

# Multiphase CT Scanning (4D-CT) In Patients with Parathyroid Adenoma: A New Paradigm?

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## Abstract

Patients undergoing evaluation for primary hyperparathyroidism often undergo Sestamibi scans and ultrasound examination to diagnose and localize the parathyroid tumor. Unfortunately, these studies are sometimes non-localizing. In this study, a comparison of non-localizing Sestamibi or ultrasound versus multiphase CT scan (MCT) and confirmed by pathologic findings at surgery is made.

In 6 surgical patients with pathology proven adenoma, the MCT scan was diagnostic in 6 of 7 potential parathyroid adenomas. The sensitivity rate was 86%.

In patients with negative or equivocal Sestamibi scanning or ultrasound examination, the multiphase CT scan is valuable in identifying the site of the parathyroid adenoma. This modality is emerging as an important imaging modality in patients with primary hyperparathyroidism.

## INTRODUCTION

Hyperparathyroidism due to a parathyroid adenoma is a much different disease now as compared to several decades ago. No longer do patients present with the “groans, stones, moans” of symptomatic disease but are frequently diagnosed by routine serum chemistry studies. The primary treatment modality however has remained that of surgery

With the advent of minimally invasive surgical procedures, precise localization of the pathology has become more important. Localization of parathyroid disease has typically been carried out via a Sestamibi scan to identify the presence of hyperfunctioning parathyroid tissue with subsequent localization of the abnormal gland by ultrasound examination. However, one or both of these studies may be negative or equivocal. In these cases, the MCT has proven valuable in locating hard to identify parathyroid adenomas.

By knowing the exact location of the abnormal parathyroid gland, a limited dissection with decreased complications, decreased mobility and shortened hospital stay are all possible. There is also the potential for cost savings, which are becoming more important in the current medical environment.

MCT, also known as four dimensional computer tomography (4D-CT), was initially described in 2006.<sup>1</sup> This imaging modality is based on changes in the rate of perfusion of contrast as compared to a traditional CT scan. The so called fourth dimension is related to the differences in perfusion characteristics of abnormal parathyroid glands which in turn gives functional information about the status of the gland.

## MATERIAL AND METHODS

In patients with suspected hyperparathyroidism due to parathyroid gland adenoma, a sestamibi scan and ultrasound were obtained. In cases of a negative or equivocal initial screening with the sestamibi scan or ultrasound, MCT was obtained to attempt to localize the site of abnormal parathyroid tissue. The MCT has been described as obtaining images are in 1.2 mm section thickness from the level of the mandible to the carina. This non-contrasted portion of the scan is followed by multiphase imaging following the administration of intravenous Iohexol 300 (omnipaque), a non-ionic iodinated contrast material.<sup>2</sup> This dye is administered at a dose of 2 ml/kg of patient weight with a rate of 4 ml/sec.<sup>2</sup> The current protocol used in this study consists of a 3 phase study:1) unenhanced 2.5 mm axial views from the inferior mandible to the carina.2) an early arterial phase consisting of 1.25 axial images in the same distribution with 5 mm coronal and sagittal reconstruction 3)a venous phase consisting of 2.5 mm axial images in the same distribution.(Figure1 a-d)



1a. Delayed planar image from Sestamibi scan shows no uptake to suggest parathyroid adenoma. SPECT images were also negative (not shown)



1b. Unenhanced CT image shows left parathyroid adenoma to be lower density and separate from the thyroid, both findings confirming lesion is not thyroid in origin. (This patient not a part of the current case series)



1c. and 1d. Early phase images from MCT show the classic hyper enhancement of bilateral small parathyroid adenoma in this patient. (Arrows)



There were 7 patients in whom the traditional paradigm of Sestamibi/ultrasound did not adequately localize the patient's parathyroid adenoma. In these patients the MCT was utilized in an attempt to localize the parathyroid adenoma.

## RESULTS

In the last two years, 7 patients have undergone multiphase CT scanning after the failure of Sestamibi scan and ultrasound to accurately identify the site of pathology in the course evaluation for parathyroid adenoma in a community hospital setting.

A pathologic diagnosis of parathyroid adenoma is considered the gold standard for evaluating the effectiveness of MCT in this study. One of the patients had negative Sestamibi, ultrasound and MCT studies and has elected a course of observation over a 4-gland exploration of the neck. Of the patients who have undergone surgery, there were 6 glands of the 7 identified by MCT in whom the pathology was confirmed by surgical findings and pathologic diagnosis.

