

# Correlation between serum calcium levels and dual-phase $^{99m}\text{Tc}$ -sestamibi parathyroid scintigraphy in primary hyperparathyroidism

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## Summary

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**Aim:** The goal of the study is to correlate serum calcium levels with the results of dual-phase  $^{99m}\text{Tc}$ -sestamibi parathyroid scintigraphy to find the best cut-off level of the serum calcium that correlates with a positive presurgery.

**Methods:** In 111 patients, serum calcium and plasma parathormone (PTH) levels were compared with the results of the  $^{99m}\text{Tc}$ -MIBI scintigraphy and with this data determined the level of calcium above which the  $^{99m}\text{Tc}$ -MIBI scintigraphy was likely to be positive and below which the study was likely to be negative.

**Results:** In total, 11 men (18%) and 50 women (82%) had a positive  $^{99m}\text{Tc}$ -MIBI study. Overall 67% of those patients with a positive  $^{99m}\text{Tc}$ -MIBI study had a PTH  $>200\text{ ng l}^{-1}$  compared to only 9% of those with a negative  $^{99m}\text{Tc}$ -MIBI scintigraphy; however, for those with a positive study on an early  $^{99m}\text{Tc}$ -MIBI scintigraphy, this rose to 85%. Overall a serum calcium of  $>2.70\text{ mmol l}^{-1}$  was found in 82% of patients with a positive  $^{99m}\text{Tc}$ -MIBI study but only 14% of those with a negative  $^{99m}\text{Tc}$ -MIBI study, this is rose to 97% of patients with a parathyroid adenoma identified on early images. It is also shown that patients whose serum total calcium  $<2.51\text{ mmol l}^{-1}$  rarely have positive  $^{99m}\text{Tc}$ -MIBI scintigraphy.

**Conclusion:**  $^{99m}\text{Tc}$ -MIBI parathyroid scintigraphy is most likely to yield identification and localization of a parathyroid adenoma when both PTH and calcium are elevated; however, although there is no lower limit of PTH which can predict a negative study, we cannot recommend  $^{99m}\text{Tc}$ -MIBI parathyroid scintigraphy if the serum calcium is  $<2.51\text{ mmol l}^{-1}$ .

## Introduction

Primary hyperparathyroidism (PHPT) has been diagnosed with increasing frequency in recent years owing to increased awareness and to advances in laboratory techniques especially the introduction of automated blood analysers that allowed for routine multi-channel blood chemistry testing (Health et al., 1980; Abdelhamid, 2006).

Since 1925 when Felix Mandl (1925) performed the first successful parathyroidectomy at the Hochenegg Clinic in Vienna, surgery has become recognized as the only effective therapy for PHPT. Bilateral neck exploration has been the mainstay of surgery (Van Herden & Grant, 1991), but the development of minimally invasive approaches has changed the dogma of routine bilateral neck exploration (BNE) and its attendant complications (Thomas & Wilshort, 2003; Domenico et al., 2007). Consequently, accurate preoperative localization is

absolutely critical for appropriate surgical treatment (Coakley, 1995; Mordechai et al., 2003; Thomas & Wilshort, 2003).

Of all available localizing imaging modalities, technetium  $^{99m}\text{Tc}$  sestamibi ( $^{99m}\text{Tc}$ -MIBI) scanning, which was introduced by Coakley et al. (1989), has become the imaging modality of choice (Moure et al., 2008).  $^{99m}\text{Tc}$ -MIBI localizes non-specifically in mitochondria, and to some extents in the cytoplasm, in response to elevated membrane potentials. Elevated membrane potentials are directly related to metabolic state and parathyroid adenomas typically have a very high metabolic rate for their sizes (Goran, 1997; Geoffrey, 2000; Moshe et al., 2001).

The main pathology in primary hyperparathyroidism is deficient sensitivity of the pathological parathyroid gland to inhibition by ambient calcium (Ca) (Allen, 1991; Goran, 1997; Geoffrey, 2000). This may partly results from loss-of-function mutation of CaSR and/or the PKC activity within the abnormal cells, leading to impaired feedback inhibition of parathormone

(PTH) secretion with a shift of the Ca-PTH set-point higher (Allen, 1991; Goran, 1997; Geoffrey, 2000).

