Surgical Management of Normocalcemic Primary Hyperparathyroidism and the Impact of Intraoperative Parathyroid Hormone Testing on Outcome

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Abstract

Objective. To review our surgical experience and the impact of intraoperative parathyroid hormone (IOPTH) testing among patients with normocalcemic primary hyperparathyroidism.

Study Design. Case series with chart review.

Setting. Academic referral hospital.

Subject and Methods. Normocalcemic hyperparathyroidism (NCHPT) patients were identified with normal-range blood ionized calcium and serum elevated parathyroid hormone. Patient demographics, intraoperative findings, IOPTH dynamics, and biochemical outcomes were compared with those of classic primary hyperparathyroidism (PHPT) patients.

Results. Of the 2120 patients who underwent parathyroidectomy, 616 patients met the inclusion criteria: 119 (19.5%) patients had NCHPT, and 497 (80.5%) had classic PHPT. NCHPT patients had higher rates of multigland hyperplasia as compared with classic PHPT (12% vs 4%, $P = .002$) and smaller gland size ($P < .001$). Of 119 NCHPT patients, 114 (97%) achieved ≥50% drop in IOPTH intraoperatively, as opposed to 492 (99%) among 497 classic PHPT patients ($P = .014$). IOPTH drop ≥50% had an equivalent positive predictive value for long-term cure in both groups.

Conclusions. Surgeons treating NCHPT patients should suspect the presence of multigland disease and have a low threshold for converting to bilateral exploration depending on IOPTH decay dynamics.

Keywords

normocalcemic, primary, mild, hyperparathyroidism, PTH, intraoperative parathyroid hormone monitoring

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The parathyroid hormone (PTH) molecule has a very short half-life (2-5 minutes), allowing it to serve as an accurate intraoperative measurement.1 The use of intraoperative PTH (IOPTH) testing has shifted parathyroid surgery away from traditional bilateral neck exploration to a targeted, minimally invasive approach.2 Where traditional bilateral exploration requires visual assessment of all parathyroid glands, a targeted approach allows radiographically directed surgical excision of a presumed hyperfunctioning gland with IOPTH to confirm that there are no additional hyperfunctioning glands. Persistence of relatively elevated PTH levels after parathyroid gland removal directs the surgeon to search for the presence of additional abnormal parathyroid glands.1 This targeted approach supplemented with IOPTH monitoring achieves long-term cure rates of 97% to 99% for the treatment of primary hyperparathyroidism (PHPT).3−5 Minimally invasive, targeted parathyroidectomies where IOPTH was not used to confirm complete hyperfunctioning gland excision can miss multigland disease (MGD), which occurs in about 15% of patients, resulting in a high operative failure rate.6
A subset of PHPT patients is now recognized as having mild biochemical changes that nevertheless have physiologic consequences. One such variant is normohormonal hyperparathyroidism, characterized by hypercalcemia with normal-range PTH serum levels. The other variant is normocalcemic hyperparathyroidism (NCHPT), characterized by elevated serum PTH levels with normal-range blood calcium levels. The literature shows that 5% to 28% of all patients diagnosed with PHPT have 1 of these 2 mild forms. The prevalence of NCHPT is difficult to ascertain due to inconsistent diagnostic criteria: the prevalence ranges from 0.4% to 16.7% in select populations. In 1 cohort of 1429 patients, 27% had mild PHPT disease, of which 31% had NCHPT.

A significant proportion of mild biochemical PHPT patients experience similar physiologic effects of calcium and PTH dysregulation as those with classic PHPT, such as low mineral bone density, pathologic bone fractures, or nephrolithiasis, promoting referrals for definitive surgical management. Benefits of parathyroidectomy for NCHPT patients are comparable to those of classic PHPT, as shown by improvements in bone mineral density. Mild forms of PHPT are increasingly being surgically managed, which has led to reevaluation of standard IOPTH-monitoring protocols for these patients. Studies demonstrate applicability of classic IOPTH-monitoring criteria to NCHPT patients, but the studies are limited by their small sample sizes, failure to analyze NCHPT patients in isolation, and lack of long-term outcomes.

