Is Intraoperative Parathyroid Hormone Monitoring Warranted in Cases of 4D-CT/ Ultrasound Localized Single Adenomas?

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Abstract

Objective. To analyze the utility of intraoperative parathyroid hormone (IOPTH) monitoring for patients with primary hyperparathyroidism who had evidence of single-gland disease on preoperative imaging with modified 4-dimensional computed tomography that was done in conjunction with ultrasonography (Mod 4D-CT/US).

Study Design. Case series with chart review.

Setting. Tertiary care university medical center.

Subjects and Methods. Patients were drawn from consecutive directed parathyroidectomies performed between December 2001 and June 2013 by the senior authors. All patients had primary hyperparathyroidism and underwent a Mod 4D-CT/US study that showed findings on both studies that were consistent with a single adenoma. The modified Miami criteria were used for IOPTH monitoring (parathyroid hormone decrease by >50% and into the normal range).

Results. Of 356 patients who underwent parathyroid surgery, 206 had a single gland localized on the Mod 4D-CT and the US studies. IOPTH monitoring was used in 172 cases, of which 169 had adequate clinical follow-up to assess the surgical outcome. Twenty-one patients (12.4%) had IOPTH values that did not meet modified Miami criteria after removal of one gland, of which 7 were found to have multigland disease (4.1%). Three patients (1.8%) had persistent primary hyperparathyroidism despite an IOPTH that met modified Miami criteria.

Conclusions. Although IOPTH monitoring correctly identifies a small percentage of patients with multigland disease, some patients will be subjected to unnecessary neck explorations that can result in difficult intraoperative decisions, such as whether to remove normal or equivocal-sized glands when they are encountered.

Keywords

4D CT, primary hyperparathyroidism, parathyroid surgery, intraoperative parathyroid hormone monitoring
parathyroid glands and other structures in the neck. Computed tomography series before and during contrast were compared to assess uptake. At our center, we have achieved 94% sensitivity and 96% specificity in lateralizing the hyperfunctioning parathyroid glands to one side of the neck with Mod 4D-CT/US. We found this modality had a 92% positive predictive value and 73% negative predictive value for single-gland disease.

Some surgeons use intraoperative parathyroid hormone monitoring (IOPTH) in conjunction with preoperative imaging as a test of biochemical cure.6,7 Because of the short half-life of intact parathyroid hormone (PTH) (approximately 4 minutes), it is possible to monitor the decreased production in near real time. One of the most widely accepted standards is the modified Miami criteria, defined as an IOPTH drop of 50% or more when comparing the preexcision PTH level with a sample drawn 10 minutes after gland excision as well as a value that enters the normal range.8 The reported sensitivity and specificity of the modified Miami criteria for cure are 88% and 22%, respectively.9 Importantl, IOPTH values can remain elevated during surgery for multiple reasons, including a lab drawn too soon, renal insufficiency, poor calibration of the machine, multiple gland disease, extensive manipulation of the gland prior to removal, or failure to remove a “true” adenoma. While these values are often quoted, a 10-year prospective study using IOPTH in previously unexplored parathyroidectomy cases found a 93.4% cure rate.10 Other studies have documented similar results.11

This study represents the first attempt, to our knowledge, to examine the utility of IOPTH monitoring in patients with PHPT who have a single, concordant gland localized by Mod 4D-CT/US.

Methods

Patient Population

We retrospectively reviewed the medical records of 356 patients who underwent parathyroidectomy for PHPT at a single institution from December 2001 to June 2013. Patients with multiple endocrine neoplasia and secondary, tertiary, and familial hyperparathyroidism or lithium use were excluded. This study was approved by the institutional review board of Weill Cornell Medical College.

Imaging Technique

All patients underwent a Mod 4D-CT/US study at our facility. The Mod 4D-CT/US protocol used in this study is documented in detail in a prior publication.4 In total, 150 patients were excluded because the suspected gland was seen only on the 4D-CT or ultrasound but not on both, because multiple glands were identified, or because other imaging modalities (sesta-mibi) were used. A total of 206 patients were found to have a localized single adenoma on both studies.