The degree of hypercalcaemia in primary hyperparathyroidism seems to be closely related to defective regulation of PTH secretion, metabolic rate and elevated membrane potential, than to increased mass of parathyroid tissue (Geoffrey, 2000). Indeed, in some patients, the hypercalcaemia may be surprisingly marked despite only modest glandular enlargement (Allen, 1991). Therefore, serum calcium level in primary hyperparathyroidism may play a key role in modifying  $^{99m}\text{Tc}$ -MIBI kinetics by influencing the membrane potential (Geoffrey, 2000; Pons et al., 2003). However, there is paucity of studies comparing serum calcium levels and dual-phase  $^{99m}\text{Tc}$ -MIBI parathyroid scintigraphy.

This study is therefore intended to determine whether serum calcium level correlates with positive  $^{99m}\text{Tc}$ -MIBI scintigraphy in localization of pathological parathyroid tissue. It also aimed to determine the serum calcium level at which the hyperfunctioning parathyroid gland is likely to be detected by  $^{99m}\text{Tc}$ -MIBI dual-phase scintigraphy and to find out if there is a significant difference in serum calcium level in patients whose abnormal gland was localized on early imaging and in those that are localized on later images only.

## Materials and methods

This was a cross-sectional prospective study carried out in department of Nuclear Medicine, Steve Biko Academic Hospital/University of Pretoria, and this study was approved by the joint ethics committee of Steve Biko Academic Hospital/University of Pretoria.

All adult patients with a diagnosis of primary hyperparathyroidism and referred to department of Nuclear Medicine for  $^{99m}\text{Tc}$ -MIBI parathyroid imaging were recruited randomly for the study after giving written informed consent.

Those excluded were pregnant women, and those with known co-morbidities that were likely to increase serum calcium other than primary hyperparathyroidism, e.g., malignancies and obvious granulomatous diseases. Also excluded were patients on anti-thyroid medications as part of the standard imaging protocol was to perform a thyroid scintigraphy in addition to the  $^{99m}\text{Tc}$ -MIBI dual-tracer washout study. Also any patients in whom current (<2 weeks) plasma PTH and calcium levels were not available.

### $^{99m}\text{Tc}$ -MIBI imaging

The dual-phase, dual-tracer method of parathyroid imaging was conducted using departmental standard protocols.

After a thorough explanation of the imaging procedure to patients and emphasis on the importance of lying still during imaging, intra-venous access was obtained. All patients received 148 MBq  $^{99m}\text{TcO}_4^-$ , pertechnetate, intravenously, 15 min later 40 ml Perchloride was given orally to facilitate washout of  $^{99m}\text{TcO}_4^-$  from the thyroid gland. Planar images of

the neck were acquired using low-energy, high-resolution collimator positioned as near as possible to the neck, using a  $256 \times 256$  matrix in a  $2\times$  zoom with a photopeak set at  $140 \text{ keV} \pm 10\%$ . All images were performed on a dual detector gamma camera (Infinia Hawkeye; GE, Milwaukee, MN, USA) 20 min after the pertechnetate injection for 5 min or at least 800 000 counts. With the patient's head and neck in the same position, 925 MBq  $^{99m}\text{Tc}$ -MIBI was administered. Three static images were acquired in anterior, left and right anterior  $30^\circ$  oblique view 20 min after tracer administration. A mediastinal image without zoom was acquired. This is followed immediately with SPECT/CT of the neck and upper thorax. This was acquired into a  $128 \times 128$  matrix with 30 s per step and 60 steps over a full  $360^\circ$  orbit. A low-dose (2.5 mAS, 140 kVp) CT was also performed covering the area of the SPECT acquisition. The patient was allowed to leave the imaging couch but returned at 2 h for a similar set of planar and SPECT/CT images. Imaging using a pinhole collimator was performed of the thyroid at 3 h.

The patient was then taken off the imaging bed and similar planar views were obtained starting at 2 h post- $^{99m}\text{Tc}$ -MIBI injection (delayed images) and were acquired for identical times. A pinhole imaging was performed 3 h post- $^{99m}\text{Tc}$ -MIBI injection.