To address this gap in the literature, we examined the surgical management of NCHPT patients by assessing their operative outcomes and the efficacy of IOPTH testing in predicting long-term surgical success.

Methods
After obtaining approval from the Johns Hopkins University’s Institutional Review Board, we conducted a retrospective analysis of a prospectively maintained database of patients with biochemical evidence of PHPT who underwent initial parathyroidectomy between December 2004 and June 2014 at Johns Hopkins Hospital. The following diagnoses were excluded from our analysis: recurrent/persistent primary, secondary (including renal failure, vitamin D deficiency, renal leak, or chronic malabsorption), and tertiary hyperparathyroidism, as well as familial hypocalciuric hypercalcemia, multiple endocrine neoplasia syndromes, and long-standing lithium use. Subsequently, only patients with confirmed diagnosis of PHPT were included. As documented in their medical records, all other isolated causes of hypercalcemia and hyperparathyroidism were carefully ruled out before surgery was considered for our NCHPT cohort. Only patients who underwent IOPTH monitoring during parathyroidectomy were included in this study.

For the purposes of our study, 2 comparison groups were identified with preoperative whole blood ionized calcium and serum PTH levels. Classic PHPT patients were identified by elevated preoperative ionized calcium and PTH serum levels (>1.35 mmol/L and 65 pg/mL, respectively). NCHPT patients were identified by normal-range preoperative ionized calcium with elevated PTH levels (≤1.35 mmol/L and >65 pg/mL, respectively). There were no normohormonal hyperparathyroid patients included in this study. Ionized calcium was used to select NCHPT patients because it is the most accurate reflection of biologically active calcium and the ion used by the calcium-sensing receptor to regulate PTH secretion. Total serum calcium was not used to select NCHPT patients, because protein-adjusted values were not widely available.

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Per our center’s protocol, patients with PHPT who have positive localization radiographic studies were treated with a targeted approach. These imaging studies included ultrasound, dual-phase planar sestamibi single-photon emission computed tomography, multiphase computed tomography fused with sestamibi, or magnetic resonance imaging. The selected imaging modality for each patient depended on the practice of each surgeon within our institution over time. Most often, patients had at least 2 preoperative imaging studies. A targeted, minimally invasive approach was planned when patients had ≥1 localizing and concordant imaging studies. IOPTH was used to confirm resection of all hypersecreting glands. When preoperative imaging was discordant or negative, bilateral exploration was considered with the use of IOPTH testing to guide the extent of surgical exploration. In both cases, image guidance and IOPTH monitoring helped guide the extent of surgery and most often triggered conversion to bilateral exploration if IOPTH levels did not fall appropriately.

IOPTH measurements were taken on the day of operation at the following times: baseline IOPTH was drawn in the preoperative holding area; t0 at the time of gland excision; and t5, t10, and t20 at 5, 10, and 20 minutes after gland excision, respectively. In the event that IOPTH did not drop by >50% (from baseline or t0) after excision of suspected hyperfunctioning glands, the surgeon performed further dissection in an attempt to identify additional glands for analysis. Further IOPTH measurements were taken after subsequent gland resection. The protocols for IOPTH monitoring used by our surgeons consisted of the Miami protocol or normal-range (dual-criteria) protocol.

