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ORIGINAL RESEARCH

# Preoperative Localization of Parathyroid Adenomas with Methoxyisobutylisonitrile and Ultrasonography: Are There Advantages of a Combined Approach?

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## ABSTRACT

**Aim:** To identify whether the combination of Methoxyisobutylisonitrile (MIBI) and ultrasound scan (USS) in localizing the parathyroid gland preoperatively is more effective than either MIBI or USS alone.

**Materials and methods:** Retrospective manual analysis of patients' operative and medical notes was undertaken. Patients presenting with raised serum calcium and parathyroid hormone (PTH) between February 2009 and April 2012 (n = 76) were included in the study.

The sensitivity of localizing parathyroid adenomas via MIBI and USS with confirmation by histological evaluation of tissue following parathyroidectomy was assessed.

**Results:** The combination of MIBI and USS provided a statistically significant improvement in preoperative localization of parathyroid adenoma over MIBI or USS alone ($p = 0.033$ and $p = 0.043$ respectively).

**Conclusion:** Ultrasound scan alone had a statistically much higher sensitivity to localize a parathyroid adenoma than MIBI and we therefore advise USS to be a first-line investigation with MIBI in reserve for when USS fails to identify an abnormality. However, the combination of both USS and MIBI provides a statistically improved preoperative visualization of parathyroid adenoma and thus reduces the risk of requiring further surgery.


**Keywords:** Adenoma, MIBI, Parathyroid, Ultrasound.

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## INTRODUCTION

The pathophysiology of primary hyperparathyroidism is characterized by a raise parathyroid hormone (PTH) due to underlying parathyroid pathology. The most common cause is due to parathyroid adenoma formation in 80 to 85%; however, parathyroid glandular hyperplasia (10%) or carcinoma may also be a cause.[1] A raised PTH causes a subsequent hypercalcemia. Most patients with primary hyperparathyroid disease present asymptomatically; however, a smaller population of patients may present with symptoms of lethargy, memory problems, myalgia, bone pain, constipation and acid reflux. More rarely patients may present with kidney complaints, such as nephrolithiasis and bone disease including osteoporosis.

The mainstay of treatment for primary hyperparathyroidism (HPT) historically included bilateral neck exploration (BNE) accompanied with four-gland exploration, followed by the identification and removal of the pathological parathyroid gland. The advent of imaging techniques, such as technetium-99m Methoxyisobutylisonitrile (MIBI) (99mTc-MIBI or MIBI), high resolution ultrasound scan (USS) and single positron emission computed tomography (SPECT) has facilitated the preoperative visualization of the parathyroid gland. Preoperative localization of the pathological parathyroid gland meant BNE and four-gland exploration was no longer required and quicker, less invasive unilateral neck exploration (UNE) could take place.[2]

Methoxyisobutylisonitrile scintography is a dual phase procedure which specifically localizes hyperfunctioning parathyroid tissue. Although MIBI is successful in locating solitary adenomas, it has some limitations.[3,4] False-negatives can occur in small and less metabolically active adenomas, posteriorly located adenomas and parathyroid hyperplasia. The sensitivity of MIBI for parathyroid adenomas varies between 39 and 92% in the literature depending on technique and the experience of the interpreter. False-positives have been documented in thyroid adenoma, carcinoma, reactive lympth nodes and more rarely in breast and lung cancer as well as myeloma.[5]

High resolution USS performed with a high frequency transducer (12–15 Hz) also allows preoperative visualization of parathyroid tissue. Adenomas appear hypoechoic against thyroid tissue and thus can be differentiated. Ultrasound scan has been shown to be effective in locating parathyroid adenomas in 90% of cases; however, this is lower in cases of multiglandular

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disease and ectopic adenomas. Ultrasound scan is effective at distinguishing parathyroid adenomas from multinodular thyroid disease which have been shown to retain tracer in MIBI and cause false-positives. Methoxyisobutylisonitrile, however, has a higher sensitivity for ectopic parathyroid adenomas over USS.[2]

The limitations of both imaging modalities mean UNE have a higher failure and reoperative rate than BNE.[6] The combination of both MIBI and USS is postulated to give a better overall localization of the parathyroid adenoma and therefore reduce the failure rate of UNE and subsequent need for reoperation or conversion intraoperatively to BNE. This study evaluates whether the combination of MIBI and USS gives a better preoperative localization than either MIBI or USS alone.

