Accuracy of 4-dimensional computed tomography in poorly localized patients with primary hyperparathyroidism

Carrie C. Lubitz, MD,a George J. Hunter, MD, PhD,a Leena M. Hamberg, PhD, DSc,a Sareh Parangi, MD,a Daniel Ruan, MD,b Atul Gawande, MD, MPH,b Randall D. Gaz, MD,a Gregory W. Randolph, MD,a Francis D. Moore Jr, MD,b Richard A. Hodin, MD,a and Antonia E. Stephen, MD,a Boston, MA

Background. Four-dimensional computed tomography (4D-CT) utilizes multiplanar images and perfusion characteristics to identify abnormal parathyroid glands. We assessed the role of 4D-CT in patients with inconclusive preoperative ultrasound and sestamibi localization studies.

Methods. Adult patients with primary hyperparathyroidism with negative or discordant standard imaging who underwent both localization with 4D-CT and operative intervention for curative intent were included. Patient characteristics, 4D-CT scan results compared with operative findings, and curative proportion were assessed.

Results. Of the 60 patients, 4D-CT accurately lateralized 73% and localized 60% of abnormal glands found at operation. Single candidate lesions (46/60) were confirmed at operation in 70%. When multiple lesions were identified on 4D-CT (14/60), accuracy dropped to 29% (P = .03). The accuracy of 4D-CT was not different between primary and reoperative cases (P = .79). Of the 8 patients with multigland disease diagnosed perioperatively, 5 had multiple candidate lesions noted on 4D-CT. In 94% (48/51) of patients, a >50% drop in intraoperative parathormone (IOPTH) level was achieved after resection and 87% (48/55) had long-term cure with a median follow-up of 221 days.

Conclusion. 4D-CT identifies the more than half of abnormal parathyroids missed by traditional imaging and should be considered in cases with negative or discordant sestamibi and ultrasound. Bilateral exploration is warranted when multiple candidate lesions are reported on 4D-CT. Multigland disease remains a challenging entity. (Surgery 2010;148:1129-38.)

From the Departments of Surgery and Radiology,a Massachusetts General Hospital; and the Department of Surgery,b Brigham and Women’s Hospital, Boston, MA

Primary hyperparathyroidism (PHPT) affects approximately 1% of Americans and is more than twice as common in women.1 This disorder is characterized by hypercalcaemia caused by ≥1 autonomous hyperfunctioning parathyroid gland(s). Single adenomas account for 75–85% of cases, double adenomas for 2–12%, and hyperplasia in up to 10–15%.2,3 Parathyroidectomy is safe, durable, and cost effective in reversing and preventing the complications of PHPT including incidence of kidney stones, bone density, fracture, cardiovascular disease, and health-related quality of life.3–11 Over the past decade, there has been a significant shift in surgical practices, from conventional 4-gland exploration to limited parathyroidectomy. Focused or unilateral parathyroidectomy requires reliable preoperative localization, traditionally with ultrasonography (US) and sestamibi scan. Four-gland bilateral exploration is usually required when these modalities fail or are discordant.

In 2006, four-dimensional computed tomography (4D-CT) was introduced as an alternative to traditional imaging. This contrast CT protocol formats multiplanar images illustrating perfusion characteristics over time. Using precontrast, postcontrast, and delayed images, 4D-CT demonstrates precise anatomic localization of abnormal parathyroid glands characterized by rapid uptake and washout. In the initial report comparing 4D-CT with US and sestamibi, Rodgers et al12 found a
sensitivity of 4D-CT for lateralization and localization of hyperfunctioning parathyroids of 88% and 70%, respectively. A follow-up study by the same group documented similar rates of success in reoperative patients.\textsuperscript{15} Our aim in this study was to assess the utility of 4D-CT in both primary and reoperative patients with poor localization by sestamibi and US.

**METHODS**

**Patients.** The study population consisted of adult patients with biochemically confirmed PHPT with inconclusive standard imaging (US and sestamibi) who underwent both localization with 4D-CT and operative intervention for curative intent by 1 of 8 endocrine surgeons at 2 tertiary care, academic hospitals from May 2008 to October 2009. Indications for operation included symptomatic disease or qualification for operative intervention by the recommended guidelines for the management of asymptomatic PHPT.\textsuperscript{14} All data were obtained in accordance with the internal review board.