Preoperative patient characteristics, surgical procedure, laboratory values, intraoperative findings, and final pathology were recorded. Preoperative PTH was defined as the most recent PTH measurement taken before the planned operation (during preoperative assessment in clinic), while baseline serum PTH (or baseline IOPTH) was the first PTH measurement taken on the day of surgery in the preoperative area and used in the IOPTH protocol. Intraoperative surgical success was defined as achieving a >50% IOPTH drop from the highest preexcision value (baseline or at the time of gland excision, “t0,” whichever value was higher). Our primary outcome was long-term cure determined by PTH levels measured postoperatively, and our secondary outcome was long-term cure determined by total serum calcium (not adjusted for albumin). Recurrent disease (defined as
elevated PTH or calcium levels at ≥6 months postoperatively) was reported only for patients who had available follow-up data. The positive and negative predictive value of >50% IOPTH drop in predicting cure was calculated for the primary (PTH) and secondary (total serum calcium) outcomes measured. Total serum calcium (not adjusted for protein) was used to determine outcome for practical reasons—the majority of patients were followed by total serum calcium rather than ionized calcium in the outpatient setting. Ionized calcium was not routinely measured postoperatively and was dependent on surgeon practice; in the cases where ionized calcium was measured, the surgeon obtained values 10 to 14 days postoperatively.

To address the potential bias introduced by using ionized calcium as an inclusion criterion but total serum calcium as an outcome measure, we performed a sensitivity analysis in which NCHPT patients were defined by normal-range total serum calcium and/or ionized calcium (if available), while excluding patients with discordant ionized and total serum calcium. The sensitivity analysis compared PHPT patients (PTH >65 pg/mL, total serum calcium >10.5 mg/dL, and if available, ionized calcium >1.35 mmol/L) with NCHPT patients (PTH >65 pg/mL, total serum calcium ≤10.5 mg/dL, and if available, ionized calcium ≤1.35 mmol/L).

Statistical analysis was done on Microsoft Excel and GraphPad Prism (San Diego, California). Distributions were compared by the Mann-Whitney U test. The rate of decline in IOPTH (IOPTH drop) was determined by linear regression with IOPTH values at baseline, t0, t5, t10, and t20. Population proportions were compared with the Z test. Significance was determined at P < .05.

Results
Demographics and Preoperative Characteristics
A total of 2120 parathyroidectomy patients were identified; 722 patients had ionized calcium levels, of which 616 were included in the analysis (Figure 1). There were 119 NCHPT (19%) and 497 PHPT (81%) patients. Patient demographics and preoperative characteristics are listed in Table 1: preoperative ionized calcium and PTH were significantly lower among NCHPT patients versus classic PHPT. Baseline IOPTH was also significantly lower in NCHPT than classic PHPT.

Of 119 NCHPT patients, 21 (18%) had planned bilateral exploration based on nonlocalizing or discordant imaging or identification of multigland disease on preoperative imaging studies, as opposed to 64 of 497 (13%) of classic PHPT patients, but this difference was not significant (P = .19).

Intraoperative Findings
There was a higher rate of intraoperative conversion to bilateral exploration with NCHPT: 15 (13%) NCHPT patients versus 22 (4%) classic PHPT patients initially underwent a planned targeted approach but were ultimately converted to a bilateral exploration based on intraoperative findings and/or lack of IOPTH drop (P < .001).

Single adenomas were identified in 74% of NCHPT patients and 78% of classic PHPT patients (P = .34). Double adenomas were identified in 14% of NCHPT patients and 18% of classic PHPT patients (P = .37). Multigland hyperplasia was identified in 12% of NCHPT patients as opposed to just 4% of classic PHPT patients (P = .002). Overall, the mean ± SD weight of each parathyroid gland resected in NCHPT was significantly less than that of classic PHPT (582 ± 887 mg vs 1175 ± 2497 mg, P < .001). For patients with single-gland disease, NCHPT also had smaller glands than those of classic PHPT. Similarly, among patients with multigland hyperplasia, NCHPT patients had significantly smaller glands when compared with classic PHPT patients (Table 2).

The IOPTH decay kinetics are shown in Figure 2 for all patients who achieved 50% IOPTH drop. Initially, classic PHPT patients had higher baseline IOPTH (P < .001), but at each subsequent time point, the IOPTH dropped to similar values between the groups. The ratio of IOPTH change at each time point is shown in Table 2. Classic PHPT patients showed greater reduction in IOPTH at each time point as compared with NCHPT patients. The overall IOPTH decay rate ± SEM was similar between groups: –2.8 ± 1.5 pg/min for NCHPT and –3.8 ± 1.9 pg/min for classic PHPT (P = .69). The IOPTH decay curves were further divided by each patient’s disease status (Figure 3). We observed decreases in IOPTH decay rates in both groups when stratified by single adenomas, double adenomas, and multigland hyperplasia; however, these differences were not
The distribution of patients based on IOPTH results is shown in Figure 4.

