OPEN ACCESS

GAVIN PUBLISHERS

Archives of Surgery

Research Article

McManus C, et al. Arch Surg 2: 112.

DOI: 10.29011/AOS-112.000112

A comparison of 4DCT-MIBI-SPECT, 4DCT and MIBI-SPECT: 4DCT is sufficient preoperative imaging to guide parathyroidectomy in patients with primary hyperparathyroidism

Catherine McManus[1], Randy Yeh[2], Abbey Fingeret[3], John A. Chabot[1], James A Lee[1], Jennifer H. Kuo[1*]

[1]Department of Surgery, Section of Endocrine Surgery, Columbia University Medical Center, USA

[2]Department of Radiology, Memorial Sloan Kettering Cancer Center, USA

[3]Division of Surgical Oncology, University of Nebraska Medical Center, USA

[*]**Corresponding Author:** Jennifer H Kuo, Herbert Irving Pavilion, 161 Fort Washington Avenue, Floor: 8, Suite 829, New York, NY 10032, USA. Tel: +12123056969, Fax: +12123050445; Email: Jhk2029@cumc.columbia.edu

Citation: McManus C, Yeh R, Fingeret A, Chabot JA, Lee JA, et al. (2019) A comparison of 4DCT-MIBI-SPECT, 4DCT and MIBI-SPECT: 4DCT is sufficient preoperative imaging to guide parathyroidectomy in patients with primary hyperparathyroidism. Arch Surg: AOS-112. DOI: 10.29011/AOS-112.000012

Received Date: 01 February, 2019; **Accepted Date:** 11 February, 2019; **Published Date:** 18 February, 2019

Abstract

Background: The role of combined four-dimensional computed tomography and 99mTc-sestamibi-single photon emission computed tomography (4DCT-MIBI-SPECT) imaging in parathyroid surgery is not well defined. The purpose of this study is to determine if 4DCT is sufficient to guide parathyroidectomy versus 4DCT-MIBI-SPECT or MIBI-SPECT among patients with Primary Hyperparathyroidism (PHPT).

Methods: We conducted an IRB approved single institution retrospective cohort study of patients referred for evaluation of PHPT from June 2013 to September 2014. All patients underwent 4DCT-MIBI-SPECT followed by surgery. Pathology was compared among 4DCT-MIBI-SPECT, 4DCT and MIBI-SPECT. We excluded patients who were not surgically cured. The performance of each modality in Single Gland (SG) versus Multi Gland (MG) disease was compared using Fisher's Exact Test. We fit a Generalized Estimating Equation (GEE) comparing the modalities in their ability to predict the location of diseased gland(s).

Results: Of the 150 patients evaluated, 146 were included in the final analysis. 4DCT-MIBI-SPECT, 4DCT and MIBI-SPECT localized the quadrant of the abnormal gland in 88.4%, 82.9%, and 62.3% of patients, respectively. Localization of MIBI-SPECT was lower for MG compared to SG disease (23.8% versus 68.8%, $p<0.001$). 4DCT and 4DCT-MIBI-SPECT had higher odds of agreement between disease on imaging and disease on pathology compared to MIBI-SPECT (3.27, $p<0.001$ and 3.51, $p<0.001$, respectively).

Conclusions: 4DCT-MIBI-SPECT and 4DCT were superior to MIBI-SPECT in predicting the location of the diseased gland by quadrant. There was no significant difference in the localization of diseased glands between 4DCT and 4DCT-MIBI-SPECT, suggesting that 4DCT is sufficient to localize abnormal glands in PHPT.