**Definitions.** PHPT was defined as hypercalcemia (serum Ca\textsuperscript{2+} >10.4 mg/dL) and nonsuppressed parathyromone (PTH). The extent of operative exploration was defined as focused (single gland), unilateral (both glands on same side), and bilateral (4 glands). We defined multigland disease as >1 abnormal gland (ie, double adenoma or hyperplasia) as determined by intraoperative findings and frozen section analysis. Glands were considered lateralized if the side of the abnormal parathyroid was identified (right vs left of midline) by 4D-CT, but not site (inferior or superior), and localized if a specific parathyroid gland was correctly identified (ie, right superior). Adequate surgical resection of abnormal parathyroid(s) was defined by an intraoperative PTH (IOPTH) drop of >50% at 10 minutes postexcision and long-term cure by normocalcemia (serum Ca\textsuperscript{2+} <10.4 mg/dL) approximately 6 months after surgery. If a patient underwent reoperative parathyroidectomy within the first 6 months after their initial operation, it was considered persistent disease.

**Imaging.** All patients underwent preoperative US and sestamibi scanning. The results of these studies were negative, discordant, or otherwise inconclusive. Results of sestamibi and US were available to the radiologist (GH) for review during evaluation of the 4D-CT and all imaging was available to the surgeon. In all cases, the official radiology report was compared with the operative findings to assess accuracy of the 4D-CT scan. When determining the utility of the 4D-CT scan overall, the primary diagnosis was compared with the operative findings. For example, if 4-gland hyperplasia was diagnosed by the radiologist and 4-gland hyperplasia was found intraoperatively, this was considered an accurate test. Likewise, if a double adenoma was reported on 4D-CT (eg, right superior adenoma and left inferior adenoma) and these exact 2 glands were considered abnormal intraoperatively, then 4D-CT was considered accurate. If, on the other hand, a double adenoma was called (eg, right superior adenoma and left inferior adenoma) but different glands were found to be abnormal at surgery (eg, 4-gland hyperplasia; right superior and left superior; or only right superior), the test was considered wrong or negative. The cases we discuss termed “multiple candidates” means that there was a primary diagnosis (or lesion) identified on CT and a less likely secondary diagnosis (or lesion) (eg, “right superior adenoma, much less likely left inferior adenoma”). In these cases, the primary diagnosis alone was used for accuracy of 4D-CT. Parathyroid hyperplasia was distinguished from parathyroid adenoma by rapidity of contrast uptake and washout, and noted on the radiologic report. In the 1 case where 4-gland hyperplasia was called on 4D-CT, 4-gland hyperplasia was considered the primary diagnosis for comparison. Operative findings were considered the gold standard for localization and sensitivity analysis.

4D-CT imaging was undertaken using a 16-slice MDCT scanner (LightSpeed 16, GE Medical Systems, Waukesha, WI). There are 4 phases that comprise the complete protocol. Each phase consists of a helical scan from the top of the carina to the bottom of the maxilla. A 10-mm x-ray beam width is used with the detector configuration that acquires sixteen 0.625-mm slices, using 140 kVp, 180–300 mA and a pitch of 1.375 with a 1-second rotation time and a body scan field of view. Phase 1 is the precontrast scan and forms the baseline for perfusion analysis. Phase 2 is the arterial phase and starts 30 seconds after onset of injection of 100 mL of iodinated contrast material (Iopamidol 370; Bracco Diagnostics Inc., Princeton, NJ). Phase 3 starts 30 seconds after completion of phase 2, and phase 4 starts 45 seconds after the end of the phase 3 scan (Fig 1).

Each phase is reconstructed to a final 1.25-mm axial slice thickness centered at 1-mm intervals, using a 25-cm display field of view. These data are then postprocessed on a GE Advantage Windows workstation (GE Medical Systems) into a standard format comprising 2.5-mm oblique slices rendered at 2.0-mm centers. Five projections are generated: true axial images that are parallel to the vocal cords, true coronal images that are orthogonal to
the true axial slices, true sagittal images that are orthogonal to the true coronal slices, and bilateral 45° oblique images parallel to the sternocleidomastoid muscles.

**Operative procedures.** The operative approach was left to the discretion of the attending surgeons and included focused, unilateral, and 4-gland explorations. All patients underwent general anesthesia. The location (right/left, inferior/superior) of normal and abnormal glands as assessed by the surgeon in their operative report was considered the gold standard and used to assess sensitivity and specificity of 4D-CT. In most cases, the surgeon stated in the operative report if, in their opinion, the lesion found intraoperatively was or was not the lesion identified on 4D-CT. The procedure was terminated when either the IOPTH levels dropped appropriately, when the surgeon had seen all remaining parathyroid glands, or when the surgeon felt that it was unsafe to continue with the procedure (3 cases).