Both statics and SPECT/CT images were analysed on Xeleris workstation (GE) by visual inspection. In addition, an isocontour region of interest was drawn automatically over the thyroid gland and subtraction images (early minus thyroid and delayed minus thyroid) with different subtraction factors were produced. All images were read by an experienced nuclear medicine specialist who was blind to the patient's serum calcium and PTH.

A positive study was defined when a solitary focus of  $^{99m}\text{Tc}$ -MIBI greater than background neck activity was noted on the early/or delayed imaging. The site of such uptake was also noted.

Serum calcium was analysed by SYNCHRON System (Beckman Coulter, Brea, CA, USA), using Ion-selective electrode method (Anker et al., 1981) and corrected serum total calcium ( $\text{mmol l}^{-1}$ ) reported.

Parathormone was estimated by Access Immunoassay System (Beckman Coulter) which uses two-site immunoenzymatic (Sandwich) assay (Souberbielle et al., 2006).

Data were analysed using STATA 11 (Statacorp LP, Station College, TX, USA). Summary descriptive statistics for each variable were determined. Correlation studies were performed for serum calcium and PTH and scan result.

Statistical significance was defined as  $P \leq 0.05$ .

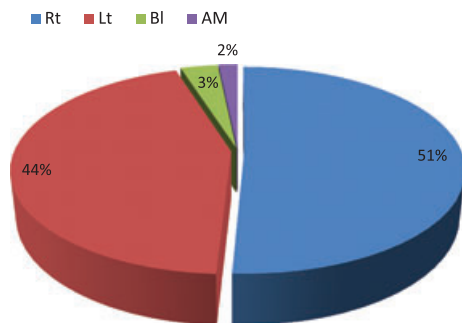
## Results

A total of 111 patients completed the study, with a mean age 55 years (range 13–87 years). All but the 13-year old were adults. Of the 23 men, 11 (48%) had a positive  $^{99m}\text{Tc}$ -MIBI scintigraphy compared to 50 of 88 (57%) women (Table 1).

**Table 1** Demography of patients who completed the study.

Variable	Positive (%)	Negative (%)	Total (%)
Total	61 (55)	50 (45)	111 (100)
Men	11 (10)	12 (11)	23 (21)
Women	50 (45)	38 (34)	88 (79)
PTH > 87 (ng l <sup>-1</sup> )	60 (54)	36 (32)	96 (86)
PTH ≤ 87 (ng l <sup>-1</sup> )	01 (1)	14 (13)	15 (13)
Normocalcaemia	05 (5)	31 (28)	36 (33)
Hypercalcaemia	56 (50)	18 (16)	74 (66)
Hypocalcaemia	0 (0)	0 (1)	1 (1)

PTH, parathormone.

**Sites of location of abnormal parathyroid gland****Figure 1** A pie chart showing percentage of sites of identified adenomas.

Of the 61 patients where <sup>99m</sup>Tc-MIBI localized a parathyroid adenoma, 31 (51%) were associated with the right lobe (24 at the lower pole, seven at the upper pole) (Fig. 1). There were 27 patients (44%) associated with the left lobe (26 at the lower pole, one at the upper pole). Two patients had bilateral adenomas; and in a single patient, an anterior mediastinal site was found.

Among the patient with a positive scintigraphy, one patient had a plasma PTH (87 ng l<sup>-1</sup>) at the upper limit of reference range (16–87 ng l<sup>-1</sup>). Meanwhile, 14/50 patients (28%) with a negative <sup>99m</sup>Tc-MIBI study had plasma PTH results lower than the upper limit of the normal range. There were 5/61 patients (12%) with a positive <sup>99m</sup>Tc-MIBI had a serum calcium close to the upper limits of reference range (2.05–2.56 mmol l<sup>-1</sup>). All other patients had hypercalcaemia. There was a single patient with hypocalcaemia (Ca <2.05 mmol l<sup>-1</sup>) who had a negative <sup>99m</sup>Tc-MIBI study. Of the other patients with a negative <sup>99m</sup>Tc-MIBI study, 31 were normocalcaemic and 18 had hypercalcaemia.