Keywords: 4DCT; Focused parathyroidectomy: MIBI-SPECT: Primary Hyperparathyroidism

Introduction

Parathyroid imaging techniques have evolved over the last twenty-five years. Guided by imaging, surgeons are frequently able to perform a focused parathyroidectomy and avoid a bilateral neck exploration in patients with single gland disease [1-3]. Preoperative localization of abnormal parathyroid glands is a vital part of planning for focused parathyroid surgery. There are several imaging modalities used for preoperative localization including ultrasound, 99mTc-Sestamibi (MIBI), 99mTc-Sestamibi-Single Photon Emission Computed Tomography (MIBI-SPECT), and more recently Four-Dimensional Computed Tomography (4DCT) [3-6]. MIBI-SPECT is a functional imaging study based on mitochondrial uptake of sestamibi and thus is valuable in identifying hyperactive glands with increased sestamibi uptake [3-7]. The sensitivity and specificity of the MIBI-SPECT ranges

from 50-70% and from 77-87%, respectively [1,3,7,8]. However, MIBI-SPECT is limited in the ability to detect abnormal glands in patients with multi gland parathyroid disease including four-gland hyperplasia [9-11].

The 4DCT provides anatomic information about the parathyroid glands including position, shape, and size and thus is valuable in identifying abnormally enlarged parathyroid glands [3,9]. In contrast to the traditional Three-Dimensional-CT (3DCT), the 4DCT has an additional dimension that demonstrates how contrast perfusion changes over time. Consequently, the 4DCT allows for greater detail of the uptake and washout of contrast in the parathyroid glands and can thus more accurately distinguish a normal parathyroid gland from a hyper functioning parathyroid gland or lymph node [3]. According to the 2016 AAES Guidelines for Primary Hyperparathyroidism Management, while traditional 3DCT has little utility, the 4DCT protocol is a useful modality in single gland disease [12]. The sensitivity of 4DCT ranges from 70% to 93% [3,8,13,14]. Studies have demonstrated the superiority of 4DCT compared to MIBI-SPECT to localize parathyroid glands by quadrant among all patients and among patients undergoing preoperative parathyroidectomy [3,13,15-17]. However, 4DCT is not widely used as a first line study for imaging localization at initial operation. According to a multi-institutional international survey in 2016, the majority of radiologists who use 4DCT will use it as a second line study after ultrasound or sestamibi [18]. Thus, the MIBI-SPECT may still play an important role in preoperative imaging.

In an attempt to fully optimize the advantages of 4DCT with MIBI-SPECT technology, our institution began using a combined imaging technique, 4DCT-MIBI-SPECT, in which the patient undergoes both a 4DCT and a MIBI-SPECT scan at one time. This allows for the simultaneous interpretation of anatomic information from the 4DCT and functional information from the MIBI-SPECT. Figure 1 demonstrates a comparison between 4DCT-MIBI-SPECT, 4DCT and MIBI for a patient with multi gland primary hyperparathyroidism.