**Analysis.** Patient characteristics, 4D-CT scan results as compared with intraoperative and pathologic findings, and curative proportion were assessed retrospectively. Normal, continuous data measures are expressed as mean values (± standard deviations), and non-normal data as median (interquartile range and/or range). Univariate analyses used the Student t test for normal continuous data; the Wilcoxon rank-sum test for continuous, non-normal data; and the Fisher exact test for discrete data. Body mass index (BMI), parathyroid size and volume, age, and laboratory values were treated as continuous variables. The 25-OH vitamin D level was considered categorical based on normal range values for the specific assay. P < .05 was considered significant. All abnormal glands noted on the report were considered a positive test for sensitivity analysis. All parathyroids assessed intraoperatively (normal and diseased) were used to assess sensitivity, specificity, and positive and negative predictive values of 4D-CT and were calculated using the following: abnormal gland(s) identified on both 4D-CT and intraoperatively are true positives; those identified on 4D-CT but found to be normal intraoperatively are false positives; those verified to be normal intraoperatively are true negatives; and those only identified as abnormal intraoperatively are false negatives.

**RESULTS**

**Patient characteristics.** Sixty patients met the inclusion criteria (Table I). Ninety-two percent of the cohort was female with a mean age of 60 years (range, 27–85). Twenty-one patients had prior neck explorations: 18 previous parathyroidectomies, 2 total thyroidectomies, and 1 hemithyroidectomy. The mean preoperative serum calcium was 10.9 mg/dL (±0.61; normal, 8.4–10.2) and the median preoperative PTH was 96 pg/dL (range, 52–288;
normal, 10–60 at Massachusetts General Hospital; normal, 11–80 at Brigham and Women’s Hospital). Of the 72% of patients that had preoperative 25-OH vitamin D levels assessed, 81% were within normal ranges (normal, 33–100 ng/mL at Massachusetts General Hospital; normal, 25–80 ng/mL at Brigham and Women’s Hospital). All patients underwent preoperative US and sestamibi scans, which were either both negative (**n** = 48; 80%), inconclusive (eg, US was negative and sestamibi stated ‘possible focus adjacent to left thyroid, thyroid nodule versus adenoma’; **n** = 11), or discordant (**n** = 1). Two reoperative patients also underwent venous sampling and 4 of 7 patients had confirmatory fine needle aspiration biopsies with measurement of PTH in the aspirate.

**Operative procedures.** Of the 60 patients in the cohort, 40 underwent bilateral exploration, 6 with simultaneous total thyroidectomy; 12 patients underwent unilateral exploration, 1 with simultaneous hemithyroidectomy; and 8 patients had a focused exploration (Table II). Patients undergoing their primary operation were more likely to have a bilateral exploration (**P** < .01). In the subset of patients undergoing a primary parathyroid operation, 39 out of 42 patients were found to have a single adenoma intraoperatively. Sixty-four percent of these 39 patients were accurately localized by 4D-CT preoperatively.

**Operative outcomes.** Fifty-one of the 60 patients had IOPTH values recorded. Ninety percent (46/51) of these patients had a >50% drop in IOPTH level and an additional 2 patients had IOPTH fall into the normal PTH range after excision, suggesting adequate resection of abnormal parathyroid(s) in 94% (48/51). Three patients failed intraoperative cure, 2 of whom had persistent disease and have undergone reoperation. Eighty-seven percent (48/55) of the cohort were normocalcemic at median follow-up of 221 days (interquartile range: 146, 283). We have both IOPTH and 6-month calcium levels on 48/60 patients: 85% were concordant. Four of the 48 with a >50% drop in IOPTH level showed hypercalcemia at follow-up, 2 of whom were reoperative patients with 4-gland hyperplasia. Two of 3 patients with a <50% drop in IOPTH, but with long-term cure, had IOPTH drop into normal range. Thirty-two of the 46 patients with 1 candidate lesion reported on 4D-CT had their findings confirmed at surgery; of these, 90% were cured.

**Reoperative cases.** There were 18 patients with previous parathyroid surgery, 10 who presented with persistent disease and 8 who presented with recurrence. Six out of the 18 patients with prior parathyroid operations had multiple glands removed on prior operations. Nine out of 18 (50%) were localized by 4D-CT. We have long-term follow-up on 16 of these patients thus far, and 12 of the 16 were cured. Of the remaining 2, 1 had elevated calcium and PTH at 49 days post operatively and the other was normocalcemic at the 2-week post-operative visit. Long-term cure rates were not significantly different between prior and reoperative parathyroid patients (**P** = .17).

