

A Study on Imaging Modalities in Primary Hyperparathyroidism

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Abstract

Background: Hyperparathyroidism (HPT) is the third most common endocrine disease. The rate of incidence is increasing with the more extensive availability of early screening methods including levels of serum parathyroid hormone (PTH) and calcium. Primary HPT (PHPT) results from unregulated overproduction of the PTH, usually due to a parathyroid adenoma or hyperplasia. With the advent of minimally invasive parathyroid surgeries, the need to differentiate between the two has arisen in clinical practice.

Materials and Methods: A total of 32 cases of PHPT were studied. Pre-operative localization was done using ultrasonography (8-12 MHz linear transducer probe), magnetic resonance imaging (1.5 Tesla), and technetium 99 m–methoxyisobutyl isonitrile (Tc^{99m} Sesta MIBI) scan. Parathyroidectomy was performed, and histological analysis was done to confirm the clinical diagnosis. The expression of Ki-67 and p53 was analyzed in the tumor tissue in 22 patients.

Results: It was found that double imaging modality had higher sensitivity and specificity for adenomas as compared to either individual scan. Immunohistochemical analysis showed increased uptake of Ki67 in adenomas and hyperplasia as compared to normal tissue. P53 uptake was seen on both adenomas and hyperplasia.

Conclusion: Double imaging modality is better than using single imaging modality in the identification of HPT.

Key words: Hyperparathyroidism, Ki67, p53, Parathyroid adenoma, Parathyroid hyperplasia, SESTAMIBI scan, Ultrasound

INTRODUCTION

Primary hyperparathyroidism (PHPT) is the inappropriate or unregulated overproduction of parathyroid hormone (PTH) resulting in an abnormality of calcium and phosphorus metabolism. The incidence of HPT, the third most common cause of endocrine disease, is increasing. Routine screening and yearly checkups are making early detection a possibility, promoting prompt intervention. It has been found that, while the incidence and prevalence globally are similar to that of the US, but presentation varies greatly. In the US and Europe, most (80%) patients present with asymptomatic disease, but

in resource-poor nations, most (>80%) patients present with symptoms.^[1]

PHPT is a relatively common disorder affecting 1 in 500 women and 1 in 2000 men over 40 years of age. The best estimate of incidence is 22/100,000/year, and prevalence is approximately 1/1000.^[2] Over 80% of patients with PHPT have solitary adenomas, the remaining having multiple adenomas, hyperplasia, or carcinomas.

Studies have suggested three different mechanisms for parathyroid gland dysfunction in PHPT: (1) A defect in calcium recognition, (2) a monoclonal tumor from overexpression of a growth stimulator, or (3) a monoclonal tumor from inactivation of a growth inhibitor.^[3]

p53 mutations have been found to play a role in the development of many common human malignancies.^[4] Ki-67 gene is present in all proliferating cells, and there is great interest in its role as a marker of proliferation.^[5] Recently, gene array techniques have revealed the Ki-67

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gene's role in several "proliferation signatures," showing that a set of genes with increased expression patterns is correlated with a tumor cell.

At present, PHPT, whether caused by an adenoma or hyperplasia, can be cured surgically with a high rate of success. With the advent of more advanced surgical techniques including minimally invasive parathyroidectomy, the need for more accurate pre-operative localization of lesion is gaining importance. It has been found that with optimized pre-operative mapping, the success rate of less invasive techniques equals that of the traditional bilateral approach.^[6-11]

The commonly used non-invasive imaging techniques are sonography, scintigraphy, computed tomography, and magnetic resonance imaging (MRI). Our study has compared the sensitivity and specificity of these modalities and compared the results of each. We also examine the efficacy of using multiple modalities. Sonography and ^{99m}Tc-SESTAMIBI scintigraphy have emerged as dominant, and potentially complementary, techniques in the pre-operative evaluation of PHPT.

MATERIALS AND METHODS

The study sample included 32 cases of PHPT (as documented by elevated serum PTH and calcium levels), 9 male and 23 female, of a mean age group of 44.66 years with a standard deviation (SD) of 11.406. The mean pre-operative PTH value was 638.47 (range), and the mean pre-operative serum calcium level was 12.32 mg/dL. Pre-operative localization was done using ultrasonography (USG) (8-12 MHz linear transducer probe), MRI (1.5 Tesla) and ^{99m}Tc-methoxyisobutyl isonitrile (^{99m}Tc Sesta MIBI) scan. Parathyroidectomy was performed, and histological analysis was done to confirm the clinical diagnosis.

Histology

After surgical excision, the specimens were fixed and buffered in formalin, embedded in paraffin, sectioned, stained with hematoxylin and eosin, and classified as adenomas according to the Ghandur-Mnaymneh and Kimura classification.