## MATERIALS AND METHODS

### Subject Information

A retrospective manual review of patients' notes and operative notes took place in those who underwent surgery for primary HPT. Seventy-six operations were reviewed which took place between February 2009 and April 2012. Patients with raised serum calcium and PTH suggestive of primary hyperparathyroidism underwent MIBI and/or USS investigation to facilitate preoperative localization of the parathyroid glands. Parameters reviewed included preoperative serum calcium and the first two postoperative serum calcium measurements, preoperative serum PTH and the first two postoperative serum PTH measurements as well as excised tumor volume and tumor weight.

### Imaging

Imaging included either USS or MIBI alone or a combination of the two.

### Surgical Procedure

Unilateral neck exploration was performed on each patient in whom preoperative localization of a parathyroid adenoma was possible using MIBI, USS or both. A 3 to 4 cm horizontal midline incision was made halfway between the suprasternal notch and thyroid gland. The recurrent laryngeal nerve and inferior thyroid artery were identified and isolated in every case. The surgery was aimed at correctly identifying the parathyroid adenoma and this was confirmed intraoperatively using fresh frozen sampling for histological identification. In the minority of patients were the pathological parathyroid tissue could not be located the procedure was converted to a BNE by extending the incision and exploring the contralateral side.

## STATISTICAL ANALYSIS

The data from this study were analyzed using the statistics computer software SPSS version 16 (SPSS, Chicago, IL). Normality was tested for using the Kolmogorov-Smirnov test. Logarithmic transformation was used to correct the positive skew in serum calcium results. We compared the confirmed diagnostic rate of MIBI and USS combined with the individual diagnostic rates of MIBI and USS alone using Chi-squared testing. Preoperative serum calcium and serum PTH and subsequent diagnosis of parathyroid adenoma were analyzed using the correlation coefficient as was the correlation between tumor volume and weight and subsequent visualization on MIBI and USS. We also analyzed postoperative changes in serum calcium and PTH using ANOVA. Probability of less than 0.05 was considered significant. Data are reported as mean ± SD.

### Ethical Considerations

Written consent gained from patient whose intraoperative photographs are detailed below.

## RESULTS

A total number of seventy-six patients were operated on for primary HPT with an age range spanning between 26 and 85 (mean 62.30 ± 12.50) and a male-to-female ratio of 1:4. Preoperative serum calcium levels ranged from 2.42 to 3.42 mmol/l and preoperative serum PTH levels ranged from 8.00 to 943.00 pg/ml. Preoperatively, an abnormal focus of activity suspicious of an adenoma was detected in 47 patients on MIBI and in 67 patients on USS. On histological diagnosis, 61 patients were confirmed to have a parathyroid adenoma. The remainder of the samples were normal (n = 2), parathyroid cyst (n = 1), suppressed (n = 1) or hyperplastic parathyroid tissue (n = 10) on histology. The average weight of a sample sent for histology was 8.23 gm and the average sample volume was 473.35 $mm^3$. There was no significant association between weight and volume of sample sent and subsequent histological diagnosis of a parathyroid adenoma.

In terms of tumor size, there was no significant correlation between tumor volume and preoperative visualisation on MIBI and USS ($p = 0.193$ and $p = 0.309$ respectively). Furthermore, there was no correlation between tumor weight and subsequent preoperative visualization on MIBI or USS ($p = 0.716$ and $p = 0.229$ respectively).