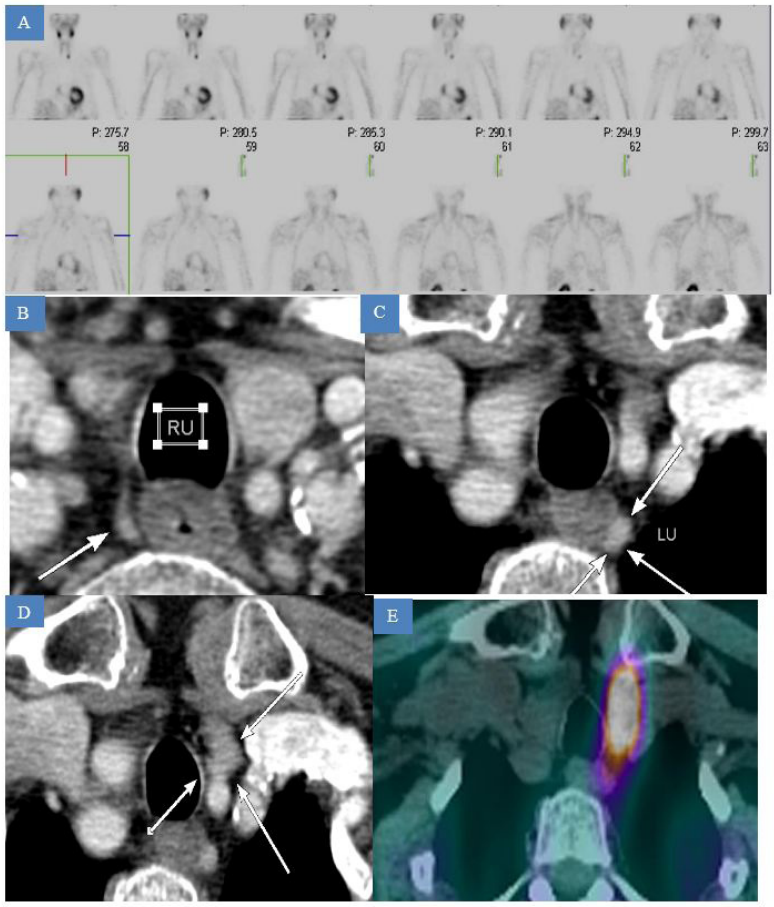

Figure 1: Images from an 80-year-old woman with primary hyperparathyroidism. Coronal MIBI images **(A)** demonstrate that the only MIBI avid gland was in the left lower quadrant. The three 4DCT images **(B-D)** show enlarged and enhancing glands in the right upper, left upper and left lower quadrants, respectively. All three abnormal glands on 4DCT were diseased glands on pathology. The 4DCT-MIBI-SPECT imaging **(E)** demonstrates the combination of 4DCT and MIBI-SPECT technologies in the diseased left lower quadrant.

The purpose of this study was to evaluate whether combining 4DCT-MIBI-SPECT improved localization of abnormal parathyroid glands by quadrant compared to 4DCT alone and MIBI-SPECT alone among patients with single and multigland disease.

Materials and Methods

Subjects and Methods

We conducted a single institution retrospective cohort study of 150 patients who were referred consecutively to Columbia University Medical Center for surgical evaluation of primary hyperparathyroidism from June 2013 to September 2014. All patients underwent preoperative localization with the 4DCT-MIBI-SPECT combined imaging technique and proceeded with surgical resection. We excluded patients who did not have cure of their disease at the index operation. This study was approved by our Institutional IRB Committee, Protocol AAAD4780.

Imaging interpretation

Two radiologists, one of whom trained and supervised the other, interpreted the images. Interpretation of the images consisted of evaluating each of the four parathyroid glands by quadrant (left upper, left lower, right upper and right lower) simultaneously using characteristics from both the 4DCT and from the MIBI-SPECT technologies. A gland was characterized as abnormal on 4DCT if there was enlargement and/or enhancement. A gland was characterized as abnormal on MIBI-SPECT if there was increased sestamibi uptake. A gland was characterized as abnormal on 4DCT-MIBI-SPECT combined imaging if there was enlargement, enhancement, and/or increased sestamibi uptake.

Operation

Patients went to the operating room with one of three surgeons for a parathyroidectomy. If single gland disease was suspected, the surgeon began by identifying the abnormal gland localized on imaging and removing it if operative findings and imaging were concordant. Intraoperative Parathyroid Hormone (IOPTH) monitoring with the Miami criterion protocol was used to help determine the adequacy of resection [19-20]. If multi gland disease was suspected on preoperative imaging or the Miami criterion was not fulfilled, the patient underwent a bilateral neck exploration. After removal of each gland, IOPTH monitoring was conducted. All surgically removed glands were analyzed by pathology and patients were characterized as having single gland disease (a single parathyroid adenoma) or multi gland disease (two or more parathyroid adenomas or four-gland hyperplasia). The number and quadrant of abnormal gland(s) based on pathology were compared to the number and quadrant of abnormal gland(s) based on preoperative imaging for 4DCT, for MIBI-SPECT, and for 4DCT-MIBI-SPECT combined. Glands were localized to quadrant if the abnormal quadrant(s) on imaging correlated to abnormal gland(s) on pathology.

Postoperative Monitoring

All patients presented one month after surgery for a postoperative evaluation and obtained lab work six months postoperatively.