**Biochemical Outcomes**

Postoperative laboratory values were available for the following patients: 58% had ionized calcium (drawn within 10-14 days postoperatively); 72% had total serum calcium; and 31% had PTH (both measured at 1 and ≥6 months postoperatively). Postoperative laboratory values are shown in Table 1. NCHPT patients had significantly lower ionized calcium levels than classic PHPT patients. Normalization of PTH at postoperative 1 and ≥6 months was similar between groups.

We found no difference in the rate of recurrent disease between the groups (Table 2). No NCHPT patients out of 45 and 1 classic PHPT patient out of 144 (0.7%) had recurrent hyperparathyroidism.

Long-term cure was determined by the primary outcome measure of normalized PTH. PTH was used as a surrogate marker for cure, as NCHPT patients had normal-range ionized calcium preoperatively. Greater than 50% IOPTH drop had equal positive predictive value of long-term cure, defined by long-term normalization of PTH levels: 82.9% for NCHPT and 82.1% for classic PHPT patients ($P = .90$). The secondary outcome was long-term cure as defined by sustained eucalcemia measured with total serum calcium. When sustained eucalcemia was used as an indication of long-term cure, both groups had equal positive predictive value for cure: 98.8% for NCHPT patients and 98.9% for classic PHPT patients ($P = .96$). None of the patients with follow-up data who achieved

| Table 1. Patient Demographics, Clinical Characteristics, and Laboratory Data.a |
|---------------------------------|-----------------|-----------------|-----------------|
| Patient Demographics           | Classic PHPT (n = 497) | NCHPT (n = 119) | $P$ Value       |
| Age, y, mean ± SD              | 57 ± 14          | 60 ± 12         | .16             |
| Female, %                      | 367 (74)         | 94 (79)         | .22             |
| Male, %                        | 130 (26)         | 25 (21)         |                 |
| Laboratory Data                | Mean or n        | Min-Max (SD) or % | Mean or n        | Min-Max (SD) or % |
| Preoperative ionized calcium, mmol/L | 1.50             | 1.36-2.47 (0.13) | 1.28             | 1.05-1.35 (0.11) | <.001 |
| Normal range, 1.1-1.35         | 0                | 0               | 119             | 100             |      |
| Elevated, > 1.35               | 497              | 100             | 0               | 0               |      |
| Preoperative serum calcium, mg/dL | 11.3             | 8.4-15.7 (0.7)  | 10.7            | 9.3-12.1 (0.6)  | <.001 |
| Normal range, 8.5-10.5         | 55               | 11              | 53              | 44              | <.001 |
| Elevated, > 10.5               | 440              | 89              | 67              | 56              |      |
| Preoperative serum PTH, pg/mL   | 155              | 66-2890 (173)   | 116             | 66-787 (71)     | .0013 |
| Normal range, 10-65            | 0                | 0               | 0               | 0               |      |
| Elevated, > 65                 | 497              | 100             | 119             | 100             |      |
| Baseline serum PTH, pg/mL       | 136              | 22-2293 (133)   | 106             | 34-802 (79)     | <.001 |
| Normal range, 10-65            | 45               | 9               | 22              | 18              | <.003 |
| Elevated, > 65                 | 452              | 91              | 97              | 82              |      |
| Postoperative ionized calcium, mmol/L | 1.3             | 1.0-1.7 (0.1)   | 1.2             | 0.6-1.5 (0.1)   | .003  |
| Normal range, 1.1-1.35         | 256              | 89              | 71              | 96              | .06   |
| Elevated, > 1.35               | 33               | 11              | 3               | 4               |      |
| Postoperative serum calcium < 1 mo, mg/dL | 9.5             | 6.7-13.4 (0.7)  | 9.3             | 7.3-11.1 (0.7)  | .07   |
| Normal range, 8.5-10.5         | 363              | 95              | 89              | 98              | .54   |
| Elevated, > 10.5               | 18               | 5               | 3               | 2               |      |
| Postoperative serum calcium ≥6 mo, mg/dL | 9.5             | 1.2-12.4 (0.7)  | 9.5             | 7.6-11.1 (0.6)  | .65   |
| Normal range, 8.5-10.5         | 351              | 99              | 87              | 97              | .22   |
| Elevated, > 10.5               | 5                | 1               | 3               | 3               |      |
| Postoperative serum PTH < 1 mo, pg/mL | 50              | 3-236 (36)      | 45              | 2-114 (26)      | .73   |
| Normal range, 10-65            | 268              | 79              | 65              | 77              | .77   |
| Elevated, > 65                 | 72               | 21              | 19              | 23              |      |
| Postoperative serum PTH ≥6 mo, pg/mL | 55              | 7-383 (50)      | 48              | 4-111 (24)      | .72   |
| Normal range, 10-65            | 113              | 79              | 38              | 84              | .44   |
| Elevated, > 65                 | 30               | 21              | 7               | 16              |      |