In those patients with positive <sup>99m</sup>Tc-MIBI study, the mean (±SEM) PTH was 432 ng l<sup>-1</sup> (±57) and calcium, 2.84 mmol l<sup>-1</sup> (±0.03) both significantly greater than the corresponding figures for those with a negative <sup>99m</sup>Tc-MIBI study where the mean PTH was 145 ng l<sup>-1</sup> (±17) and the calcium, 2.48 mmol l<sup>-1</sup> (±0.03) (Table 2). In addition, the inorganic phosphate was significantly lower at 0.86 mmol l<sup>-1</sup> (±0.02) in

**Table 2** Comparisons of mean ± SEM biochemical parameters and age between patients with positive scan results and those with negative scan results.

Variables	Positive (M ± SEM)	Negative (M ± SEM)	P-values (S/NS)
PTH (ng l <sup>-1</sup> )	432 ± 57	145 ± 17	0.000 (S)
Calcium (mmol l <sup>-1</sup> )	2.84 ± 0.03	2.48 ± 0.03	0.000 (S)
Albumin (g l <sup>-1</sup> )	37.5 ± 0.6	39.4 ± 0.6	0.033 (S)
Magnesium (Mg <sup>2+</sup> ) (mmol l <sup>-1</sup> )	0.86 ± 0.01	1.53 ± 1.66	0.320 (NS)
Inorganic phosphate (mmol l <sup>-1</sup> )	0.86 ± 0.02	1.12 ± 0.03	0.000 (S)
Alk phosphatase (U l <sup>-1</sup> )	95.8 ± 4.4	92.0 ± 7.3	0.793 (NS)
Age (years)	55.8 ± 1.8	53.5 ± 2.3	0.427 (NS)

PTH, parathormone.

those with a positive study than those with a negative study where it was 1.12 mmol l<sup>-1</sup> (±0.03). Although both the serum albumin and magnesium were lower in patients with a positive <sup>99m</sup>Tc-MIBI study, these differences were not significant. Similarly, neither the patient's age nor alkaline phosphatase was significantly different in those patients with a positive or negative <sup>99m</sup>Tc-MIBI study.

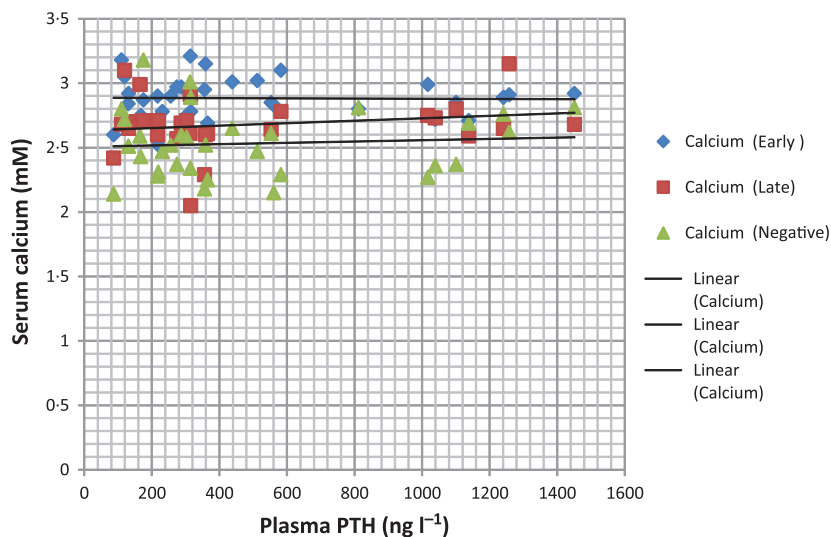
<sup>99m</sup>Tc-MIBI scintigraphy identified a parathyroid adenoma on the early images in 34 patients (56%) and the remaining 27 patients were positive on later images only. Both the PTH and calcium were significantly higher and inorganic phosphate lower, in those patients seen with the early images compared to the late images only (Table 3).

Therefore the higher the PTH, the greater the likelihood that a parathyroid adenoma will be identified on early imaging so that any patients with a PTH <200 ng l<sup>-1</sup> is unlikely to have a positive <sup>99m</sup>Tc-MIBI study (Fig. 2). Of those patients, 67% with a positive <sup>99m</sup>Tc-MIBI parathyroid scan had a PTH >200 ng l<sup>-1</sup>. Overall 67% compared to only 9% of those with a negative <sup>99m</sup>Tc-MIBI study; however, for those with a positive early <sup>99m</sup>Tc-MIBI scan, this rose to 85%.