Of the 10 patients with persistent disease, 1 had an undescended left superior adenoma correctly identified on 4D-CT; 8 had a single abnormal gland reported, 4 of which were confirmed at surgery and

### Table I. Patient variables associated with localization by 4D-CT

<table>
<thead>
<tr>
<th>Patient characteristic</th>
<th>Measure (n = 60)</th>
<th>4D-CT localized (n = 36)</th>
<th>No 4D-CT localization (n = 24)</th>
<th><strong>P</strong> value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean yrs (SD)</td>
<td>60 (±12.8)</td>
<td>58 (±13.7)</td>
<td>61 (±11.3)</td>
<td>.39</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>55 (92%)</td>
<td>32 (86%)</td>
<td>23 (96%)</td>
<td>.64</td>
</tr>
<tr>
<td>BMI, mean (SD)</td>
<td>28.9 (±6.2)</td>
<td>28.4 (±6.2)</td>
<td>29.4 (±6.3)</td>
<td>.61</td>
</tr>
<tr>
<td>Primary operation, n (%)</td>
<td>39 (65%)</td>
<td>24 (67%)</td>
<td>15 (63%)</td>
<td>.79</td>
</tr>
<tr>
<td>Preoperative serum calcium (mg/dL), mean (SD)</td>
<td>10.9 (±0.61)</td>
<td>10.9 (±0.61)</td>
<td>10.9 (±0.63)</td>
<td>.61</td>
</tr>
<tr>
<td>Preoperative serum PTH (pg/dL), median (range)*</td>
<td>96 (52–288)</td>
<td>102.0 (61–288)</td>
<td>81.0 (52–222)</td>
<td>.09</td>
</tr>
<tr>
<td>Normal preoperative Vitamin D (%)†</td>
<td>35/43 (81%)</td>
<td>19/25 (76%)</td>
<td>16/18 (89%)</td>
<td>.43</td>
</tr>
</tbody>
</table>

*Normal ranges: 10–60 pg/dL, Massachusetts General Hospital; 11–80 pg/dL, Brigham and Women’s Hospital.
†Normal ranges 33–100 ng/mL, Massachusetts General Hospital; 25–80 ng/mL, Brigham and Women’s Hospital.

### Table II. Procedures performed after preoperative localization with 4D-CT

<table>
<thead>
<tr>
<th>Exploration</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Focused</td>
<td>8 (14)</td>
</tr>
<tr>
<td>Unilateral</td>
<td>12 (20)</td>
</tr>
<tr>
<td>Bilateral w/o thyroidectomy</td>
<td>35 (55)</td>
</tr>
<tr>
<td>Combined w/ thyroidectomy</td>
<td>7 (12)</td>
</tr>
<tr>
<td>Total</td>
<td>60 (100)</td>
</tr>
</tbody>
</table>
4 that were not; and 1 patient had reimplantation tissue that was correctly identified on 4D-CT. Of the 8 patients for whom we have long-term follow-up data, 5 were cured and 3 continue to have persistent disease. Of the remaining 2 with short-term follow-up, 1 likely has persistent disease (Ca$_{2+}$, 11 mg/dL; PTH, 85 pg/dL at 49 days) and the other was normocalcemic at 13 days postoperatively. Of the 8 patients with recurrent disease, I had a hyperplastic remnant found at operation (not identified by 4D-CT); 4 had a single focus reported on 4D-CT, 3 of which were confirmed at operation and 1 that was not; 2 had reimplants excised, 1 identified by 4D-CT; and 1 patient with 4-gland hyperplasia (single abnormal gland reported on 4D-CT). Seven out of 8 recurrent disease patients achieved long-term cure.