Abbreviations: NCHPT, normocalcemic hyperparathyroidism; PHPT, primary hyperparathyroidism; PTH, parathyroid hormone.

*aPreoperative serum PTH is based on preoperative workup; baseline serum PTH is the first intraoperative PTH value taken. Normal ranges: ionized calcium, 1.1-1.35 mmol/L; serum calcium, 8.5-10.5 mg/dL; serum PTH, 10-65 pg/mL.*
intraoperative surgical success had recurrent classic hyperparathyroidism (n = 41 for NCHPT and n = 140 for PHPT).

The negative predictive value for patients who never achieved a 50% drop was 25% of NCHPT patients (1 of 4 patients had elevated PTH levels) and 75% of classic PHPT patients (3 of 4 patients had elevated PTH levels). The negative predictive value defined by hypercalcemia was 40% for NCHPT patients (2 of 5 patients manifested with hypercalcemia) and 20% for classic PHPT patients (1 of 5 patients had recurrent hypercalcemia; P = .49). Of all the patients who never achieved a 50% IOPTH drop, there was only 1 case of recurrent hyperparathyroidism, which occurred in the classic PHPT group (1 of 4 patients and 0 of 4 in NCHPT; Figure 4).

A sensitivity analysis was performed comparing NCHPT patients identified with total serum calcium (not adjusted for protein) and, if available, ionized calcium with PHPT patients who were also identified with total serum and ionized calcium (if available). Patients with discordant total serum calcium and ionized calcium were excluded. A total of 1235 PHPT patients and 214 NCHPT patients were identified with these criteria. Patient demographics, operative outcomes, and recurrence rates were analyzed. This analysis demonstrated the similar trends as reported in the analysis with small variations in the P values (Supplemental Table S1, available in the online version of the article). The pattern of IOPTH decay of patients with single-gland disease