Average preoperative serum calcium was 2.83 ± 0.18 mmol/l (2.12–2.65 mmol/l) and was significantly reduced postoperatively to 2.43 ± 0.17 mmol/l at the 1st reading and 2.42 ± 0.15 mmol/l at the 2nd reading ($p \leq 0.0005$). Average preoperative PTH was 179.15 ± 138.59 pg/ml (10–60 pg/ml) and this was also

significantly reduced postoperatively to 68.75 ± 44.42 pg/ml at the 1st reading and 64.59 ± 51.77 pg/ml at the 2nd reading ($p \leq 0.0005$). There was no significant correlation between preoperative serum calcium and visualization on MIBI and USS ($p = 0.286$ and $p = 0.062$ respectively). There was also no significant correlation between preoperative PTH and visualization on MIBI ($p = 0.068$). There was, however, significant positive correlation between preoperative PTH and subsequent visualization on USS ($p = 0.013$).

Methoxyisobutylisonitrile localized an abnormality in 47 cases (64.47%, sensitivity 71.76%). However, MIBI incorrectly localized a focus of abnormal activity in one patient (false-positive rate 6.67%) and failed to identify an abnormality in patients whom were later diagnosed histologically with an adenoma in 24 cases (false-negative rate of 39.30%). In the 47 patients in whom an abnormality was detected on MIBI, 46 were later histologically diagnosed as having a parathyroid adenoma [positive predictive value (PPV)—97.29%].

Ultrasound scan localized an abnormality in 67 cases (89.47%, sensitivity 92.42%). In contrast to MIBI, USS incorrectly localized an abnormality in two patients (false-positive rate 13.33%) and failed to identify pathology in five patients who were later diagnosed histologically with a parathyroid adenoma (false-negative rate 8.20%). In the 67 patients in whom an abnormality was detected on USS, 59 were later histologically proven to have a parathyroid adenoma (PPV 96.42%). Overall MIBI and USS combined provided a localization rate of 94.73% and a PPV of 96.83%. This is significantly better than the use of either MIBI or USS alone ($p = 0.043$ and $p = 0.033$ respectively).

## DISCUSSION

Sixty-one of the 76 patients who underwent surgery for primary hyperparathyroidism were histologically proven to have a parathyroid adenoma. Of the remaining 15 patients, 11 had parathyroid hyperplasia and four were normal (i.e. free from hyperfunctioning parathyroid tissue). In the four patients who were normal, two patients had USS changes suggestive of parathyroid adenoma, giving a specificity of 50%. However, this study looked specifically at patients who underwent parathyroidectomy for primary HPT thus the likelihood of finding a parathyroid adenoma or hyperplastic parathyroid tissue would be expected to be high. Consequently, the value for specificity for USS in this group of patients is misleading due to the small sample of patients without parathyroid pathology.

Where parathyroid adenoma was predicted on MIBI and USS the histological diagnosis of adenoma was made in 97.29 and 96.42% of cases respectively. Combined they had a PPV of 98.38% which is significantly better than either modality used alone. Arici et al[7] reported similar findings in 105 patients and the combination of MIBI and USS had a PPV of 96.00% and Miura et al[8] found a PPV of 95.00% in a study of 39 patients undergoing surgery for primary HPT.

## KEY FINDINGS

This study shows that the combination of MIBI and USS together provides a statistically significant better preoperative localization rate of parathyroid adenomas to the correct side of the neck than either MIBI or USS alone ($p = 0.033$ and $p = 0.043$ respectively). The localization of an abnormal focus of activity occurred in 64.47% of cases in MIBI and 89.47% in USS, providing a combined localization rate of 94.73%. Methoxyisobutylisonitrile and USS have limitations which have been well documented.[2] In this study MIBI had a false-negative rate of 39.30%. It has been suggested that MIBI localization is influenced by parathyroid adenoma type, in particular being related to the oxyphil cell concentration that are rich in mitochondria which trap the MIBI tracer and provide localization.[9,10] Thus, MIBI has a lower sensitivity to tumors which are less metabolically active due to their lower oxyphil cell content. Furthermore, MIBI has a lower sensitivity to hyperplastic parathyroid tissue and two patients in whom MIBI failed to identify an abnormality had parathyroid hyperplasia. This could account for the increased false-negative rate of MIBI compared to USS which in contrast had a false-negative rate of 8.20%. On the other hand USS had a higher false-positive rate of 13.33% compared to MIBI which had a false-positive rate of 6.62%. Ultrasound scan is known to give false-positive results in multinodular thyroid disease[2] and indeed thyroid disease was subsequently described in one of the two patients in whom a false-positive result was attained.