**Imaging.** 4D-CT correctly lateralized the primary abnormal parathyroid gland found intraoperatively in 73% of cases and localized the gland(s) in 60%. Ability to localize the abnormal gland was not correlated with prior operation, both when including ($P = .79$) and excluding ($P = .39$) the 3 patients with prior thyroidectomy alone. All patients had >1 candidate lesion noted on official 4D-CT report and 14 (23%) had >1 candidate lesion named. When multiple candidate lesions were identified on 4D-CT, the accuracy of the primary lesions for localization dropped from 70% (single candidate) to 29%. Age ($P = .39$), gender ($P = .64$), BMI ($P = .61$), preoperative serum calcium ($P = .61$), preoperative serum PTH level ($P = .09$), and preoperative 25-OH vitamin D level ($P = .43$) were not significantly correlated with accuracy of 4D-CT on univariate analysis (Table I). Size ($P = .03$) and volume ($P = .05$) of the parathyroid gland, were significantly associated with localization of abnormal gland(s) by 4D-CT (Table III). The sensitivity, specificity, and positive predictive values of 4D-CT comparing imaging with all parathyroids that were assessed intraoperatively (normal and diseased; $n = 173$) were 67%, 69%, 65%, and 71%, respectively.

In the large majority of our patients (48/60), traditional imaging (both US and sestamibi) failed to definitively localize any abnormal parathyroid(s). The remaining 12 patients had either discordant or otherwise inconclusive results (eg, US was negative and sestamibi stated “possible focus adjacent to left thyroid, thyroid nodule versus adenoma”). Of these 12 patients, 5 were US localized, sestamibi negative. In 3 of these 5 cases, the US agreed with the 4D-CT localization and all were cured. Two of the 3 cases that had discordant localization with US and 4D-CT were confirmed intraoperatively. There were 3 cases in which both studies were “wrong.” Likewise, 6 patients were US negative, sestamibi positive. In 4 of these 6, the sestamibi agreed with 4D-CT localization, and 5 of 6 were cured (1 patient refused consent to sternotomy preoperatively and has subsequently undergone reoperation and cure for mediastinal adenoma). In 1 of these 6 cases, both sestamibi and 4D-CT indicated a left inferior parathyroid adenoma, but the surgeon called it a “descended left superior adenoma.” This was considered a negative localization by 4D-CT. In the last case, the 4D-CT localized the abnormal gland, whereas the sestamibi was false positive, as confirmed by operative findings. With regard to operative approach, 9 of the 12 (75%) cases with both 4D-CT and either US or sestamibi localization underwent bilateral explorations. Thirty-one of the 48 cases (65%) with no US or sestamibi localization underwent bilateral explorations, and the remaining 17 underwent a unilateral or focused exploration.

Nearly all patients for whom 4D-CT failed to identify the primary lesion (21 out of 24) underwent bilateral explorations. We have long-term follow-up on 22 of the 24 patients with negative 4D-CT. Of these, 18 of 22 (82%) were cured. This compares with 30 of 33 (91%) cured among those who were localized on CT ($P = .41$). Nineteen out of 36 patients in the 4D-CT localized group underwent unilateral ($n = 10$) or single-gland ($n = 7$) exploration, limiting the extent of exploration ($P = .006$ for accurate 4D-CT localization versus bilateral exploration).

**Multigland disease.** Multigland disease was found in 13% of cohort as determined by the surgeon; 6 patients with parathyroid hyperplasia and 2 with double adenomas. Notably, 5 of 8 patients with multigland disease found intraoperatively had multiple candidate lesions noted on 4D-CT. In 4 of the 8 cases that the surgeon deemed the patient to have multiglandular disease intraoperatively, the postexcision IOPTH was not drawn until the subtotal parathyroidectomy (3 cases) or double adenoma excision (1 case) was performed. In all 4 of these cases, the IOPTH halved. In 1 case deemed 4-gland hyperplasia, a level was drawn after 1.5 glands

---

**Table III. Correlation of parathyroid size and volume with 4D-CT localization**

<table>
<thead>
<tr>
<th>4D-CT Localization</th>
<th>Yes</th>
<th>No</th>
<th>Wilcoxon P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Largest dimension, median mm (IQR)</td>
<td>12 (6.0)</td>
<td>10 (4.0)</td>
<td>.03</td>
</tr>
<tr>
<td>Volume, median mm$^3$ (IQR)</td>
<td>300 (574)</td>
<td>195 (176)</td>
<td>.05</td>
</tr>
</tbody>
</table>
were removed and the PTH dropped from 140 to 23 pg/dL. Given the appearance of a third enlarged, abnormal-appearing gland, frozen section results, and likely diagnosis of 4-gland hyperplasia, the surgeon proceeded to remove a third gland. In another case, subtotal parathyroidectomy was performed without IOPTH. In 1 case of a double adenoma (correctly identified by 4D-CT) the IOPTH failed to decrease by >50% after resection of 1 gland. Specifically, after removal of 1 of the 2 abnormal-appearing glands (ie, right inferior), the IOPTH dropped from 87 to 55 pg/dL. After the removal of the second “abnormal” gland (ie, left inferior), the IOPTH dropped to 15 pg/dL. In the last case, the surgeons chose to send an IOPTH after removal of 2.5 abnormal glands. The IOPTH level dropped from 57 preoperatively to 40 pg/dL after removal of 2.5 glands and to 7 pg/dL after the removal of the additional gland. Frozen section analysis confirmed hyperplastic parathyroid tissue was used in all cases.