Operative Technique

Patients with presumptive single-gland disease on preoperative imaging studies underwent a directed parathyroidectomy (DP). Most patients opted for local anesthesia with sedation. The use of IOPTH was not influenced by the type of anesthesia used. Of the 206 patients who met preoperative imaging inclusion criteria, 169 patients had IOPTH monitoring as part of the procedure, as the senior surgeon has begun to omit IOPTH monitoring from favorable concordant single-gland cases. A baseline IOPTH value was obtained in the operating room prior to making an incision, with normal ranges of 12 to 44 pg/mL (December 1, 2001, to January 1, 2008) and 12 to 88 pg/mL (January 1, 2008, to present). The abnormal parathyroid gland was classified as an inferior or superior gland based on its anatomic location and relationship to surrounding structures. Ten minutes after removal of the suspected adenoma, which was routinely sent for frozen section, a second PTH level was drawn. The authors do not have equipment to measure the intraoperative PTH in the operating room so specimens were sent to the central lab, which added about 15 minutes to the operative time. In most cases, if the PTH level decreased by greater than or equal to 50% compared with the preoperative, the operation was terminated. Analysis employed the modified Miami criteria, which is the favored IOPTH interpretation technique, defined as a >50% drop from preincision values as well as a level that enters the normal range.

Postoperative Evaluation and Follow-up

Patients were released after meeting the postanesthesia care unit discharge criteria. After discharge from the hospital, serum calcium and PTH levels were monitored on an outpatient basis. Postoperative serum intact PTH and calcium levels were used to assess for surgical cure. Of 169 patients, 131 (78%) had an available postoperative intact PTH value while 38 patients (22%) had only calcium levels available. Of note, serum calcium levels have been used in most prior IOPTH-related research to determine surgical success, with serum calcium <10.6 mg/dL defining normal parathyroid function. We propose that this may incorrectly characterize a small number of patients with an elevated PTH value in the setting of a calcium level in the high-normal range as cure when in fact they have persistent PHPT. Within our subset of patients without postoperative PTH values, there were only 3 patients with a serum calcium >10.0 mg/dL, whom we excluded for statistical analysis, since these cases could not definitely be characterized as cure or persistent disease in the absence of a PTH value. The PTH normal range varied depending on the testing center.

Statistical Analysis

Documentation from imaging studies, operative findings, pathologic data, and biochemical assessment for each patient was compiled into a database. When IOPTH correctly predicted normal parathyroid function postoperatively, the fall in IOPTH level was considered a true-positive (TP) result. A true-negative (TN) result was defined as the failure to meet IOPTH criteria in the setting of multigland disease. A false-positive (FP) result was assigned
when the IOPTH testing predicted normal parathyroid but the interval follow-up revealed persistent PHPT. A false-negative (FN) result was assigned when IOPTH testing predicted multigland disease but the actual result was normal parathyroid function. These definitions were used to calculate the sensitivity (TP/[TP + FN]), specificity (TN/[TN + FP]), positive predictive value (TP/[TP + FP]), and negative predictive value (TN/[TN + FN]) for each set of criteria examined.

**Results**

**Demographics**

The 169 patients in the study included 133 women (79%) and 36 men (21%). The mean age was 63 years at the time of surgery. The mean gland weight removed was 759 mg. Complications occurred in 5 patients (3.0%), including 2 minor hematomas, 1 wound abscess, and 2 suture granulomas.

**IOPTH Monitoring**

IOPTH values met modified Miami criteria following suspected adenoma removal in 148 cases (88%). Of the 21 patients who did not meet the modified Miami criteria, 7 had additional diseased parathyroid glands removed (4%). We found that IOPTH confounded surgical management in 17 cases (10%). *Tables 1 and 2* show cases in which IOPTH was either falsely negative or positive.

