

# The investigative evolution of primary hyperparathyroidism: an update

## Abstract

Primary hyperparathyroidism (PHPT) is the most common cause of hypercalcaemia encountered in the general population. Traditional investigation of PHPT consisted of Sestamibi and ultrasound (US) scanning followed by a bilateral neck exploration (BNE), which remains the gold standard surgical approach. Newer imaging modalities have however facilitated the movement toward minimally invasive parathyroidectomy and these are discussed.

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**Abbreviations:** PHPT, primary hyperparathyroidism; US, ultrasound; BNE, bilateral neck exploration; MIP, minimally invasive parathyroidectomy; PPV: positive predictive value

## Introduction

Primary hyperparathyroidism (PHPT) is the most common cause of hypercalcaemia encountered in the general population.<sup>1</sup> Whilst these patients traditionally presented with symptoms including bone pain, fatigue, nephrolithiasis and depression, the majority of patients are now recognized during routine biochemical screening and are asymptomatic on presentation.<sup>1,2</sup> Traditional investigation of PHPT consisted of Sestamibi and ultrasound (US) scanning followed by a bilateral neck exploration (BNE), which remains the gold standard surgical approach.<sup>3</sup> More recently however there has been a shift toward less invasive more focused surgery in the form of minimally invasive parathyroidectomy (MIP). The utilization of this technique is dependent upon accurate pre-operative localization of the adenoma.<sup>4</sup> Newer imaging modalities including SPECT, SPECT/CT as well as 4D CT scanning has revolutionized the management of PHPT, however each of these have certain limitations and the selection of the most appropriate modality is an important consideration to maximize operative success. The aim of this update was to evaluate current localization strategies in the management of PHPT.

## Discussion

Primary hyperparathyroidism affects 1% of the population with the vast majority (85-96%) of cases secondary to a single adenoma and the remainder due to double adenomas or multigland hyperplasia.<sup>1,4</sup> Parathyroidectomy is the treatment of choice for symptomatic patients and there is a growing body of evidence to support surgical intervention in asymptomatic patients with mildly elevated serum calcium levels, as a significant improvement in both post-operative bone density and quality of life has been demonstrated in this patient group.<sup>5</sup>

In experienced hands, MIP performed in conjunction with intra-operative PTH monitoring offers success rates comparable to those observed in bilateral<sup>6</sup> gland exploration.<sup>1,5</sup> Compared to traditional BNE, MIP is associated with a reduction in cost, less post-operative pain, decreased morbidity and improved cosmesis due to smaller incision size<sup>1,3</sup>. MIP is however entirely dependent upon accurate pre-operative localization of the lesion.

Sestamibi scanning utilizes technetium (Tc99m), which becomes concentrated within intracellular mitochondria following injection. Two hours after injection thyroid cells demonstrate a significant decrease in Tc99m uptake whilst abnormal parathyroid oxyphil cells retain the marker in high mitochondrial concentrations, which is the basis of localization with this technique.<sup>1</sup> A gamma camera is used to obtain planar two dimensional images. Limitations of this technique include the presence of multi-nodular thyroid disease,<sup>6</sup> gland hyperplasia, patients with mildly elevated serum calcium (<2.8mmol/L), small adenomas (< 500mg) and obese patients.<sup>1,3,5-8</sup> SPECT scanning is a variation of Sestamibi scanning and utilizes the same radio-active tracer (Tc99m) however is able to provide 3D reconstruction of multiple 2D images obtained during the scan. The addition of CT scanning (SPECT/CT) adds anatomical localization to the functional information obtained during SPECT scanning.<sup>1</sup>