<table>
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<tr>
<th>Operative Findings</th>
<th>Classic PHPT (n = 497)</th>
<th>NCHPT (n = 119)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single adenoma</td>
<td>389 (78)</td>
<td>88 (74)</td>
<td>.34</td>
</tr>
<tr>
<td>Double adenoma</td>
<td>87 (18)</td>
<td>17 (14)</td>
<td>.37</td>
</tr>
<tr>
<td>Multigland hyperplasia</td>
<td>21 (4)</td>
<td>14 (12)</td>
<td>.002</td>
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<td>Gland weight, mg</td>
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<tr>
<td>Overall</td>
<td>1175 ± 2497</td>
<td>582 ± 887</td>
<td>&lt;.001</td>
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<tr>
<td>Single-gland disease</td>
<td>1277 ± 2142</td>
<td>711 ± 996</td>
<td>&lt;.001</td>
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<tr>
<td>Multigland hyperplasia</td>
<td>264 ± 281</td>
<td>133 ± 86</td>
<td>.02</td>
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<td>IOPTH decay, pg/min</td>
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<tr>
<td>Single-gland disease</td>
<td>−3.9 ± 2.0</td>
<td>−3.0 ± 1.6</td>
<td>.74</td>
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<tr>
<td>Double adenoma</td>
<td>−3.5 ± 2.0</td>
<td>−2.2 ± 1.2</td>
<td>.60</td>
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<tr>
<td>Multi-gland hyperplasia</td>
<td>−3.3 ± 2.0</td>
<td>−1.6 ± 0.9</td>
<td>.47</td>
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<td>IOPTH, %</td>
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<tr>
<td>At 0 min</td>
<td>45 ± 22</td>
<td>49 ± 21</td>
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<tr>
<td>At 5 min</td>
<td>37 ± 22</td>
<td>44 ± 23</td>
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<tr>
<td>At 10 min</td>
<td>30 ± 19</td>
<td>38 ± 28</td>
<td>.002</td>
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<tr>
<td>At 20 min</td>
<td>24 ± 16</td>
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<td>Recurrence</td>
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<tr>
<td>Total serum calcium</td>
<td>5 of 356 (1.4)</td>
<td>3 of 90 (3.3)</td>
<td>.22</td>
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<td>Serum PTH only</td>
<td>28 of 143 (19.6)</td>
<td>8 of 45 (17.8)</td>
<td>.80</td>
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<tr>
<td>Total serum calcium</td>
<td>1 of 143 (0.7)</td>
<td>0 of 45</td>
<td>.58</td>
</tr>
</tbody>
</table>

Abbreviations: IOPTH, intraoperative parathyroid hormone; NCHPT, normocalcemic hyperparathyroidism; PHPT, primary hyperparathyroidism; PTH, parathyroid hormone.

*Postoperative recurrence defined as elevated laboratory values at ≥6 months: total serum calcium >10.5 mg/dL, serum PTH >65 pg/mL. Values are presented as n (%) or mean ± SD, unless noted otherwise.

Mean ± SEM.

Figure 2. Box plot of intraoperative parathyroid hormone (IOPTH) measurements for patients who achieved 50% drop. Values are presented as median, interquartile range, 95% CI, and outliers. BL, baseline IOPTH; NCHPT, normocalcemic hyperparathyroidism; PHPT, primary hyperparathyroidism; t0, IOPTH taken at time of gland excision; t5, t10, t20, IOPTH taken at 5, 10, and 20 minutes postexcision.

Figure 3. Mean intraoperative parathyroid hormone (IOPTH) values expressed as a ratio of the highest preexcision value for patients who achieved 50% drop, stratified by each patient’s disease status. BL, baseline IOPTH; DA, double adenoma and multigland hyperplasia; NCHPT, normocalcemic hyperparathyroidism; PHPT, primary hyperparathyroidism; SGD, single-gland disease; t0, IOPTH taken at time of gland excision; t5, t10, t20, IOPTH taken at 5, 10, and 20 minutes postexcision.
and hyperplasia was not evident in the sensitivity analysis. In the analysis presented here, NCHPT (and PHPT) patients with hyperplasia had the slowest rate of IOPTH decline (vs those with single and double adenomas; not statistically significant). However, in the sensitivity analysis, NCHPT patients with hyperplasia had a IOPTH decay rate similar to that of patients with single adenoma resected. On review of the sensitivity analysis data, the NCHPT hyperplasia group included patients with baseline IOPTH comparable to that of PHPT patients which exhibited rapid decline of their IOPTH. The profile of this IOPTH decline is in keeping with PHPT, which implies that inclusion of nonadjusted total serum calcium in identifying NCHPT confounds this population with patients who likely do not have true NCHPT and, in fact, behave more similarly to PHPT patients.