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Baseline IOPTH</th>
<th>Baseline IOPTH Level (Norm Range)</th>
<th>Baseline IOPTH Change, %</th>
<th>Additional Gland(s) Removed</th>
<th>Additional IOPTH Level</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>69</td>
<td>179</td>
<td>115 (12-44)</td>
<td>-36</td>
<td>1, 1100 mg</td>
<td>150</td>
<td>Cure</td>
</tr>
<tr>
<td>84</td>
<td>146</td>
<td>47 (12-44)</td>
<td>-68</td>
<td></td>
<td></td>
<td>Cure</td>
</tr>
<tr>
<td>89</td>
<td>210</td>
<td>229 (12-44)</td>
<td>+9</td>
<td></td>
<td>23</td>
<td>Cure</td>
</tr>
<tr>
<td>119</td>
<td>170</td>
<td>94 (12-44)</td>
<td>-45</td>
<td></td>
<td>45</td>
<td>Cure</td>
</tr>
<tr>
<td>121</td>
<td>98</td>
<td>73 (12-44)</td>
<td>-26</td>
<td>1, 40 mg</td>
<td>31</td>
<td>Cure</td>
</tr>
<tr>
<td>123</td>
<td>247</td>
<td>48 (12-44)</td>
<td>-81</td>
<td></td>
<td></td>
<td>Cure</td>
</tr>
<tr>
<td>136</td>
<td>175</td>
<td>53 (12-44)</td>
<td>-70</td>
<td></td>
<td></td>
<td>Cure</td>
</tr>
<tr>
<td>178</td>
<td>190</td>
<td>53 (12-44)</td>
<td>-72</td>
<td></td>
<td></td>
<td>Cure</td>
</tr>
<tr>
<td>220</td>
<td>141</td>
<td>68 (12-44)</td>
<td>-54</td>
<td></td>
<td></td>
<td>Cure</td>
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<tr>
<td>277</td>
<td>86</td>
<td>55 (12-88)</td>
<td>-36</td>
<td></td>
<td>17</td>
<td>Cure</td>
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<tr>
<td>295</td>
<td>99</td>
<td>58 (12-88)</td>
<td>-41</td>
<td>1, 45 mg</td>
<td>16</td>
<td>Cure</td>
</tr>
<tr>
<td>310</td>
<td>122</td>
<td>95 (12-88)</td>
<td>-22</td>
<td></td>
<td>17</td>
<td>Cure</td>
</tr>
<tr>
<td>319</td>
<td>115</td>
<td>83 (12-88)</td>
<td>-28</td>
<td></td>
<td></td>
<td>Cure</td>
</tr>
<tr>
<td>328</td>
<td>94</td>
<td>55 (12-88)</td>
<td>-41</td>
<td></td>
<td></td>
<td>Cure</td>
</tr>
</tbody>
</table>

**Table 2. IOPTH False-Negative Cases.**

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Baseline IOPTH</th>
<th>Baseline IOPTH Level (Norm Range)</th>
<th>Baseline IOPTH Change, %</th>
<th>Additional Gland(s) Removed</th>
<th>Additional IOPTH Level</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>208</td>
<td>97</td>
<td>18 (12-44)</td>
<td>-81</td>
<td></td>
<td></td>
<td>PHPTH</td>
</tr>
<tr>
<td>264</td>
<td>217</td>
<td>88 (12-88)</td>
<td>-59</td>
<td></td>
<td></td>
<td>PHPTH</td>
</tr>
<tr>
<td>267</td>
<td>153</td>
<td>16 (12-88)</td>
<td>-90</td>
<td></td>
<td></td>
<td>PHPTH</td>
</tr>
</tbody>
</table>

**Table 1. IOPTH False-Positive Cases.**

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Baseline IOPTH</th>
<th>Baseline IOPTH Level (Norm Range)</th>
<th>Baseline IOPTH Change, %</th>
<th>Additional Gland(s) Removed</th>
<th>Additional IOPTH Level</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>208</td>
<td>97</td>
<td>18 (12-44)</td>
<td>-81</td>
<td></td>
<td></td>
<td>PHPTH</td>
</tr>
<tr>
<td>264</td>
<td>217</td>
<td>88 (12-88)</td>
<td>-59</td>
<td></td>
<td></td>
<td>PHPTH</td>
</tr>
<tr>
<td>267</td>
<td>153</td>
<td>16 (12-88)</td>
<td>-90</td>
<td></td>
<td></td>
<td>PHPTH</td>
</tr>
</tbody>
</table>

Abbreviations: IOPTH, intraoperative parathyroid hormone; PHPTH, persistent hyperparathyroidism.

