Parathyroid 4D CT and Scintigraphy: What Factors Contribute to Missed Parathyroid Lesions?

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Abstract

Objective. To determine the prevalence of missed lesions for parathyroid 4-dimensional computed tomography (4D CT) and scintigraphy and to describe the factors leading to missed lesions for both modalities.

Study Design. Case series with chart review.

Setting. Single center, hospital based.

Subjects and Methods. Forty patients undergoing 4D CT and scintigraphy before parathyroidectomy between July 2009 and October 2013 were included. Radiology reports and imaging were reviewed and correlated with operative notes to identify cases with missed lesions and the reasons for those misses. All lesions were then classified according to the following factors: multigland disease, lesion size, patient body weight, and multinodular goiter.

Results. Of the 40 patients, 6 had multigland disease, resulting in 51 lesions; 12 and 29 lesions were missed on 4D CT and scintigraphy, respectively. The sensitivity for detection of all lesions was 76% for 4D CT and 43% for scintigraphy. Sensitivities for single-gland disease were 88% for 4D CT and 50% for scintigraphy. Sensitivities for multigland disease were 53% for 4D CT and 24% for scintigraphy. Rates of multigland disease in patients with missed lesions were 75% on 4D CT and 48% on scintigraphy, as compared with patients with detected lesions, 23% and 18%, respectively (P ≤ .04). Mean weight of lesions missed on 4D CT was 0.3 and 0.6 g in detected lesions (P = .15). Mean weight of lesions missed on scintigraphy was 0.4 and 0.8 g in detected lesions (P = .03).

Conclusion. 4D CT has higher sensitivity than scintigraphy. Missed lesions are more likely to occur with multigland disease for both modalities and in smaller lesions for scintigraphy.

Keywords
parathyroid adenoma, parathyroid hyperplasia, 4D CT, sestamibi scintigraphy

Preoperative imaging is a routine part of the workup of patients with primary hyperparathyroidism. Traditional imaging modalities are ultrasound and parathyroid scintigraphy, but over the last few years, parathyroid 4-dimensional computed tomography (4D CT) has emerged as an alternative modality for imaging primary hyperparathyroidism.1 Although additional imaging increases costs and radiation exposure, studies have shown that the approach of using 4D CT as a third-line modality is cost-effective, as it reduces the need for repeat surgery and may allow for less invasive surgery.2-5 Furthermore, the role of 4D CT is changing as experience with reading and interpretation increases among radiologists and surgeons. In some institutions, 4D CT is now utilized for first-line imaging or routinely used with either ultrasound or scintigraphy.1,6,7

If 4D CT is a preferred study in a dual-modality imaging algorithm, we expect that it will replace scintigraphy rather than ultrasound—since ultrasound has an additional role of evaluating the thyroid for the need for concomitant thyroid surgery, is commonly performed by the surgeon, and does not expose the patient to ionizing radiation. Thus, a key question is how 4D CT compares with scintigraphy and if there are conditions or patients in which one study will outperform the other. Previous studies have reported higher...
sensitivity for 4D CT versus ultrasound and scintigraphy, but the reasons for missed lesions are unclear.\textsuperscript{6-8}

The purpose of this study was to determine the prevalence of missed lesions for parathyroid 4D CT and scintigraphy and to describe the factors leading to missed lesions for both modalities as compared with surgical results. Our hypothesis was that there were certain conditions, such as small lesion size, multigland disease, patient body habitus, and multinodular goiter, that would influence the performance of 4D CT as compared with scintigraphy. Identifying the reasons for missed lesions could either help to improve radiologists’ performance in interpreting these respective studies or have implications for the surgeon on the choice of imaging study.

**Materials and Methods**

**Study Group**

This study was granted approval by the Duke University Health System Institutional Review Board in February 2013 (Duke eIRB No. Pro00050951) with waiver of informed consent and was compliant with the Health Insurance Portability and Accountability Act. A case series with chart review of patients with primary hyperparathyroidism who underwent parathyroid surgery between July 2009 and October 2013 identified 42 patients who had both 4D CT and scintigraphy and successful surgery. Two patients were excluded because their scintigraphy studies were performed at an outside institution and did not have images for review. The final cohort consisted of 40 patients who had imaging performed at our institution. Among these patients, 29 had ultrasound, which was the first-line imaging modality in 9 patients.