Immunohistochemical (IHC) analysis

Paraffin slides were xylene washed, rinsed twice with alcohol (18:1:1 100% ethanol:100% ethanol:100% isopropanol) and several times with deionized water. The slides were incubated 5 times at room temperature. Counterstaining and visualization of nuclear staining were done. Semiquantitative analysis was done for scoring the IHC staining. The staining pattern for Ki-67 was taken as, 0 = no staining; 1 = faint reaction; 2 = moderate reaction; and 3 = strong reaction.

The expression of Ki-67 and p53 was analyzed in the tumor tissue in 22 patients only and subsequently discontinued as it did not have any diagnostic value.

RESULTS

The mean age group was found to be 44.6, with a SD of 11.406, with maximum clustering seen between 50 and 60 years. A clear female preponderance was observed (28.1% male: 71.9% female.) The most common clinical presentation was found to be body pain, followed by urolithiasis, as a part of a master health check-up, abdominal pain, and neck swelling, in that order.

A marked decline in serum PTH levels were observed post-operative, and serum calcium levels came back to normal ($P < 0.001$).

When comparing imaging modalities, it was found that USG was found to have give a false negative result in 56.3% and true positive in 43.8%. MRI and SESTAMIBI scan both were found to have a true positive rate of 93.8% and false negative rate of 6.2%. 13 patients were subject to MRI as well as SESTAMIBI scan. On using this double imaging modality, it was found that sensitivity was 83% and positive predictive value was 71.4%.

IHC analysis showed, out of 22 samples of parathyroid adenoma, positive uptake of Ki67 in 14 samples. 8 samples did not show any uptake. It was found that Ki67 uptake in normal parathyroid tissue was seen in 3 out of 8 specimens.

p53 staining was positive in 21 specimens of parathyroid adenoma out of a total of 22, while 7 out of 8 normal parathyroid tissue showed positivity for the same.

DISCUSSION

Parathyroid lesions in our study were found to be common in the 5th decade. The mean age was 46.86 years, which was found to be comparable to the mean age in the study, done by Afshin *et al.* (52.2) but did not correlate with the study done by Gopal *et al.* (33.5).

In our study, the male to female ratio is 1:1.75, which was comparable to the study done by Gopal *et al.* (1:2), does not correlate with the study done by Afshin *et al.* The incidence of parathyroid lesions was higher in females in our study but not as high as the study done by Afshin *et al.* (1: 4)

Polyuria, polydipsia, and weakness accompanied with skeletal abnormality, nephrocalcinosis, nephrolithiasis,

peptic ulcer disease, and psychiatric disorder are the most common clinical manifestation of HPT.

Nearly 45.4% of our patients presented with bone pain and 40.1% of patients presented with urolithiasis comparable to the most of the studies. The mean pre-operative PTH value was found to be 611.18, found to be comparable to that of study done by Afshin *et al.* mean serum intact PTH level was 584, while study done by Gopal *et al.* had elevated mean PTH value of 866. The mean pre-operative serum calcium was found to be 12.43, found to be comparable to that of study done by Gopal *et al.* (12.55).

A total of 13 patients underwent ultrasound neck (38.5%). Lesion was localized in 5 patients. Lesion could not be localized in 8 patients. Whereas in the study done by Afshin *et al.* USG revealed 34 lesions out of 36 patients (94.4%). In study done by Gopal *et al.* USG revealed 44 lesion out of 79 patients (55.6%).

Our study did not correlate with either of them.

Of the 22 study patients, 20 patients were localized preoperatively by Sesamibi scan. Whereas in study done by Afshin *et al.* ($n = 36$) MIBI scan showed 26 parathyroid lesion in patients with PHPT. In study was done by Saengsuda MIBI scintigraphy correctly laterized and localized 17 of 19 abnormal parathyroid glands with sensitivity 90%, specificity 100%, and positive predictive value (PPV) 100%.

In our study (on using combined modality), 13 patients were subject to USG and SESTAMIBI scan. USG and SESTAMIBI scan were found to have 46% sensitivity, 100% specificity with a positive predictive value of 100% and negative predictive value of 25%.

In our study $n = 22$ with PHPT, 14 patients had solitary adenomas and 8 patients had parathyroid hyperplasia. In study done by Gopal *et al.*, 69 patients diagnosed to have adenoma and 10 patients had parathyroid hyperplasia. In our study p53, immunostaining had 100% positivity for adenomas and 87.5% positivity in normal tissue not

comparable any of the other studies. Ki 67 had 64.2% positivity to adenomas which were comparable to study done by Ricci *et al.* (57.2%). Ki 67 positivity (37.5%) was seen in normal tissue which did not correlate with other studies.

CONCLUSION

Using double imaging modality increases the diagnostic accuracy of HPT than using a single modality, and hence, it is strongly recommended. Ki67 and p53 assays in the specimens did not prove to be of any beneficial value. It probably needs a larger cohort to arrive at a meaningful value of these assays.

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