*aCases of IOPTH false positives, in terms of intraoperative findings. Parathyroid hormone values are given in pg/mL.

The baseline IOPTH values given represent the maximum values either at presentation or preincision as specified by the modified Miami criteria.

Abbreviations: IOPTH, intraoperative parathyroid hormone.

*aCases of IOPTH false negatives and positives, in terms of intraoperative findings. Parathyroid hormone values are given in pg/mL.

The baseline IOPTH values given represent the maximum values either at presentation or preincision as specified by the modified Miami criteria.
to prevent one case of missed multigland disease in our series is 25.

At last follow-up, 166 patients (98%) achieved surgical cure while 3 patients (2%) had persistent PHPT. Patient 208 had a PTH of 96.6 pg/mL 2 months after parathyroidectomy. Patient 264 was documented to have recurrent PHPT (PTH = 146 pg/mL) approximately 2 weeks following surgery while patient 267 was documented to have recurrent PHPT (156 pg/mL) 10 days postsurgery. None of these patients underwent further surgery at our center. All had borderline-high calcium levels that made the diagnosis of secondary HPTH less likely.

**Discussion**

This is the first study to our knowledge to investigate the pitfalls of IOPTH when a Mod 4D-CT/US protocol localizes a single enlarged parathyroid gland. We found that in some cases, IOPTH prompted futile neck explorations, and in some cases, it increased the complexity of surgical decision making, forcing the surgeon to make a judgment as to whether equivocal glands were diseased or normal based on visual inspection. Figure 1 displays a decision tree that illustrates the complexity of the decision making that can occur when the IOPTH does not meet the modified Miami criteria following resection of the suspected adenoma.

It is important to recognize that many patients with PHPT have a mild biochemical abnormality and are asymptomatic. In this setting, we feel that it is inappropriate to remove potentially normal parathyroid glands on the basis of an elevated IOPTH value, when the patient may already be cured surgically following the resection of the suspected single adenoma. On the other hand, if the patient has persistent hyperparathyroidism because apparently normal or equivocal glands were left in situ, revision surgery will be more difficult due to fibrosis.

Of 169 studied cases, 21 patients did not meet the Miami criteria following removal of the suspected adenoma (12%). Of these, there were 14 cases in which no other abnormal parathyroid glands were identified (67%) while 7 proved to have multigland disease (33%). If IOPTH had not been used in our population, 5.9% of the cases would have required reoperation, compared with 1.8% without (absolute increase of 4.1%). While some may argue that the need to do a second operation on 4% of patients is problematic, we feel this is an acceptable and safe strategy because those patients with persistent PHPT can easily be brought back to surgery for a subtotal parathyroidectomy with the knowledge that they have confirmed multigland disease. In addition to allowing for improved surgical planning, the approach that we advocate would reduce the morbidity of the unnecessary contralateral explorations that occurred in 5% of the patients in this series. The differential outcome of our cohort with or without IOPTH monitoring is shown in Figure 2.

This study is not the first to describe problems that can occur with IOPTH monitoring. Ozimek et al12 examined the validity of IOPTH in 235 cases of PHPT and reported an NPV of 54% and a PPV of 99.6%. In our hands, we observed an IOPTH NPV of 33.3% (PPV, 98.0%). These results suggest that with IOPTH monitoring, 67% (14/21) of patients with IOPTH values not meeting modified Miami criteria following removal of the suspected adenoma will be subjected to unnecessary surgical explorations (14 false negatives and 7 true negatives; see Table 2).