Similarly to this study, Grosso et al[11] found USS to be more sensitive than MIBI at detecting an abnormal focus of activity (89.00 and 76.00% respectively). Ultrasound scan correctly localized an abnormality to the correct side of the neck in 51 cases compared to 34 with MIBI. The overall concordance rate between USS and MIBI was 86.11%. As USS is more sensitive than MIBI (92.42 and 71.76% respectively) it could be used as the first-line investigation, with MIBI in reserve for when USS fails to identify an abnormality. This finding was also noted by Grosso et al.[11]

Methoxyisobutylisonitrile has been shown to be especially sensitive in picking up ectopic parathyroid adenomas and this would be one of its strengths as a second-line investigation when USS fails to identify an

abnormality. Ultrasound scan is far less sensitive to ectopic adenomas, especially when they are located in retrotracheal or other deep seated positions where the adenoma is surrounded by other anatomical structures. Although in this study there were no cases of ectopic parathyroid adenoma, it is estimated that the parathyroid glands can be ectopic in location in upto 20% of the population[2] and this highlights the need for the combination of the two imaging modalities. Furthermore the two modalities provide different types of information about the tumor with MIBI giving functional information and USS allowing the anatomical details of the tumor to be assessed.

## CLINICAL APPLICABILITY

Preoperative localization of a parathyroid adenoma facilitates effective surgical UNE. In comparison to BNE it requires a smaller incision which provides better postoperative cosmesis as well as a shorter time in theater and reduced postoperative complications, such as bleeding, injury to the recurrent laryngeal nerve and postoperative hypoparathyroidism.[12] Where a combination of USS and MIBI was used localization of an abnormal focus of activity was achieved in 98.38% of cases and thus the conversion to BNE upon negative findings intraoperatively was low. A study by Moure et al[12] found a similar conversion rate of 3.70% to BNE when operating on patients with primary HPT. Overall, it has been shown that the benefits of UNE are achieved in most cases where preoperative localization is used.

The average 2nd postoperative serum calcium measurement was 2.42 ± 0.15 mmol/l (2.12–2.65 mmol/l) which was significantly reduced from the preoperative average of 2.83 ± 0.18 mmol/l. Similarly, a significant reduction in PTH was achieved postoperatively with the 2nd postoperative PTH measurement dropping to 64.59 ± 51.77 pg/ml (10–60 pg/ml). A study by Marc SO et al[6] where 149 patients were operated on for primary HPT average postoperative serum calcium was 2.30 ± 0.07 mmol/l and postoperative serum PTH was 136.10 ± 74.8 pg/ml. Cure is defined as having normal serum calcium levels (2.25–2.50 mmol/l) 6 months postoperatively.[12] One limitation of our study is that serum calcium was not measured 6 months postoperatively rather the first two postoperative measurements of serum calcium were taken. In our study, normocalcemia was achieved in 60 patients by the 2nd reading. Out of the remaining 16 patients, five were hypocalcemic and 11 remained hypercalcemic. To date, none of the 76 patients included in the study have undergone reoperation.

## CONCLUSION

The combination of MIBI and USS in the preoperative localization of parathyroid adenomas is more effective than either MIBI or USS alone. Ultrasound scan, however, has a much higher sensitivity than MIBI and therefore could be used as first-line with MIBI in reserve for when USS fails to identify an abnormality, most likely when an ectopic adenoma is present. Preoperative localization allows UNE to take place which is quicker, less invasive and results in fewer postoperative complications as well as a shortened hospital stay for patients.

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