**Surgical Approach**

All parathyroidectomies were performed by 1 of 6 surgeons in a single institution. Intraoperative parathyroid hormone (PTH) assays were taken in every case at baseline (during anesthesia induction), immediately prior to resection following operative visualization of the abnormal glands and at short intervals immediately following resection. Inappropriate sequential drop in PTH following gland resection prompted further 4-gland exploration for additional adenomas or hyperplasia. All operations were initially performed with a mini-incision laparotomy; 4-gland exploration where required as outlined above. Inappropriate decline is confirmed (50% and into the normal range). This typically occurs in 10 to 20 minutes, depending on the extent of dissection and renal function (for clearance). Successful surgery is determined by the drop in PTH from baseline to the final postresection value. Since the PTH can spike upward due to dissection and stimulation of the culprit parathyroid to secrete PTH, the time point 0 minutes is checked to determine how far the PTH is required to return to the normal range and the time line to do so.

**Imaging Techniques**

The 4D CT protocol consisted of scanning in 3 separate phases: noncontrast, arterial, and venous. Before September 2012, studies were performed with only arterial and delayed phases and did not include a non-contrast-enhanced study.\textsuperscript{10} The parathyroid scintigraphy protocol consisted of sequential planar imaging and SPECT (single-photon emission computed tomography)–CT after administration of a standard adult dose of technetium sestamibi.

**Identifying Missed Lesions**

All parathyroid lesions were classified as correctly or incorrectly localized on 4D CT and scintigraphy by correlating the operative notes with the original radiology reports by a radiologist with 6 years of experience (L.G.). Correct localization by imaging required the parathyroid lesion in the radiology text report to match the surgical findings for exact anatomic quadrant location, depth in neck, and approximate size of the adenoma. A lesion could be reported with high or low confidence, but if it was reported in the impression section, it was regarded as being a candidate lesion on imaging.

Parathyroid lesions were categorized according to the following 4 groups: (1) both modalities correctly identified the lesion; (2) neither modality correctly identified the lesion; (3) 4D CT was correct and scintigraphy incorrect; and (4) scintigraphy was correct and 4D CT incorrect. The latter 2 groups were considered to be discordant on 4D CT and scintigraphy.

**Identifying Factors Contributing to Missed Lesions**

All missed lesions on 4D CT and scintigraphy were selected for a consensus imaging review with a fellowship-trained neuroradiologist (J.K.H.) with 13 years of experience (L.G.). Correct localization by imaging required the parathyroid lesion in the radiology text report to match the surgical findings for exact anatomic quadrant location, depth in neck, and approximate size of the adenoma. A lesion could be reported with high or low confidence, but if it was reported in the impression section, it was regarded as being a candidate lesion on imaging.

Parathyroid lesions were categorized according to the following 4 groups: (1) both modalities correctly identified the lesion; (2) neither modality correctly identified the lesion; (3) 4D CT was correct and scintigraphy incorrect; and (4) scintigraphy was correct and 4D CT incorrect. The latter 2 groups were considered to be discordant on 4D CT and scintigraphy.
multinodular goiter, and parathyroid lesions factors of surgical size, ectopic location, and multigland disease. Multigland disease was defined as patients with ≥2 adenomas or parathyroid hyperplasia.

The radiologist with 6 years of experience (L.G.), characterized correctly identified lesions by the same factors as the missed lesions.

Outcomes and Statistical Analysis
Sensitivities of 4D CT and scintigraphy for lesion detection were calculated. The characteristics of parathyroid lesions that were detected preoperatively were compared with lesions that were missed to identify limiting factors that decrease the sensitivity of 4D CT and scintigraphy. The unpaired t test was used for comparison of continuous data. The chi-square test or Fisher’s exact test was used for categorical data. Fisher’s exact test was used when expected cell frequencies were <5. P values <.05 were regarded as statistically significant. The data were entered into an Excel spreadsheet (2007 version; Microsoft, Redmond, Washington). Statistical analyses were performed with SAS Enterprise (version 4.2; SAS Institute, Cary, North Carolina).