As with any medical testing, increasing the threshold for positivity results in an increase in false negatives. Of the 14 cases classified as false negatives in this study, a second intraoperative PTH level dropped to <50% without further dissection in 4 and with further dissection in another 2. This suggests that if the intraoperative PTH had been drawn later than 10 minutes, the number of false-negative cases would have been reduced to 8; however, there is an optimal time point that maximizes sensitivity and specificity. The Vienna, Halle, and Miami criteria all reflect different positivity thresholds, of which the Vienna criteria have been shown to result in a lower incidence of false positives.8 While decreasing the rate of false positives results in fewer missed multigland cases, it results in more frequent neck explorations for a nonexistent second lesion. A recent study of MIBI-only DP compared to MIBI with IOPTH monitoring found that in the IOPTH group, 5 patients had an unnecessary bilateral neck exploration as a result of an inadequate drop in PTH levels (6.2%).13

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**Table 3. IOPTH Statistical Outcomes (Miami Criteria).**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Definition</th>
<th>Cases, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>True negative</td>
<td>Cured hyperparathyroidism following an initial IOPTH drop of &lt;50% resulting in additional pathologic gland(s) removed and eventual IOPTH drop of &gt;50% and into the normal range</td>
<td>7 (4.1)</td>
</tr>
<tr>
<td>False negative</td>
<td>Cured hyperparathyroidism following an initial IOPTH drop of &lt;50% and into the normal range</td>
<td>14 (8.3)</td>
</tr>
<tr>
<td>True positive</td>
<td>Cured hyperparathyroidism following an IOPTH drop of &gt;50% and into the normal range following suspected adenoma removal</td>
<td>145 (85.8)</td>
</tr>
<tr>
<td>False positive</td>
<td>Persistent hyperparathyroidism following an IOPTH drop of &gt;50% and into the normal range following suspected adenoma removal</td>
<td>3 (1.8)</td>
</tr>
</tbody>
</table>

*Reported statistical definitions and values for intraoperative parathyroid hormone (IOPTH) testing in the study cohort.*
Omission of IOPTH monitoring is only possible when preoperative localization is sufficiently accurate to predict single-gland disease. Our initial study, which indicated a correct-side localization of 94%, was reproduced by Hunter et al.14 (93.7%), confirming that these results can be achieved at other institutions.15 In this study, we found that when single-gland disease was predicted based on the imaging studies, this was correct 92.9% of the time.

The 4D-CT/US-based parathyroid visualization protocols are dependent on the ability of the radiologist and the surgeon to interpret the study correctly. Detecting small adenomas with sufficient sensitivity and specificity requires meticulous examination of the usual and ectopic positions of the parathyroid glands. We communicate the intraoperative findings to our radiologists, which enables them to further hone their diagnostic acumen. The accuracy of single-

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**Figure 1.** A decision tree analysis. A square node represents a decision, a circular node represents chance, and a triangle represents an end point. Of the study cases, 12.4% would enter this decision tree. IOPTH, intraoperative parathyroid hormone.

**Figure 2.** Percentages at that branch assume either all or no patients underwent intraoperative parathyroid hormone (IOPTH) testing. Percentages of the total population are given in parentheses. Square node = decision; circular node = chance; triangle = end point.
gland localization will continue to improve with further experience and improvements in imaging capabilities.

We contend that when a single gland is identified using Mod 4D-CT/US, the risks of using IOPTH monitoring outweigh the benefit of avoiding revision surgery for the small percentage of patients with multigland disease who can be identified by using the IOPTH assay. We acknowledge that one of the weaknesses of our study is its retrospective nature. And we are aware that 4D-CT/US is not yet available at every medical center, although the fact that 9 studies on 4D-CT have been published in the first 3 months of 2015 suggests that this imaging modality is becoming more widely available.

In summary, Mod 4D-CT/US localization studies often provide sufficient accuracy in patients with single-gland primary hyperparathyroidism to forgo intraoperative PTH monitoring, thereby avoiding a complex decision analysis and the potential surgical complications that can occur when IOPTH measurements are used to determine whether or not to perform a bilateral operation.

**Author Contributions**

Thomas E. Heineman, conception, data collection, drafting, final approval, accountability agreement; David I. Kutler, data interpretation, drafting, final approval, accountability agreement; Marc A. Cohen, data interpretation, drafting, final approval, accountability agreement; William I. Kuhel, conception, drafting, final approval, accountability agreement.

**Disclosures**

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**References**