Four dimensional CT scanning of the parathyroid's was first introduced in 2006.<sup>3</sup> It is a contrast CT scan which depends on the perfusion characteristics of parathyroid adenomas as these typically demonstrate a rapid uptake and washout of contrast, which accounts for the fourth dimension.<sup>7</sup> Four separate CT scans are obtained, the first without contrast (pre contrast), the second scan (Immediate post contrast) 25seconds after injection of contrast, the third (early delayed) is performed 30seconds after the second and the fourth (late delayed) 45seconds after completion of the early delayed phase scan. The pre contrast scan clearly outlines the iodine rich thyroid gland, whilst the three subsequent post contrast scans clearly demonstrate the vascular characteristics (early washout of contrast) of adenomas compared to the surrounding thyroid gland and lymph nodes.<sup>9</sup> It provides both anatomical (3D CT) and functional information (perfusion characteristics) that can easily be interpreted by the operating surgeon. 4D-CT scanning has gained popularity as an adjunct should sestamibi and ultrasound prove inconclusive<sup>3,6</sup> and it has even been proposed as a first line localization technique by some.<sup>7</sup> In contrast to Sestamibi and SPECT imaging, 4D-CT scanning is accurate even in those patients with mildly elevated serum calcium (< 2.7 mmol/l) and adenomas of less than 500mg. An observation which has led some to suggest 4D-CT as the investigative modality of choice in PHPT patients presenting with mild hypercalcaemia (<2.7 mmol/l).<sup>6</sup>

If the accuracy of these different techniques are considered it becomes apparent that 4D CT scanning is able to more accurately lateralize and localize the adenoma compared to ultrasound and sestamibi as reported by Starker, et al.,<sup>7</sup> In their series of 87 patients

4D CT scanning was able to identify the correct side of the neck in 93.9% of cases and the correct quadrant in 85.7% of cases which proved superior to both US (lateralization = 71.2% and localization = 48%) and sestamibi (lateralization = 61.6% and localization = 40%) scanning. Furthermore 4DCT scanning was able to identify multigland hyperplasia in 85.7% of cases, a well-recognized Achilles heel of sestamibi and SPECT scanning.<sup>7</sup> These findings are supported by the findings of Cheung et al. Whilst their meta-analysis was hampered by the relative paucity of published data on the use of 4D-CT scanning they recorded a sensitivity and positive predictive value (PPV) of almost 90% and 93.5% respectively for 4D-CT which compared favorably to both ultrasound (sensitivity = 76.1%; PPV = 93.2%) and SPECT scanning (sensitivity = 78.9%; PPV = 90.7%).<sup>4</sup>

If 4D-CT scanning has superior accuracy rates, is able to identify smaller adenomas and is more accurate in multigland hyperplasia, the question is why not use it routinely as a first line investigation? Annual background radiation exposure amounts to 3milliSiverts (mSv). SPECT scanning amounts to 7.8mSv compared to 10.4mSv overall exposure for a 4D-CT. The radiation exposure to the thyroid gland however with a 4D-CT is 57times higher compared to SPECT scanning. It has been established that early radiation exposure to the thyroid gland is associated with an increased risk of thyroid carcinoma and in the case of 4D CT scanning it has been calculated that a 20year old woman has a 0.1% risk of developing a 4D-CT related thyroid carcinoma. This risk is age related with a substantial reduction noted in older patients, with 0.01% risk recorded in a 40year old female and 1 in 100 000 amongst 60year old females.<sup>8</sup> It is important to recognize that the mean reported age at presentation of PHPT patients in several case series is around 60years old<sup>6</sup> which would translate to a low associated risk in the majority of patients (0.00001% risk of developing a thyroid carcinoma secondary to the radiation exposure from a 4D CT scan), however in the younger patient these risks warrant serious consideration and discussion with the patient when deciding upon the investigation of choice.

## Conclusion

There has been a dramatic shift in both the presentation and management of PHPT patients. The majority of PHPT patients is now diagnosed following routine biochemical screening and is often asymptomatic<sup>6</sup>. This is in stark contrast to the traditional presenting features of nephrolithiasis, osteoporosis, peptic ulcer disease and even pancreatitis.<sup>11</sup> This has coincided with a movement toward focused minimally invasive surgery which is dependent upon accurate localization. Traditional localization strategies often prove inconclusive in those patients that are asymptomatic on presentation with mildly elevated serum calcium, which has resulted in the development of newer imaging modalities. Based on the serum calcium on presentation, a 4D-CT scan should be considered as the initial investigative modality in those patients that present with a mildly elevated serum calcium (< 2.8mmol/l) as sestamibi and SPECT imaging often is not accurate in these patients. In the remainder of patients SPECT scanning should remain the investigation of choice, reserving 4D-CT scanning as an adjunct in inconclusive cases.

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## Conflicts of interest

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