(Table 1). Inpatients 1, 3, and 5 the MCT was valuable in localizing the tumor mass specifically to the tracheoesophageal groove. In patient #2 the Sestamibi only localized the PTA to the left thyroid area while the MCT correctly localized the PTA to the superior thyroid area which was confirmed at surgery. In patient #4 the MCT correctly identified an ectopic PTA beneath the manubrium. In patient #6, the only false positive in the series, the MCT indicated bilateral PTA but only one was found at surgery. This patient is eucalcemic at one year postop. Overall the sensitivity was 86% as is the positive predictive value. As normal glands by imaging are rarely examined at surgery in a minimally invasive approach the specificity could not be calculated.

Patient	Age	Sex	Sestamibi	U/S	MCT	Surgery	Path, mg
1	76	M	R side	NL	R TEG	R TEG	840
2	22	M	L, side	NL	L, superior	L, superior	180
3	68	F	Bilateral Uptake	NL	L, TEG	L, TEG	350
4	82	F	L inferior thyroid	NL	Ectopic, L Mediastinum	L, posterior to manubrium	1720
5	79	F	R,inferior	NL	R TEG	R TEG	3420
6	56	F	NL	NL	Bilateral	L, inferior	190
7	66	F	NL	NL	NL	NA	NA

Table 1: Patient Series. All of the surgical patients had confirmed PTA. (R= Right, L=Left, TEG= Tracheoesophageal Groove, NL= non-localizing, NA= not applicable, \* in this patient a second U/S exam obtained after the MCT did localize the PTA)

## DISCUSSION

As noted previously, not only patients with symptomatic primary hyperparathyroidism but those with asymptomatic disease are considered for surgery as well. Asymptomatic patients who meet any of the following guidelines should be referred for surgery. These include serum calcium of 1 mg/dl above the upper limit of normal, impaired renal failure (GFR less than 60 ml/min), a negative T-score or history of previous fracture or bone fragility in those less than 50 years old.<sup>3</sup>

Currently the Sestamibi scan has been utilized to indicate physiologic activity of the abnormal parathyroid gland while the ultrasound examination has been utilized to provide anatomic location. It should be noted that the ultrasound examination is operator dependent and additionally cannot adequately visualize the areas such as the retrosternal and retro esophageal areas. The range of sensitivity for localization of a parathyroid adenoma ranges from 57-86% for ultrasound examination and 54-96% for the nuclear medicine Sestamibi study.<sup>4,5,6</sup> A meta-analysis of 43 studies regarding the preoperative evaluation for primary hyperparathyroidism included 19 studies that utilized ultrasound, this modality had a pooled sensitivity and positive predictive value of 76% and 93.2%.<sup>7</sup> In the same meta-analysis were 9 studies involving Sestamibi-SPECT with a pooled sensitivity and positive predictive value of 78.9 and 90.7%. There were only 2 studies regarding MCT, the results indicated a sensitivity of 89.4% and a positive predictive value of 93.5%.<sup>7</sup>

Several examples of the use of MCT are illustrative. An 82year-old female had become progressively disoriented at home and fell fracturing her pelvis. During hospitalization for her pelvic fracture, she was found to have hypercalcemia at 12 mg/dl with a parathyroid hormone assay of 532.1 pg/ml. Sestamibi scan was equivocal with some uptake in the left inferior thyroid area, but the ultrasound did not identify a definitive parathyroid mass. MCT was obtained and indicated an ectopically located parathyroid adenoma in the superior mediastinum on the left side. After removal of the adenoma, her parathyroid assay returned to normal at 71 pg/ml with normal calcium of 9.0. She is now some nine months post surgery and is living independently at home. (Figure 2) In this patient, the MCT was valuable in localizing an ectopically located gland which was removed expeditiously, sparing an elderly patient a bilateral neck exploration.