Results
Study Group
The final cohort consisted of 40 patients (mean age, 60 years; 31 female) with the sequence of imaging as follows: scintigraphy was performed before 4D CT in 22 patients (median interval, 19.5 days); 16 patients had both modalities on the same day; and 2 patients had 4D CT before scintigraphy (median, interval, 17.5 days; range, 12-23).

Thirty-four patients had solitary adenomas, and 6 patients had multinodular disease. The patients with multinodular disease had 17 lesions, resulting in a total of 51 parathyroid lesions (Table 1). Mean maximum diameter and weight of pathologic specimens were 14.2 mm (SD, 6) and 0.6 g (SD, 0.6; Table 1). Ten (20%) lesions in 9 patients were in ectopic locations: 6 lesions were in the mediastinum; 3 were retropharyngeal; and 1 was in a high parapharyngeal space. Five patients had prior parathyroidectomies with recurrent or residual disease.

Missed Lesions and Sensitivities
4D CT correctly localized 39 of 51 (76%) parathyroid lesions in 32 of 40 (80%) patients, and scintigraphy correctly localized 22 of 51 (43%) lesions in 19 of 40 (48%) patients (Table 2). Both modalities were correct for 20 of 51 (39%) lesions. Both modalities missed 10 of 51 (20%) lesions. The remaining 21 of 51 (41%) lesions in 17 (43%) patients were considered to be discordant. The discordant cases fell into 2 groups: 19 of 51 (37%) lesions were correctly localized by 4D CT but were missed on scintigraphy, and 2 of 51 (4%) lesions were correctly localized on scintigraphy but missed on 4D CT.

For the 34 cases of solitary adenomas, the sensitivities were 88% (30 of 34) for 4D CT and 50% (17 of 34) for scintigraphy. For multigland disease, the sensitivities were 53% (9 of 17) for 4D CT and 24% (4 of 17) for scintigraphy. 4D CT correctly localized all 10 ectopic lesions, while scintigraphy missed 5 lesions. In the patients with prior failed parathyroidectomies, 4D CT correctly localized all lesions in the 5 patients, while scintigraphy missed the lesions in 2 patients.

In the 29 patients with ultrasound imaging, the sensitivity of ultrasound was 35% (8 of 23) when performed by the surgeon and 20% (3 of 15) when performed by the radiology department (9 patients had ultrasound by both).

Factors Contributing to Missed Lesions
When imaging studies from patients with missed lesions were specifically reviewed, 3 of 12 (25%) lesions missed on 4D CT were evident on retrospective review (Figure 1). The reasons attributed to these missed lesions were multinodular goiter, noisy images in patients with large body habitus, and unsuspected multigland disease (Table 2).

On review of the 29 lesions not seen initially on scintigraphy, 8 (28%) could be found retrospectively. Reasons attributed to missed lesions for scintigraphy included multigland disease, poor tracer uptake in the parathyroid lesion (Figure 2), or uptake masked by adjacent retained radio-pharmaceutical activity in the thyroid (Figure 3) or submandibular gland.

When compared with true positive lesions identified on original 4D CT radiology reports, missed lesions were more likely to represent multigland disease at 23% and 75%, respectively (P = .002). Multigland disease was also significantly associated with missed lesions on scintigraphy: present in 18% of detected lesions versus 48% of missed lesions (P = .04). Parathyroid lesions missed on both modalities were smaller than those seen on imaging preoperatively. Mean weight of lesions detected on 4D CT was 0.6 g, as compared with 0.3 g for missed lesions (P = .15). Mean weight of lesions detected and missed on scintigraphy was 0.8 g and 0.4 g, respectively (P = .03). Of note, the smallest lesion correctly identified on 4D CT had a diameter of 4 mm on pathology, while the smallest lesion detected on scintigraphy was 10 mm in diameter.

The association between missed lesions and both multinodular goiter and patient’s body habitus was not found to be statistically significant, on either 4D CT or scintigraphy. Neither did the preoperative PTH values have any significant association with missed lesions on either imaging modality.