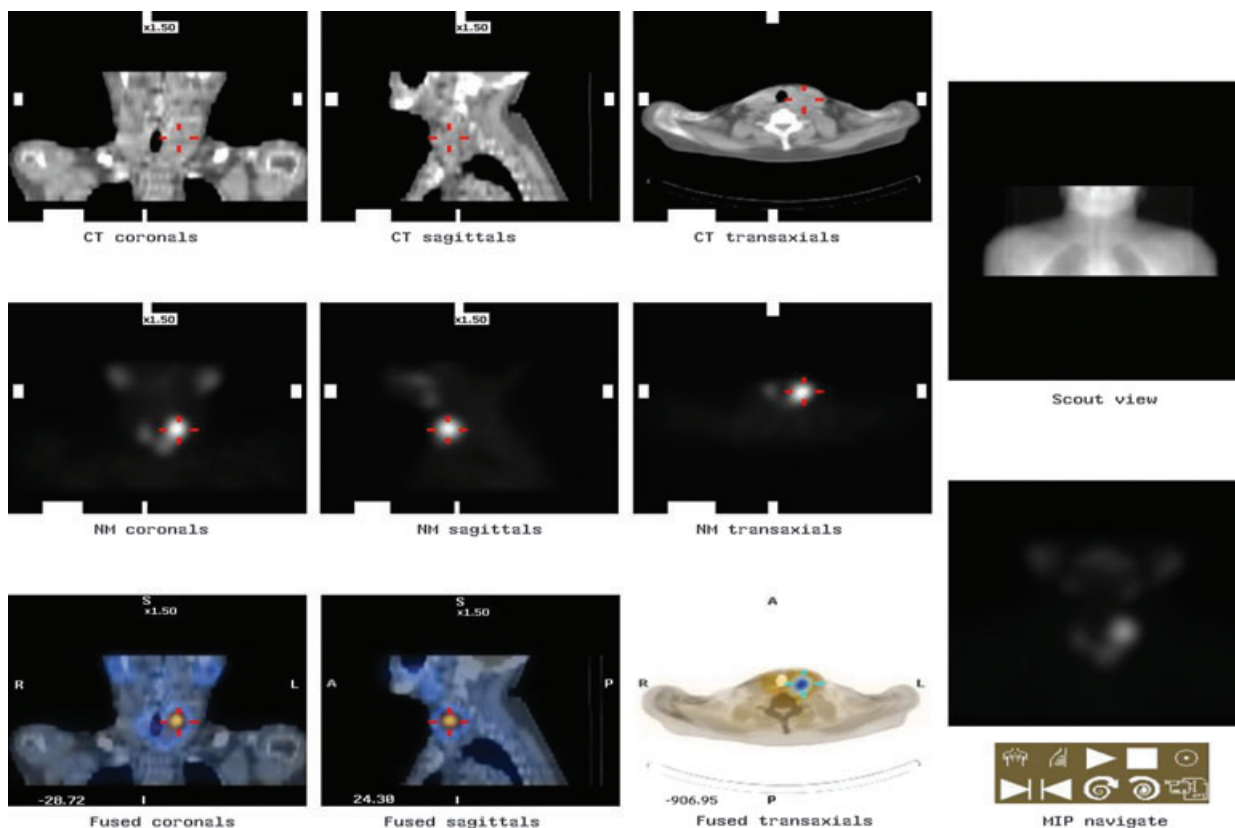
**Table 3** Comparisons of mean ± SEM biochemical parameters and age between patients with positive results located on early images and those with positive results located on later images only.

Variables	Positive on early images (M ± SEM)	Positive on later images (M ± SEM)	P-values (S/NS)
PTH (ng l <sup>-1</sup> )	613 ± 91	204 ± 18	0.000 (S)
Calcium (mmol l <sup>-1</sup> )	2.90 ± 0.04	2.75 ± 0.03	0.005 (S)
Albumin (g l <sup>-1</sup> )	37.2 ± 0.9	37.9 ± 0.7	0.553 (NS)
Magnesium (mmol l <sup>-1</sup> )	0.85 ± 0.02	0.87 ± 0.02	0.418 (NS)
Inorganic phosphate (mmol l <sup>-1</sup> )	0.82 ± 0.03	0.92 ± 0.04	0.03 (S)
Alk phosphatase (U l <sup>-1</sup> )	95.4 ± 5.4	93.2 ± 7.0	0.927 (NS)
Age (years)	53.2 ± 2.7	59.0 ± 2.3	0.106 (NS)

PTH, parathormone.