**DISCUSSION**

Traditional, 4-gland exploration for hyperparathyroidism has largely been replaced by focused exploration assisted by localization studies and IOPTH monitoring, as documented in a recent survey of general and endocrine surgeons. The majority of surgeons who perform limited explorations argue that minimally invasive parathyroidectomies result in decreased morbidity, improved costs (by decreasing the length of stay), and lower rates of hypoparathyroidism, while still obtaining similar success rates. Limited parathyroid explorations require reliable and accurate preoperative imaging. Traditional imaging with US and sestamibi has wide-ranging reported sensitivities based on study design and varying technical protocols. Overall, US and sestamibi have sensitivities of 53–98% and 41–86%, respectively, with 52–71% concordance. Historically, patients undergo 4-gland exploration in the event that these modalities are discordant or negative. In this study, we aimed to assess the utility of 4D-CT for preoperative localization in patients with PHPT and unsuccessful localization by conventional imaging. When using the primary diagnosis on 4D-CT report, we found lateralization and localization rates of 76% and 60%, respectively. Although we are cautious in drawing any major conclusions given the heterogeneous group of patients and treatment strategies, we can make a number of important observations from this work.

As per convention for poorly localized patients, the majority of patients in this cohort still underwent a planned bilateral exploration regardless of if the gland identified on 4D-CT was found to be abnormal on the initial surgical approach. Notably, 34% of patients, who arguably would have undergone a bilateral exploration without 4D-CT, did undergo a focused or unilateral exploration. In fact, a significantly greater proportion of patients with accurate 4D-CT localization underwent unilateral exploration (P = .006). Moreover, 3 quarters of the cohort had single adenomas: 70% of these, missed by traditional imaging, were identified on 4D-CT. Although the surgeons still pursued bilateral explorations in some of these cases, this represents a substantial group of patients that could benefit from limited exploration guided by 4D-CT. Perhaps as we gain more confidence in the 4D-CT scan, more US/sestamibi-negative patients will undergo a targeted exploration, aided by IOPTH and based solely on 4D-CT. However, a prospective study designed to assess the utility of 4D-CT in decreasing the extent of an operation is warranted.

Patients with previous neck surgery, high BMI, persistent or recurrent hyperparathyroidism, ectopic parathyroids, and multigland disease are diagnostically and clinically challenging. Our results support the conclusion reported by Mortenson et al that accuracy of 4D-CT is not reduced in patients undergoing reoperation. In our cohort, neither 4D-CT accuracy nor long-term cure differed between primary and reoperative parathyroid patients. Although 4D-CT was only accurate in identifying 50% of abnormal glands in this subset, we still feel that this modality is helpful in this group of otherwise nonlocalized patients. For example, 1 patient had undergone a previous extensive operation, including hemithyroidectomy and thymectomy after the identification of only 3 normal glands. Postoperative 4D-CT revealed an undescended left parathyroid, not identified on US or sestamibi, allowing for a focused exploration with appropriate incision placement.

With regard to BMI, previous work has shown that US and sestamibi are less accurate in obese patients. We did not find 4D-CT accuracy to be correlated with BMI in our study. Not surprisingly, larger parathyroid gland size and volume were correlated with accuracy of 4D-CT, similar to findings by traditional imaging. Importantly, 2 patients with undescended ectopic glands were correctly identified by 4D-CT, allowing for appropriate initial incision placement (Fig 2).

Multigland disease remains a dilemma. Sestamibi is known to be inaccurate at identifying multigland disease. Rodgers et al reported 45% sensitivity in detecting >1 abnormal gland and 27% in detecting all abnormal glands in their study comparing 4D-CT with US and sestamibi. In
this study, 8 patients were identified by the surgeon as having multigland disease. One case of 4-gland hyperplasia and another with double adenoma were correctly identified by 4D-CT (all abnormal glands were identified). In the remaining cases, 5 additional cases of hyperplasia and 1 double adenoma, not all glands were specifically identified. Overall, 5 of the 8 patients with multigland disease did have multiple lesions noted on 4D-CT, alerting the surgeon to consider bilateral exploration.

