlarged parathyroid glands while as MIBI scan was not able to detect any of the parathyroid glands in this patient.

Table 1: Preoperative and postoperative serum calcium, phosphate and IPTH.

	Pre op	Post op	P-value
Calcium			
Mean ±SD	11.5±1.00	9.52±0.90	< 0.001
Median	11.3	9.7 (1.4)	
Range	9.1-15.6	7.7-11.0	
Phosphorus			
Mean±SD	2.31±0.54	3.16±0.77	< 0.001
Median	2.2	3.2 (1.0)	
Range	1.5-3.5	1.0-4.0	
iPTH	337.6 ±386.1	58.3±39.0	< 0.001
Mean±SD	22457	48.2 (28.5)	
Median range	70-1900	4.8-154	

**Table 2: Histopathological findings.** 

Histopathological diagnosis	N (percent)
Single adenoma	55 (90.2%)
Double adenoma	5 (8.2%)
4 gland hyperplasia	1 (1.6%)

Table 3. Accuracy of imaging with intra-operative findings and histopathologically proven parathyroid adenoma / hyperplasia.

	Correct side	Correct site		
USG				
Sensitivity	90%	63%		
Positive predictive value	95.7%	96.9%		
Likelihood of correct positive test	0.9	1.3		
Accuracy	86.3%	62.7%		
MIBI				
Sensitivity	92%	86%		
Positive predictive value	96.1%	97.7%		
Likelihood of correct positive test	0.9	1.7		
Accuracy	89.1%	84.3%		
Both USG and MIBI				
Sensitivity	95%	88%		
Positive predictive value	97.6%	97.4%		
Likelihood of correct positive test	1.0	0.9		
Accuracy	93.2%	86.4%		

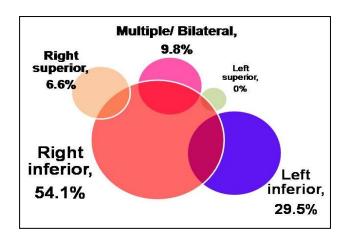


Figure 1: Surgical findings-site of parathyroid lesion.

On surgical exploration right side parathyroid lesions were encountered in 62.3% of patients, left side in 31.1% and bilateral 6.6%. Right lower parathyroid gland was the most common gland involved (54.1%) followed by left lower parathyroid gland (29.5%), right upper (6.6%), left upper (0%) and multiple / bilateral (9.6%) (Figure 1).

#### **DISCUSSION**

In this study we have shown the accuracy of USG in detecting parathyroid adenomas and compared the results with the results of MIBI scan, further confirmed by intera-operative and histopathological findings. In our study USG had side sensitivity of 90% and site sensitivity of only 63% in picking single parathyroid adenoma side sensitivity of USG was lower than MIBI scan (90% versus 92%) and the site sensitivity of USG was also much lower than MIBI scan (63% versus 85%). In case of patients with double adenomas USG showed better results than MIBI scan (100% versus 80%).

In Parathyroid hyperplasia it detected three out of four abnormal parathyroid glands. USG have limited accuracy when used alone and is highly operator dependent however it is very cheap, portable, easily available and can be done in clinic or even in operation theater. Parathyroid adenoma is easily detected by USG and can be easily differentiated from thyroid tissue. The ability of USG to detect enlarged parathyroid glands ranges from 34% to 92%.5-7 This variable accuracy of USG for preoperative localization of enlarged parathyroid glands is due to its high operator dependence, his experience, skill and other factors like weight of the enlarged gland. Higher the weight of gland easily it will be picked up by USG. Thyroid nodular disease as it decreases the sensitivity of USG, persistent or recurrent disease after previous neck exploration, involvement of more than one parathyroid glands, ectopic location of parathyroid glands, parathyroid hyperplasia. 20-22,24,29

In this study none of the patients had ectopic location of parathyroid glands or undergone previous neck exploration. In patients with double adenomas USG

picked up enlarged parathyroid glands in all the five patients with sensitivity of 100%. One of our patients with double adenoma had thyroid nodular disease but USG picked up both enlarged glands in this patient while another patient with hyperplasia USG picked three out of four enlarged glands. The sizes of the enlarged glands have directly effect on the results of USG. The weight of the smallest gland picked up by USG in our study was 1.4 grams however USG can pick up the parathyroid adenomas with weight up to 1 gram. The reason for higher sensitivity of USG in our study may be due to advanced disease at the time of presentation with higher mean weight of parathyroid adenomas as compared to data from western countries.

In this study 99mTc-MIBI Scan was able to pick up parathyroid adenoma in forty six out of fifty patients who had undergone MIBI scan with a sensitivity of 92% and positive predictive value of 96%. The sensitivity of MIBI scan in our study was higher than USG (92% versus 90%). The sensitivity of MIBI scan in our study was comparable with the studies done by other authors which ranged from 71 to 94%. 12,17-19

The reason for higher sensitivity of MIBI scan over the USG has been attributed to its ability to pick up the abnormal parathyroid glands related to their functional activity irrespective of their side and site. In patients with double adenomas the MIBI scan was able to pick up eight out of ten parathyroid adenomas (80%). MIBI scan had failed to pick up abnormal parathyroid glands in one patient with parathyroid hyperplasia. The reason for the low sensitivity of MIBI scan in multiglandular disease may be possibly related to differential functional activity of various abnormal parathyroid glands, thereby making less availability of tracer to less functional glands. It has been attributed to increased expression of P-glycoprotein or multidrug resistance related protein, which prevents the accumulation of MIBI even by the abnormally functioning glands.26

Studies have shown previously that USG have good sensitivity than MIBI scan in picking up multiple hyper plastic parathyroid glands (75% versus 66%), however the combination of USG and MIBI scan have improved the sensitivity to 88%. Some studies have shown that MIBI scan is better choice than USG in detecting ectopic parathyroid adenoma. However none of our patients had ectopic parathyroid adenoma so nothing can be committed about it.

Among the studies that have compared USG with 99mTc-MIBI Scan in patients undergone par thyroidectomy for PHPT Cases et al have shown that MIBI scan was better than USG whereas the De Feo et al found similar results in both USG and MIBI scan when comparing with operative findings. <sup>28,29</sup> In another series comparing results of USG with MIBI scan, it was found that USG was better than MIBI in picking abnormal parathyroid glands. <sup>30</sup> Gathering information from all

previous data together with the present data it is clear that 99mTc-MIBI Scan is better than USG in picking single parathyroid adenomas while as in multiglandular disease USG showed better results. Combination of these two diagnostic modalities show even better results.

### **CONCLUSION**

USG is an affordable, conventional and useful tool in detecting enlarged parathyroid glands in most of patients with PHPT, but operator dependent. However, when USG can't detect enlarged parathyroid gland 99mTc-MIBI Scan is complimentary to it.

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institutional ethics committee

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