**Figure 2** A scattergram of serum calcium against plasma parathormone in patients with adenomas identified on early, later images and in those with negative scans.



**Figure 3** Showing a result in one of our patient demonstrating the value of SPECT and SPECT/CT in parathyroid scintigraphy.

A serum calcium value  $\geq 2.70 \text{ mmol l}^{-1}$  was present in 97% of patients with a parathyroid adenoma identified on early images (Fig. 3). Overall a serum calcium of  $>2.70 \text{ mmol l}^{-1}$  was found in 82% of patients with a positive  $^{99\text{m}}\text{Tc-MIBI}$  study but only 14% of those with a negative  $^{99\text{m}}\text{Tc-MIBI}$  study. It is also shown that patients whose serum total calcium  $<2.51 \text{ mmol l}^{-1}$  rarely have a positive  $^{99\text{m}}\text{Tc-MIBI}$  study.

## Discussion

This study confirms that a  $^{99\text{m}}\text{Tc-MIBI}$  scintigraphy is more likely to be positive in those patients with the highest PTH and calcium measurements. This is not entirely unexpected as both the level of PTH and its subsequent effect on increasing calcium and reducing phosphate are dependent on tumour bulk such

that the bulkier the tumour the more likely a positive  $^{99m}\text{Tc}$ -MIBI study.

Our patient group is similar to those in published studies from the studies in USA (Rao *et al.*, 2000), Japan (Yamashita *et al.*, 2002) and Europe (Carnevale *et al.*, 2004). Although patients from another developing country India (Bhansali *et al.*, 2005; Priya *et al.*, 2008) showed a lower average age but may just reflect the difference demographics of the population being studied. It is possible that the majority of the patients studied in India suffered from multiple endocrine neoplasia or benign familial hypocalcaemic hypercalcaemia which are usually manifest in younger age group (Geoffrey, 2000; Kearns & Thompson, 2002). Primary hyperparathyroidism is most commonly described as a disease of postmenopausal women (Clark, 1994). Certainly in our group, more women were imaged than men but this may also reflect social factors as men may not seek medical help for the medical symptoms related to hyperparathyroidism or are less commonly screened for osteoporosis which often results in women having a plasma calcium measurement.

Surgery is the only curative therapy for primary hyperparathyroidism and should be considered in every patient (Kearns & Thompson, 2002). The development of minimally invasive surgery places a greater emphasis on preoperative localization (Kearns & Thompson, 2002; Moure *et al.*, 2008). This depends on optimal imaging protocols and possible improved tracers to enable smaller adenomas to be visualized and methods to overcome the possible role of P-glycoprotein expression causing early washout of  $^{99m}\text{Tc}$ -MIBI (O'Doherty & Kettle, 2003; Moure *et al.*, 2008).  $^{99m}\text{Tc}$ -MIBI has reported specificities and sensitivities of 90–95% and 90–98%, respectively, especially when as with our study imaging is optimized with SPECT and SPECT/CT (Denham & Norman, 1998; Kearns & Thompson, 2002; Rubello *et al.*, 2003; Hindie *et al.*, 2009). The results of our study suggest that in those patients with the most active adenomas, these optimal imaging techniques should be applied to both the early and later images. This will be of particular importance if there is a very active adenoma with good initial uptake of  $^{99m}\text{Tc}$ -MIBI but subsequent fast efflux of the  $^{99m}\text{Tc}$ -MIBI owing to p-glycoprotein.