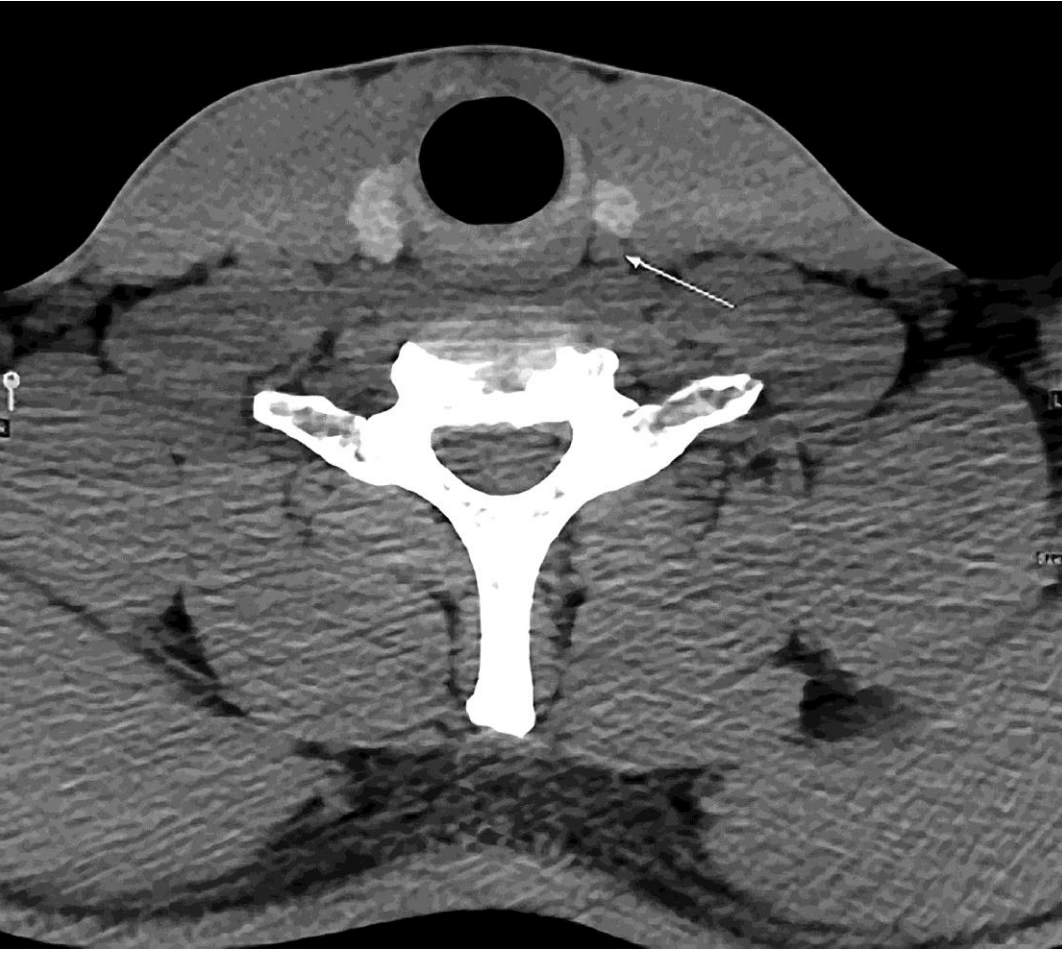
2a. and 2b. Ectopic parathyroid adenoma in left retrosternal area.

There are a number of reasons to consider MCT as the initial imaging study for patients with hyperparathyroidism. These include patients who may have multiple endocrine neoplasia syndrome, those undergoing reoperation of the neck, as well as those with smaller parathyroid tumors. On review of two patients with multiple endocrine neoplasia type II-A, Phillip et al recommend MCT as it can identify hyperfunctional parathyroid tissue and also provide anatomic information which is valuable in planning the surgical technique.<sup>8</sup>

In patients with recurrent hyperparathyroidism or a failed neck exploration, MCT is a valuable modality for locating hypercellular parathyroid disease.<sup>9</sup> a prospective data base was used to identify 45 patients undergoing reoperative parathyroidectomy using MCT preoperative localization. In patients who had had neck surgery for non-parathyroid disease, the MCT was successful in 82% of patients. In patients who had previously undergone an unsuccessful neck exploration for hyperparathyroidism, the MCT was successful in 91% of the patients. In a third group who had previously undergone resection of a hypercellular parathyroid gland but had recurrent disease, MCT was successful in localizing the tumor in 67% of the patients.<sup>9</sup> Beland et al carried out a study evaluating MCT in patients with non-localizing imaging or failed neck exploration. <sup>10</sup> In this study 25 patients underwent MCT followed by surgery. There were 20 patients with a solitary adenoma , dual adenoma in 2, four gland hyperplasia in 1, and 2 patients with no adenoma.<sup>10</sup> A retrospective blinded review by three radiologist revealed good interobserver reliability with a sensitivity of 82% (range79-88%) and a specificity of 92%( range 75-100%).<sup>10</sup>