One limitation of 4D-CT is the relatively high false-positive rate (lower specificity), leading to potential “over-operating”; gland size and appearance does not necessarily indicate hyperfunction. An IOPTH level that decreases after removal of 1 abnormal gland may indicate cure, although the temptation is to remove additional “abnormal” gland(s) indicated by 4D-CT or visualization. IOPTH was utilized in the large majority of this cohort; however, in some cases the surgeon used their judgement of the gland appearance (ie, size, shape, and color), plus his or her preoperative suspicion of multigland disease based on multiple factors including prior explorations, preoperative imaging, and frozen section analysis, as the indication for excision. This issue is illustrated by the 14 cases in this cohort where multiple candidate glands were noted on 4D-CT. Although multiple candidates were identified on 4D-CT, only 1 gland was removed in 8 out of 14 cases (all with long-term cure), suggesting that the surgeons did not “over-operate.” Although some of these “candidate lesions” noted on 4D-CT may not have been parathyroid at all (eg, lymph node or thyroid nodules), the detection of non hyperfunctioning “enlarged parathyroid glands” is an issue. Therefore, we recommend bilateral exploration using IOPTH as a guide for adequacy of resection in cases where multiple candidates are indicated by 4D-CT.

Another important concern is the potential radiation risk associated with 4D-CT. When using the published dose length product to effective dose conversion factor of 0.0054 mSv/(mGy*cm), the estimated effective dose from a 4D-CT scan is 10 mSv. This compares with an effective dose from a 99mTc-sestamibi nuclear medicine SPECT scan, which results in an effective dose of 6 mSv assuming the administered radioactivity is 740 MBq or 20 mCi. If additional CT localization is added to a SPECT scan, the effective dose increases to
about 8–9 mSv, depending on the technique factors used for the CT portion of the study.

LIMITATIONS

We acknowledge certain limitations in this study. To the best of our ability, although we attempted to determine whether or not the lesion(s) removed operatively was indeed the lesion(s) identified as abnormal on 4D-CT, this may have resulted in misclassifications in the data. In addition, the patients entered in this study were not standardized either for inclusion in the study or operative approach. The cohort represents a mixture of primary and reoperative patients with varying preoperative workups and operative strategies. Furthermore, intraoperative findings were used as the gold standard, not accounting for operative failures. Last, although the majority of patients did undergo bilateral explorations, data are missing from the limited explorations for the specificity and negative predictive value analyses.

In conclusion, we believe that 4D-CT is a usable modality with substantial accuracy in the face of negative traditional imaging in a clinically challenging group of patients. In particular, 4D-CT does identify single glands amenable to limited operative intervention in the more than half of patients with negative or discordant US and sestamibi imaging. We feel that the 4D-CT is beneficial in US/sestamibi negative cases in both primary and reoperative cases. In first-time surgeries for hyperparathyroidism, it can provide (and did in 25 of 39 cases) the localization of a single gland and therefore present the option of a focused approach. Clinically, this could potentially lead to a reduction in morbidity and costs associated with a more extensive dissection. In reoperative cases, where the standard for localization before exploration is even greater, it offers another noninvasive option and could be useful either when sestamibi and/or US are negative, or as a second confirmatory study.

Use of the 4D-CT scan could include using it as a primary study in all patients versus reserving it for cases where traditional imaging was deemed inadequate and in the surgeon’s opinion additional imaging could potentially be helpful. Our study was not designed to assess the role of 4D-CT as a primary localization modality. Until we have formal radiation dose comparisons and cost-effectiveness analyses comparing traditional imaging with 4D-CT, we are not prepared to recommend this modality as first-line imaging. We do feel that, as in the cases in this cohort, 4D-CT is beneficial in US/sestamibi-negative cases. In cases where the surgeon lacked confidence in traditional imaging, obtaining a 4D-CT was helpful in more than half of the cases, and, in particular, the cases where a single candidate was identified. Although the surgeons still pursued bilateral explorations in some of these cases, these arguably could have been targeted explorations. We do, however, recommend bilateral exploration using IOPTH as a guide for adequacy of resection in the cases where multiple candidates are indicated by 4D-CT. Studies assessing the effect of 4D-CT on planned operative approach, formal radiation dose comparisons with traditional imaging, and comparative effectiveness are warranted.

The authors thank the referring endocrinologists and participating radiologists for their contributions.