Discussion
Multiple studies have reported higher sensitivity for 4D CT compared with ultrasound and scintigraphy, but the reasons and conditions in which 4D CT outperforms other modalities have not been described.6-8 In this study, we identify the factors that contribute to missed lesions on 4D CT and scintigraphy and compare these factors in cases that were correctly identified. We find that missed lesions are more likely to occur in the presence of multigland disease for...
both 4D CT and scintigraphy and with smaller lesions for scintigraphy. Multigland disease is a difficult subgroup of patients for both 4D CT and scintigraphy. In these patients, the parathyroid lesions are likely to be smaller than a solitary adenoma, and there is the possibility of “satisfaction of search,” where a second lesion may not be suspected and thus overlooked, with the reporting radiologist having

### Table 1. Characteristics of Parathyroid Lesions That Were Correctly Localized versus Lesions That Were Missed on 4D CT and Parathyroid Scintigraphy.

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>4D CT</th>
<th>Scintigraphy</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. Patients</td>
<td>40</td>
<td>51</td>
<td></td>
</tr>
<tr>
<td>Lesions</td>
<td>39</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>P Value Correct</td>
<td>.26</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incorrect</td>
<td>.29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P Value Correct</td>
<td>.22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incorrect</td>
<td>.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>59 ± 12</td>
<td>59 ± 11</td>
<td>59 ± 12</td>
</tr>
<tr>
<td>Female</td>
<td>32 (80)</td>
<td>43 (84)</td>
<td>31 (80)</td>
</tr>
<tr>
<td>PTH, pg/mL</td>
<td>171 ± 174</td>
<td>179 ± 183</td>
<td>173 ± 176</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>87 ± 21</td>
<td>90 ± 33</td>
<td>88 ± 23</td>
</tr>
<tr>
<td>Prior parathyroidectomy</td>
<td>5 (13)</td>
<td>6 (12)</td>
<td>6 (15)</td>
</tr>
<tr>
<td>Multinodular goiter</td>
<td>4 (10)</td>
<td>9 (18)</td>
<td>5 (13)</td>
</tr>
<tr>
<td>Parathyroid lesion factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum diameter, mm</td>
<td>14.2 ± 6</td>
<td>15.3 ± 13.2</td>
<td>12.8 ± 4.3</td>
</tr>
<tr>
<td>Weight, g</td>
<td>0.6 ± 0.6</td>
<td>0.6 ± 0.6</td>
<td>0.3 ± 0.2</td>
</tr>
<tr>
<td>Multigland disease</td>
<td>6 (15)</td>
<td>18 (35)</td>
<td>9 (23)</td>
</tr>
<tr>
<td>Ectopic</td>
<td>8 (20)</td>
<td>10 (20)</td>
<td>10 (100)</td>
</tr>
<tr>
<td>Imaging algorithm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4D CT before scintigraphy</td>
<td>2 (5)</td>
<td>2 (4)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Scintigraphy before 4D CT</td>
<td>22 (55)</td>
<td>28 (55)</td>
<td>22 (56)</td>
</tr>
<tr>
<td>Both concurrently</td>
<td>16 (40)</td>
<td>21 (41)</td>
<td>15 (38)</td>
</tr>
</tbody>
</table>

### Table 2. Radiology Report Results and Factors Contributing to Missed Parathyroid Lesions.

<table>
<thead>
<tr>
<th>Radiology Report Results</th>
<th>Predominant Reasons for Missed Lesions</th>
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</thead>
<tbody>
<tr>
<td>Correct 4D CT Correct Scintigraphy</td>
<td>Multigland disease (6)</td>
</tr>
<tr>
<td>Correct 4D CT Incorrect Scintigraphy</td>
<td>Multinodular goiter (2)</td>
</tr>
<tr>
<td>Incorrect 4D CT Correct Scintigraphy</td>
<td>Large body habitus (2)</td>
</tr>
<tr>
<td>Incorrect 4D CT Incorrect Scintigraphy</td>
<td>Retained radiopharmaceutical activity in thyroid (2)</td>
</tr>
</tbody>
</table>