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Another patient in the current series had calcium of 11.5mg/dl. The Sestamibi scan indicated a possible adenoma on the patient's left side but the ultrasound exam was negative. An MCT was then obtained and indicated a solitary adenoma in the left superior thyroid area. (Figure 3) The patient underwent a directed neck exploration with excision of a small superiorly located parathyroid adenoma weighing 190 mg with and appropriate decrease in his PTH level and normalization of his serum calcium. Another advantage of MCT is identification of small parathyroid glands. In a study of 135 patients undergoing parathyroidectomy, a comparison was made between Sestamibi and MCT.<sup>11</sup> MCT was noted to be more accurate in patients who had parathyroid adenoma weights which were less than 500 mg.<sup>11</sup> Additionally, MCT was more diagnostic in patients with calcium levels of less than 10.8 as compared to sestamibi.<sup>11</sup> In a study of 142 patients the sensitivity for MCT and ultrasound together was89%in detecting adenomas that weighed <150 mg to the correct quadrant of the neck.<sup>12</sup> It is postulated that the Sestamibi scan has difficulty in detecting glands weighing <600mg.<sup>12</sup>



3a. and 3b. Small left parathyroid adenoma with classic imaging appearance (arrows)

It is becoming recognized that MCT is effective when evaluating patients who have an equivocal or negative Sestamibi or ultrasound examination.<sup>9,10</sup> In a study of 87 patients, MCT had improved sensitivity 85.7% over sestamibi 40.4% and ultrasound 48% to localize parathyroid adenoma to the correct quadrant of the neck and ability to lateralize the parathyroid adenoma to one side of the neck.<sup>13</sup> Multi-gland disease is difficult to localize by any technique, but seems to be more diagnostic when MCT is used. In the previously noted study, MCT was able to predict multiglandular disease in 85.7% of the patients, while the sestamibi and ultrasound did not detect multiglandular disease in any patient.<sup>13</sup>

There are several potential downsides to the use of MCT. These include cost but in a study of cost analysis of preoperative localization techniques for primary hyperparathyroidism, MCT compared favorably with other imaging strategies.<sup>14</sup> Also to be considered is the risk of radiation from an MCT. Currently, the MCT dose is similar to that for a CT of the abdomen and pelvis. There are currently no studies that confirm radiation exposure from medical imaging causes cancer but this is becoming a concern to the general public. Radiation doses have the potential to decline further as more experience is obtained with the technique of MCT by shortening or eliminating some of the phases currently obtained in the MCT protocol.

The current study suffers from several shortcomings. The number of patients in the case series is small and does not lend itself to statistical analysis. There is a selection bias which likely affects the sensitivity quoted in this study as only the difficult patients in whom the Sestamibi and or ultrasound studies were non-localizing underwent MCT. In the future the authors are formulating plans to utilize all three imaging modalities in a prospective fashion or to use MCT as the initial study.

## SUMMARY

The current practice consists of a two point radiographic localization (sestamibi scan and ultrasound) of parathyroid adenoma which allows a minimally invasive surgery with appropriate intraoperative decreases in the parathyroid level ("Miami criteria": 50% or greater decrease in the PTH level from preoperative value, and a drop into the normal range for parathyroid hormone) to gauge removal of the offending pathology.<sup>15,16</sup> However, the accuracy of Sestamibi and ultrasound are limited. Additionally, these tests can be expensive and inconvenient for the patient if they have to make several visits to the imaging center to have the two studies performed.

MCT holds promise for becoming a new paradigm in evaluating patients with parathyroid disease. It has increased accuracy as compared to sestamibi and ultrasound. The MCT images areas that the ultrasound cannot such as the superior mediastinum or retroesophageal area. The value of MCT is increased in the face of previous negative neck exploration when locating a parathyroid adenoma. If the MCT is negative, it suggests the possibility of multigland disease and the need for consideration of bilateral neck exploration. MCT can identify lesions too small for Sestamibi scans to localize.

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