REFERENCES


DISCUSSION
Dr Sally E. Carty (Pittsburgh, PA): Thank you for a very lucid presentation. Because persistent and recurrent hyperparathyroidism define operative failure, and because you have shown in half of your 60 patients confirmed biochemical cure, the potential exists that in the other half, you haven’t cured them. And that makes these data difficult to interpret. How do you answer that?
Dr Carrie C. Lubitz (Boston, MA): I am continuing to look at the data and trying to obtain the rest of it. I’m aware that that’s a limitation of the study. I do think that this number, the percent cure, is a selected group of patients where the surgeons were concerned for potential failure. And, in fact, 3 of those cases have already gone back for surgery.
Dr Scott Wilhelm (Cleveland, OH): I have a comment first and then a question. My comment is that I think this is a great example of how meetings like this of the AAES really reflect taking a study that was done by Dr Perrier’s group and then employing it to a new patient group and really carrying on the research. I think that’s a great thing that we see here at this meeting frequently. Very nice job with that.
My question to you is, do you think that the 4D-CT scan helped you in a patient who is a new patient, not reoperative, to really change your surgical management and change what your exploration was? If you had no findings on sestamibi, no findings on ultrasound, and you’re going to do a bilateral neck exploration anyway, do you think 4D-CT added much for what the cost would be for us to do that?
Dr Carrie C. Lubitz (Boston, MA): In reference to your question, there were a greater number of cases that were localized by 4D-CT where the surgeon still went forward and did a bilateral exploration. There were approximately 34% of cases where 4D-CT did target the exploration to either a single gland or for a unilateral exploration. So I think it does have a potential to decrease potential operative time. This is something that we will have to look at prospectively in terms of whether or not 4D-CT would actually affect operative strategy. We’re unable to really obtain that with this data with the current design.
Dr Kelly McCoy (Bethesda, MD): Thank you for a very interesting discussion. And again, any tool to add to our armamentarium of localizing parathyroid disease is welcome. In places where we don’t have the capability of 4D-CT and use other things like MRI or venous sampling, did you by chance have any patients in whom those modalities were used, and did they correlate at all?
Dr Carrie C. Lubitz (Boston, MA): Yes, there were 2 patients who underwent venous sampling and 6 who had fine needle aspiration biopsies. All of those cases were reoperative cases. In fact, surprisingly, they were not particularly helpful. I will say that it really didn’t guide us any further beyond the 4D-CT results in these cases.
Dr John Porterfield (Birmingham, AL): We also use high-resolution CT for reoperative parathyroid cases, and I would congratulate you on your presentation today. The concern that our institution has had from radiology has been the dose of radiation with the 4 high-resolution scans. And my question to you is: have you considered eliminating the noncontrast high-resolution scan to reduce that dose, and what has been your Institutional Review Board’s response in implementing this in your institution?
Dr Carrie C. Lubitz (Boston, MA): You mean the precontrast image? Yes. I will try to comment a little bit on the radiation dosage. I spoke to Dr Hunter and Dr Hamburg, who are our radiology colleagues. Although they haven’t published it, they’ve looked at the radiation dose, comparing it with sestamibi as well as SPECT CT-sestamibi. And actually, the radiation doses that they’ve calculated are similar in these cases. I think that seeing the rapid wash-in is very beneficial in terms of identifying the
parathyroid adenoma as separate from either a thyroid nodule or other surrounding structures, so I do think this is an important image.

**Dr Samuel Snyder** (Temple, TX): Thank you very much for an excellent presentation. Based on your reported experience at our institution, we started using 4D-CT scan for reoperative cases. And what we found is that we’ve had to reeducate our radiologists as to the location for some of these ectopic glands. One gland missed by the radiologist was an undescended retropharyngeal parathyroid adenoma. Looking back after we finally found the gland operatively, in retrospect, it was actually there.

So, I question: Were you able to look at your negative 4D-CT scans and reevaluate them in light of operative experience and reassess the accuracy of any interpretation?

**Dr Carrie C. Lubitz** (Boston, MA): I think there are 3 things to answer here. First, I would say all of our cases had something identified. In fact, I think the issue that most of the surgeons had was that there were false positives. We did not have any negative scans altogether. Second, I think it is very important for the surgeons to either sit down with the radiologist or look on their own and really look at the scans themselves, because they have a different knowledge set that I think has been helpful in walking both the radiologists through it as well as the surgeon.

Last, I believe the question regarding ectopic glands and the negative reports. Again, there weren’t any negative reports. We haven’t gone back and retrospectively looked at the cases yet, although that is a good idea.