In parathyroid scintigraphy, preoperative differentiation of an adenoma as left or right, superior or inferior allows the surgeon to alter the incision site, minimizes dissection and save operation time. Whilst we noted an almost equal number of adenomas in the left compared to the right lobes of thyroid (left = 27, right = 31), over six times more adenomas were localized to the lower pole than the upper pole. However, it has been noted this difference may be factious and care should be taken in interpreting these scans as superior glands can become pendulous owing to longer vascular pedicle leading to greater mobility allowing the superior glands to prolapsed to an anatomically lower position (Chan *et al.*, 1991; Manesh *et al.*, 2003; Rubello *et al.*, 2003). Similarly, accuracy of anatomical location may also be limited by patients positioning during scanning, given that the parathyroid glands can move indepen-

dently of the thyroid gland, which is the frame of reference on the scan (Chan *et al.*, 1991). Therefore it has been suggested that preoperative imaging is best used when a neck is being re-explored as scar tissue will limit parathyroid movement within the neck (Rubello *et al.*, 2003).

The diagnosis of hyperparathyroidism is based on biochemical markers. A hypercalcaemia that persists based on repeated serum calcium measurements and is accompanied by an elevated or inappropriately high-normal PTH level is diagnostic of hyperparathyroidism (Kearns & Thompson, 2002). However, a cautionary note is that a minority of patients (10–15%) with hyperparathyroidism have PTH levels at the high end of the reference range, which is inappropriately high in the presence of elevated serum calcium (Kearns & Thompson, 2002). In this study, only one patient whose scan result was positive had a normal PTH and this was at the upper limit of reference range in our institution. Although it is to be noted that the plasma calcium of the same patient was in the hypercalcaemic range. Meanwhile, five of the patients studied in our series had a positive scan result but their serum calcium levels were in the upper limit of normal reference range. This is called normocalcaemic hyperparathyroidism and may be an indication of early diagnosis of the disease (Kearns & Thompson, 2002). However, of the 18 patients who had hypercalcaemia and negative scan result, 14 had plasma PTH level lower than upper limit of reference range. In these patients, the diagnosis of primary hyperparathyroidism and request for  $^{99m}\text{Tc}$ -MIBI scintigraphy appear to be inappropriate. Possibly other causes of hypercalcaemia such as granulomatous disease should be sought. In patients with appropriately diagnosed primary hyperthyroidism, the major factor influencing scintigraphic detection of a parathyroid adenoma seems to be size of glands <500 mg are often not seen with  $^{99m}\text{Tc}$ -MIBI commonly missed (Denham & Norman, 1998; Rubello *et al.*, 2003; Hindie *et al.*, 2009). However, false-negative results have been reported in large glands while some very small adenomas have been identified seen with  $^{99m}\text{Tc}$ -MIBI imaging (Pons *et al.*, 2003). In this regard, parathyroid scintigraphy should be considered a functional test. In fact, suppression of parathyroid cell activity by calcitriol pulse therapy was confirmed by  $^{99m}\text{Tc}$ -MIBI scintigraphy and correlated well with the decrease of PTH blood level (Piga *et al.*, 1996; Pons *et al.*, 2003). Consequently the influence of other biological factors, such as increased perfusion and functional activity, abundant mitochondria-rich oxyphil cells, cell cycle phases, cannot be over emphasized (Carpentier *et al.*, 1998; Pons *et al.*, 2003).

Although the PTH is significantly higher in patients with positive scan results when compared to those with negative scan results, which is in keeping with findings in other studies where an elevated plasma PTH concentration was correlated with positive  $^{99m}\text{Tc}$ -MIBI study (Piga *et al.*, 1996). We were unable to identify a figure at which we can fully predict that any given  $^{99m}\text{Tc}$ -MIBI study will yield only a positive result. It was noted, however, that there were no positive  $^{99m}\text{Tc}$ -MIBI studies in any patient with a serum calcium <2.51 mmol l<sup>-1</sup> a figure which

although still within the normal range could be used as a cut-off below which a  $^{99m}\text{Tc}$ -MIBI does not seem to depend on frank hypercalcaemia (Pattou et al., 1998; Manesh et al., 2003).

In conclusion,  $^{99m}\text{Tc}$ -MIBI parathyroid imaging is most likely to yield identification and localization of a parathyroid adenoma

when both PTH and calcium are elevated; however, although there is no lower limit of PTH which can predict a negative study, we cannot recommend  $^{99m}\text{Tc}$ -MIBI parathyroid scintigraphy if the plasma calcium is  $<2.51 \text{ mmol l}^{-1}$ .

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