### Abbreviations:
- 4D CT, 4-dimensional computed tomography
- PTH, parathyroid hormone level (preoperative)
- One patient had planar-only imaging and was interpreted correctly with both scintigraphy and 4D CT.
already detected 1 abnormality. This is particularly relevant for the detection of multigland disease, where individual glands are likely to be less enlarged than those usually seen in solitary adenomas. Rodgers et al found 4D CT to be more accurate than scintigraphy in patients with multigland disease, with sensitivities of 45% and 9%, respectively. Starker et al demonstrated that 4D CT, when used as a first-line imaging tool, localized multigland disease with a sensitivity of 86%, whereas all these lesions were missed on scintigraphy. Compared with these prior studies, our
results show higher sensitivity for scintigraphy at 24%, likely because almost half of our cohort underwent 4D CT on the same day or before scintigraphy, rather than after a negative scintigraphy study. However, the sensitivity for 4D CT for multigland disease was still much higher than scintigraphy, at 53%. The implication is that 4D CT should be performed instead of scintigraphy when multigland disease is suspected. Signs suggestive of multigland disease include a relatively small lesion on ultrasound and a history of multiple endocrine neoplasia syndrome, mild renal insufficiency, or vitamin D deficiency that has not been corrected prior to surgical exploration.\textsuperscript{12,13} Admittedly, however, it is difficult to predict preoperatively which patients are likely to have multigland disease rather than a solitary adenoma.

An interesting finding is that smaller lesion size is a significant factor attributed to missed lesions on scintigraphy but not on 4D CT. This may indicate that the resolution of scintigraphy is too low to detect some parathyroid lesions, and it may explain why almost three-quarters of missed lesions on scintigraphy could not be seen in retrospect. The limitation of spatial resolution on scintigraphy to detect small lesions is also highlighted by the fact that the smallest lesion detected on scintigraphy was 10 vs 4 mm on 4D CT. When originally missed lesions could be seen retrospectively on scintigraphy, the main factor leading to missed lesions was close proximity to a thyroid gland that had residual radiopharmaceutical activity. This pitfall of scintigraphy is well known and described in the nuclear medicine literature.\textsuperscript{14} It is also interesting to note that preoperative PTH values in our study had no significant association with lesions missed on either modality. This concurs with previous studies that do not show any correlation between biochemical values and size of parathyroid adenoma with exception to extreme values of PTH.\textsuperscript{15,16}

While other factors attributed to missed lesions on 4D CT included multinodular goiter and noisy images from large body habitus, these were not significantly different from cases in which lesions were correctly identified. However, awareness of these factors is instructive to image interpretation and designing protocols. Radiologists should carefully review around the thyroid glands in patients who may have exophytic thyroid nodules or enlarged glands that compress or efface parathyroid adenomas. In larger patients, the tube potential or the tube current may need to be modified to maintain diagnostic image quality.

There are several limitations to this study. First, this is a retrospective study performed at a single institution, which may differ from other institutions with regard to the technique of imaging and training of radiologists. Second, there is selection bias in a cohort that has imaging with both 4D CT and scintigraphy. Third, the interpretation of imaging studies was based on the original radiology reports. This more closely represents true clinical conditions, but interpretation of 4D CT or scintigraphy could be influenced by reviewing other imaging studies. Finally, the small sample size may have led to a type II error, especially for factors limiting 4D CT. A future study with a larger sample size may find certain factors to be significantly different between detected and missed lesions.

**Conclusion**

This study finds that 4D CT has higher sensitivity than scintigraphy for single- and multigland disease. Each modality has its own limitations, but missed lesions are more likely to occur with multigland disease for both modalities and in smaller lesions for scintigraphy.

**Author Contributions**

Leo Galvin, interpretation of data; revision of manuscript; final approval of version to be published; agree to be accountable for all aspects; Jorge D. Oldan, interpretation of data; revision of manuscript; final approval of version to be published; agree to be accountable for all aspects; James D. Eastwood, interpretation of data; revision of manuscript; final approval of version to be published; agree to be accountable for all aspects; Julie A. Sosa, interpretation of data; revision of manuscript; final approval of version to be published; agree to be accountable for all aspects; Jenny K. Hoang, interpretation of data; revision of manuscript; final approval of version to be published; agree to be accountable for all aspects

**Disclosures**

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**References**