Statistical analysis

Descriptive statistics were performed using Fisher's Exact Test for categorical variables and the Mann-Whitney U test for continuous variables using a p-value of less than 0.05 to determine statistical significance. For each of the three imaging modalities we calculated the ability to localize abnormal glands by quadrant as well as the sensitivity, specificity, Positive Predictive Value (PPV), and Negative Predictive Value (NPV). We stratified patients by single gland disease and by the presence of concomitant thyroid disease and compared the ability of the three imaging modalities to localize abnormal glands by quadrant using Fisher's Exact Test. To assess the degree to which the imaging modality predicted disease on pathology and to account for the correlation of the four glands in each patient, we used a Generalized Estimating Equation (GEE). We fit a model using GEE with agreement between disease on imaging and true disease based on pathology for each gland as a binary outcome. If the patient had one or more adenomas resected (as confirmed by surgical pathology), we assumed that IOPTH dropping appropriately to below 50% of baseline indicated that the glands that remained in the patient at the time the IOPTH protocol was initiated were not diseased. For patients who had three diseased glands resected, we assigned a diagnosis of four-gland hyperplasia and categorized the remaining gland as diseased. We included imaging modality as a categorical predictor (4DCT-MIBI-SPECT, 4DCT, or MIBI-SPECT) with MIBI-SPECT as the reference group, and controlled for age (continuous) and gender (binary). We added other covariates to the model including single gland disease (binary), preoperative calcium (continuous), preoperative vitamin D (continuous), and preoperative PTH (continuous) levels and used Quasi-AIC (QIC) values (with a smaller QIC indicating a better model) to test for the best model fit. We used a compound symmetry correlation, which assumes that the correlation of the four glands within the same patient is the same across all imaging modalities. All analyses were performed with SAS software 9.4 (SAS Institute).

Results

The study population consisted of 150 patients, four of whom were excluded for lack of curative surgery, with a remaining 146 patients for final analysis. Of the 146 patients, 125 had single gland disease and 21 had multigland disease. Concomitant thyroid disease including the presence of thyroid nodules (n=63), thyroiditis (n=2) or Graves' Disease (n=1), was present in 66 of the 146 patients. Baseline characteristics of the study population are demonstrated in Table 1. When stratifying the 146 patients by single and multigland disease, there was no significant difference

between the two groups in terms of age, sex, BMI, or preoperative vitamin D levels. Compared to patients with multigland disease, those with single gland disease had significantly higher preoperative calcium (10.9 vs 10.4 mg/dL, p=0.0233) and PTH (111.3 vs 104.2 pg/mL, p=0.0256) levels, which is reflective of our patient population.

	All Patients (n=146)	Single Gland disease (SGD, n=125)	Multigland disease (MGD, n=21)	p-value (SGD vs MGD)
Age (years)	63.1 ± 1.3	63.5 ± 1.4	60.6 ± 3.1	0.283
% Female	74	73.6	76.2	0.802
% Caucasian	45.2	44.8	47.6	0.81
BMI (kg/m^2)	27.8 ± 0.6	28.3 ± 0.6	25.1 ± 1.1	0.072
% Osteoperosis	29.3, 43	27	43	0.145
% Kidney stones	23.8	25.4	23.8	0.861
Preoperative labs Calcium (mg/dL) PTH (pg/mL) Vitamin D (pg/mL)	10.9 ± 0.1 110.4 ± 5.9 31.8 ± 1.8	10.9 ± 0.1 111.3 ± 5.7 30.6 ± 1.7	10.4 ± 0.2 104.2 ± 24.0 41.3 ± 7.9	0.0233* 0.0256* 0.0826
*p-value <0.05				

Table 1: Baseline characteristics among patients with primary hyperparathyroidism for single gland versus multigland disease. Continuous variables presented as mean with standard errors.

Of the 146 patients, 50 (34.2%) underwent four-gland exploration for suspicion of multigland disease due to nonlocalization on preoperative imaging. Of those 50 patients who underwent four-gland exploration, 20 had true multigland disease and 30 had a single adenoma.

At the one-month postoperative evaluation, no patients reported any subjective symptoms of hypocalcemia, including numbness/tingling in the perioral region or in the digits. Patients obtained lab work six months postoperatively with an average PTH level of 40.1 pg/mL (3-135 pg/mL) and an average calcium level of 9.63 mg/dL (7-10.8 mg/dL). Of all 146 patients, 133 (91%) had PTH and calcium values within the normal range within six months. A total of 13 patients did not have normalization of both PTH and corrected calcium at six months, six had a normal PTH with elevated corrected calcium and seven had normal corrected calcium with elevated PTH. Of those 13 patients, six had undergone a four-gland exploration, two had multigland disease, and four had a single adenoma.

Overall, the 4DCT-MIBI-SPECT combined, 4DCT alone and MIBI-SPECT alone were able to localize the quadrant of the abnormal gland in 88.4%, 82.9%, and 62.3% of patients, respectively. The sensitivity and specificity by quadrant for 4DCT-MIBI-SPECT combined were 82.8% and 74.4% for 4DCT 78.7% and 74.9%; and for MIBI-SPECT 53.7% and 97.8% (Table 2).

	Overall localization to quadrant (n=146)	**Sensitivity (%)**	**Specificity (%)**	**PPV (%)**	**NPV (%)**
4DCT-MIBI-SPECT	129 (88.4%)	82.8	74.4	57.8	91
4DCT	121 (82.9%)	78.7	74.9	57.1	89.2
MIBI-SPECT	91 (62.3%)	53.7	97.8	91.3	83.2

Table 2: Overall performance, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of 4DCT-MIBI-SPECT, 4DCT, and MIBI-SPECT imaging among patients with primary hyperparathyroidism.

When we stratified patients by single and multigland disease, there was a significant difference in the overall performance of MIBI-SPECT for single (68.8%) versus multigland (23.8%) disease (p<0.001). However, there was no significant difference in the overall performance of 4DCT (82.4% for single versus 85.7% for multigland disease, p=1.00) or of 4DCT-MIBI-SPECT combined imaging (88.8% for single versus 85.7% for multigland disease, p=0.713) (Table 3).

	Single Gland disease (n=125)	Multigland disease (n=21)	p-value
4DCT-MIBI-SPECT	111 (88.8%)	18 (85.7%)	0.713
4DCT	103 (82.4%)	18 (85.7%)	1
MIBI-SPECT	86 (68.8%)	5 (23.8%)	<0.001*
*p-value <0.05.			

Table 3: Correct localization of abnormal parathyroid gland(s) by 4DCT-MIBI-SPECT, 4DCT, and MIBI imaging among patients with primary hyperparathyroidism with single versus multigland disease.

We found no significant difference in the ability of any of the imaging modalities to localize diseased parathyroid glands when stratifying patients based on the presence of concomitant thyroid disease (Table 4).

	Thyroid Disease (n=66)	No Thyroid Disease (n=80)	p-value
4DCT-MIBI-SPECT	57 (86.4%)	72 (90%)	0.496
4DCT	54 (81.8%)	67 (83.8%)	0.758
MIBI-SPECT	41 (62.1%)	50 (62.5%)	0.963
*p-value <0.05.			

Table 4: Correct localization of abnormal parathyroid gland(s) by 4DCT-MIBI-SPECT, 4DCT, and MIBI imaging among patients with primary hyperparathyroidism with concomitant thyroid disease versus no concomitant thyroid disease.

The final GEE model is summarized in Table 5. The variables that best predicted agreement between disease on imaging and true disease on pathology for each gland included imaging modality (categorical) and single gland disease (binary), with age (continuous) and gender (binary) also in the model. The addition of any or all of the laboratory value predictors (preoperative calcium, preoperative PTH, preoperative vitamin D) did not improve the model.

Outcome	Predictor comparisons	Odds ratio	p-value
Agreement between disease on imaging and disease on pathology	4DCT vs MIBI-SPECT	3.27	<0.001
	4DCT-MIBI-SPECT vs MIBI-SPECT	3.51	<0.001
	4DCT vs 4DCT-MIBI-SPECT	1.07	0.539
	Single gland vs multigland disease	0.79	0.202
*p-value <0.05.			

Table 5: Generalized Estimating Equation (GEE) model. A GEE model was fit to assess the ability of the different imaging modalities to predict agreement between imaging modality detecting disease and true disease on pathology.

Using the Wald test, we found that the type of imaging modality (4DCT-MIBI-SPECT, 4DCT alone or MIBI-SPECT alone) influenced the agreement between disease on imaging and true disease on pathology on a level of significance of less than 0.001. More specifically, the odds of agreement between disease on imaging and disease on pathology with 4DCT was 3.27 times the odds of agreement with MIBI-SPECT ($p < 0.001$). The odds of agreement between disease on imaging and disease on pathology with 4DCT-MIBI-SPECT was 3.51 times the odds of agreement with MIBI-SPECT alone ($p<0.001$). The odds of agreement between disease on imaging and true disease on pathology with 4DCT-MIBI-SPECT was 1.07 times the odds of agreement with 4DCT, but this was not statistically significant ($p=0.539$). When controlling for imaging modality, the odds of agreement between disease on imaging and disease on pathology for single gland disease was 0.79 times the odds of agreement for multigland disease, but this was not statistically significant ($p=0.202$).

Discussion

The concept of combining CT and MIBI technology arose in Austria where radiologists and surgeons created a 3DCT-MIBI-SPECT fusion technique to localize abnormal parathyroid glands prior to surgery [9]. Studies comparing 3DCT-MIBI-SPECT fusion to 3DCT and MIBI-SPECT alone have demonstrated the superior ability of the fusion technique to localize abnormal parathyroid glands by quadrant compared to 3DCT and MIBI-SPECT alone, even in multigland disease [7,21]. The sensitivity of 3DCT-MIBI-SPECT in correctly localizing the gland by quadrant ranged from 88- 93% and the specificity was around 99% [2,7]. Furthermore, studies comparing 3DCT-MIBI-SPECT fusion to MIBI-SPECT alone have shown that the fusion study was superior to MIBI-

SPECT alone among patients with reoperative parathyroid disease [22]. Whether the combination of 4DCT-MIBI-SPECT is superior to 4DCT and MIBI-SPECT alone has not been thoroughly investigated.

To our knowledge, this study is the first to compare the novel combined 4DCT-MIBI-SPECT imaging to 4DCT and MIBI-SPECT alone among patients with single and multigland disease. When comparing the overall ability of each of the three imaging modalities to localize the quadrant of the abnormal gland in patients with primary hyperparathyroidism, the 4DCT-MIBI-SPECT was superior to 4DCT and MIBI-SPECT alone. Additionally, the GEE analysis indicated that the 4DCT-MIBI-SPECT was significantly better than MIBI-SPECT alone in predicting agreement between disease on imaging and disease on pathology (OR 3.51 $p<0.001$). Similarly, the GEE analysis indicated that 4DCT alone was superior to MIBI-SPECT alone in predicting agreement between disease on imaging and disease on pathology (OR 3.27 $p<0.001$).

When comparing 4DCT and 4DCT-MIBI-SPECT, there was no significant difference between the two modalities in terms of predicting agreement between disease on imaging and disease on pathology (OR 1.07 $p<0.539$). Thus, the 4DCT alone may be a sufficient imaging modality to detect diseased parathyroid glands.

The 4DCT-MIBI-SPECT combined technology performed better overall in 5% of patients compared to 4DCT alone and had a higher sensitivity by almost 4%. However, the MIBI-SPECT adds 3 hours to the five-minute 4DCT scan as well as additional radiation dose. Thus, the use of the 4DCT-MIBI-SPECT combined imaging technique over 4DCT alone may not be justified given the significant additional cost, time, and radiation dose that MIBI-SPECT adds.

Upon stratifying patients by single versus multigland disease, MIBI-SPECT alone performed significantly worse in localizing the abnormal gland by quadrant in patients with multigland disease. However, there was no significant difference in the ability of the 4DCT-MIBI-SPECT combined imaging or 4DCT alone to localize abnormal gland(s) by quadrant for patients with single versus multigland disease. These results suggest that 4DCT is sufficient to localize abnormal glands by quadrant in primary hyperparathyroidism among patients with single and multigland disease.

When comparing all three modalities, it is important to consider that although MIBI-SPECT had the highest specificity and positive predictive value, it performed significantly worse among patients with multiple gland disease compared to single gland disease. This suggests that MIBI-SPECT may not be the most useful tool for all patients requiring preoperative localization compared to 4DCT-MIBI-SPECT and 4DCT alone.

Our conclusions are similar to conclusions made by other studies that have compared imaging modalities for preoperative localization of abnormal parathyroid glands. The superiority of 4DCT to MIBI-SPECT is consistent with findings from Rodgers, *et al*, and Mortensen, et al [3,13]. However, our study also compared the 4DCT-MIBI-SPECT to 4DCT and MIBI-SPECT alone. Studies that have compared the combined 3DCT and MIBI-SPECT imaging modalities to 3DCT alone and MIBI-SPECT alone have found that the combined imaging modality is superior to both 3DCT and MIBI-SPECT. In contrast, our study looks at a combined imaging that uses 4DCT rather than 3DCT. Furthermore, the study by Profanter, *et al* in 2003 had a very small sample size (24 patients) with several having had prior neck surgery and they only compared the 3DCT-MIBI-SPECT to the MIBI-SPECT alone and not to 3DCT. The study by Prommegger, *et al* in 2009 that demonstrated the superiority of 3DCT-MIBI-SPECT to 3DCT and MIBI-SPECT alone only included patients with single gland disease. Moreover, with the 3DCT-MIBI-SPECT technology developed in Europe, patients do not undergo the tests simultaneously as they do at our institution but rather, images are obtained using a head and shoulder immobilization unit developed at their institution and then results from individual 3DCT and MIBI technologies are overlapped using an image fusion software.

Our study has several important limitations. The study is a retrospective design at a single institution and thus the application of the conclusions is limited to a population of patients referred to a tertiary care center in an urban environment. Additionally, since not all glands were examined in patients who had a focused parathyroidectomy, we used the IOPTH dropping by >50% as an indication that the remaining glands were not diseased. Of the six patients who did not have normalization of PTH and calcium within six months, three of them underwent a focused parathyroidectomy based on localization on preoperative imaging and appropriate drop in their IOPTH. It is possible that multigland disease would have been discovered had they undergone a four-gland exploration. Furthermore, with no laboratory data available after six months it is possible that patients could have recurrence after this short follow up interval.

Conclusion

Our study confirms that 4DCT is a superior imaging tool compared to MIBI-SPECT in localizing abnormal parathyroid glands by quadrant among patients with single and multigland disease. Furthermore, we confirm that the use of a combined imaging technique that incorporates anatomical information from the 4DCT and functional information from the MIBI-SPECT is not significantly superior to 4DCT alone and is likely unnecessary for most patients.

References

1. Arici C, Cheah WK, Ituarte PHG, Morita E, Lynch TC. et al (2001) Can localization studies be used to direct focused parathyroid operations? Surgery 129: 720-729.
2. Prommegger R, Wimmer G, Profanter C, Sauper T, Sieb M, et al (2009) Virtual Neck Exploration: A New Method for Localizing Abnormal Parathyroid Glands. Annals of Surgery 250: 761-765.
3. Rodgers S, Hunger GJ, Hamberg L, Schellingerhout D, Doherty DB, et al (2006) Improved preoperative planning for directed parathyroidectomy with 4-dimensional computed tomography. Surgery 140: 932-940.

4. Moka D, Voth E, Dietlein M, Larena-Avellaneda A, Schicha H (2000) Technetium 99m-MIBI-SPECT: A highly sensitive diagnostic tool for localization of parathyroid adenomas. Surgery 128: 29-35.

5. Haugen B, Alexander E, Bible K, Doherty GM, Mandel SJ, et al (2016) 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid 26: 1-133.

6. Krausz Y, Bettman L, Guralnik L, Yosilevsky G, Keidar Z, et al (2006) Technetium-99m-MIBI SPECT/CT in primary hyperparathyroidism. World J Surg 30: 76-83.

7. Profanter C, Wetscher G, Gabriel M, Sauper T, Rieger M, et al (2003) CT-MIBI image fusion: A new preoperative localization technique for primary, recurrent, and persistent hyperparathyroidism. Surgery 135: 157-161.

8. Brown S, Lee JC, Christie J, Maher R, Sidhu SB, et al (2015) Four-dimensional computed tomography for parathyroid localization: a new imaging modality. ANZJ Surg 85: 483-487.

9. Profanter C, Prommegger R, Gabriel M, Moncayo R, Wetscher GJ, et al. (2004) Computed axial tomography-MIBI fusion for preoperative localization in primary hyperparathyroidism. American Journal of Surgery 187: 383-387.

10. Shen W, Sabanci U, Morita E, Siperstein A, Duh QY, et al (1997) Sestamibi Scanning Is Inadequate for Directing Unilateral Neck Exploration for First-Time Parathyroidectomy. Arch Surg 132: 969-974.

11. Galvin L, Oldan JD, Bahi M, Eastwood JD, Sosa JA, et al (2016) Parathyroid 4D CT and Scintigraphy: What Factors Contribute to Missed Parathyroid Lesions? Otolaryngol Head Neck Surg 154: 847-853.

12. Wilhelm S, Wang T, Ruan D, Lee JA, Asa SL, et al. (2016) The American Association of Endocrine Surgeons Guidelines for Definitive Management of Primary Hyperparathyroidism. JAMA Surgery 151: 959-968.

13. Mortenson M, Evans D, Lee JE, Hunter GJ, Shellingerhout D, et al. (2007) Parathyroid Exploration in the Reoperative Neck: Improved Preoperative Localization with 4D-Computed Tomography. J Am Coll Surg 206: 888-895.

14. Day K, Elsayed M, Beland M, Monchik J (2015) The utility of 4-dimensional computed tomography for preoperative localization of primary hyperparathyroidism in patients not localized by sestamibi or ultrasonography. Surgery 157: 534-538.

15. Hinson AM, Lee DR, Hobbs BA, Fitzgerald RT, Bodenner DL, et al (2015) Preoperative 4D CT Localization of Nonlocalizing Parathyroid Adenomas by Ultrasound and SPECT-CT. Otolaryngol Head Neck Surg 153: 775-778.

16. Kelly HR, Hamberg LM, Hunter GJ (2014) 4D-CT for preoperative localization of abnormal parathyroid glands in patients with hyperparathyroidism: accuracy and ability to stratify patients by unilateral versus bilateral disease in surgery-naive and re-exploration patients. AJNR Am J Neuroradiol 35: 176-181.

17. Kukar M, Platz TA, Schaffner TJ, Elmarzouky R, Groman A, et al (2015) The use of modified four-dimensional computed tomography in patients with primary hyperparathyroidism: an argument for the abandonment of routine sestamibi Single-Positron Emission Computed Tomography (SPECT). Ann Surg Oncol 22: 139-145.

18. Hoang JK, Williams K, Gaillard F, Dixon A, Sosa JA (2016) Parathyroid 4D-CT: Multi-institutional International Survey of Use and Trends. Otolaryngol Head Neck Surg 155: 956-960.

19. Caneiro DM, Solorzano CC, Nader MC, Ramirez M, Irvin GL III (2003) Comparison of intraoperative iPTH assay (QPTH) criteria in guiding parathyroidectomy: which criterion is the most accurate? Surgery 134: 973-979.

20. Carneiro DM, Irvin GL, Nader MC, Ramirez M, Irvin GL 3rd (2002) New point-of-care intraoperative parathyroid hormone assay for intraoperative guidance in parathyroidectomy. World J Surg 26: 1074-1077.

21. Wimmer G, Profanter C, Kovacs P, Sieb M, Gabriel M, et al (2010) CT-MIBI-SPECT image fusion predicts multiglandular disease in hyperparathyroidism. Lagenbecks Arch Surg 395: 73-80.

22. Wimmer G, Bale R, Kovacs P, Gabriel M, Gabriel M, et al (2008) Virtual neck exploration in patients with hyperparathyroidism and former cervical operations. Lagenbecks Arch Surg 393: 687-692.