**Discussion**

Accurate diagnosis of NCHPT requires normal-range ionized calcium, with exclusion of secondary causes of elevated PTH. As with other studies in the literature, lack of ionized calcium data may lead to inclusion of patients who are not truly normocalcemic, which can confound study results. Herein, we observed a 19% NCHPT population by identifying patients based on ionized calcium levels.

In line with other studies, we demonstrated similarly high rates of multigland disease in mild biochemical PHPT patients. The increased rate of multigland hyperplasia may make preoperative localization less successful. Given the higher rates of multigland hyperplasia among NCHPT patients, it would be expected that the average weight of parathyroid glands resected was considerably smaller versus classic PHPT. In our study, the average weight of a hyperplastic gland resected from NCHPT patients with multigland hyperplasia was 133 mg versus 264 mg for classic PHPT patients. Smaller parathyroid glands have been associated with higher rates of persistent disease: 1 study found an inverse relationship between gland size and persistent disease, with glands <200 mg associated with a 6% persistence rate (vs 2% for patients with glands >200 mg). However, that study was limited to focused parathyroidectomies without IOPTH. In another study, intraoperative discovery of a small gland (<200 mg) was associated with higher rates of multigland hyperplasia, and such patients were at increased risk of recurrent disease. While it would be rational to correlate smaller glands with lower IOPTH levels as observed among our NCHPT patients, studies that examined parathyroid gland size and function have been equivocal.

To evaluate the utility of IOPTH testing among NCHPT patients, we used postoperative PTH levels to define cure. Currently, there is no clear recommendation regarding follow-up of patients with NCHPT, which makes attributing efficacy of IOPTH testing difficult in this patient population. We found that using normalized total serum calcium as a marker for long-term cure had a high positive predictive value in both groups (99%). However, the PPV decreased to 82% when normalized PTH levels were used to define long-term cure. Isolated elevations in PTH without elevations in calcium are common postparathyroidectomy, and while such patients are not considered surgical failures, they do require closer follow-up to monitor for recurrent symptoms and/or progression to classic hyperparathyroidism. In addition...
to biochemical follow-up, these patients would benefit from
closer monitoring of other manifestations of hyperparathy-
roidism, including bone mineral density and development of
nephrolithiasis. Among all 616 patients included in the
analysis, only 1 classic PHPT patient had recurrent hyperparathyroidism. However, when IOPTH does not drop by 50%,
the negative predictive value is low—in other words, we
cannot be certain that patients who do not achieve 50% drop
will go on to develop recurrent disease. Unfortunately, our
analysis is limited by the low number of patients who did not
achieve intraoperative cure. Of the 5 patients in each group
who never achieved >50% IOPTH drop, 2 NCHPT patients
and 1 classic PHPT patient developed or maintained
hypercalcemia.

On the basis of our experience, we support the use of a
targeted approach for NCHPT patients. However, if addi-
tional enlarged glands are discovered or if IOPTH does not
drop by 50% within 10 minutes, a bilateral exploration with
4-gland visualization should be performed. Long-term stud-
ies of NCHPT patients will clarify how these patients prog-
ress and what role surgery plays in this population.

A major limitation of our study was the use of ionized cal-
cium to identify NCHPT patients, while our secondary out-
come was determined by nonprotein-adjusted total serum
calcium. In addition, over half of our patients were excluded
per the lack of ionized calcium levels, which may have intro-
duced bias. The use of nonadjusted total serum calcium to
identify NCHPT patients may erroneously categorize patients,
given that the value is not properly adjusted for protein and
that total serum calcium is not as accurate in determining a
patient’s calcemic state. In our cohort and others, there is up to
13% discordant values between total serum and ionized calcium
within the same patient. Due to these discordant values,
ionized calcium is more accurately reflective of calcium home-
ostasis and so was used to classify patients in our study.
However, it was not possible to use it as an outcome measure,
owing to the clinical practice patterns that favor measuring
serum calcium in follow-up for practical reasons.

Additional limitations to this study include a retrospec-
tive review design, selection bias (our patients were referred
to a tertiary care center, which could include diagnostically
equivocal patients or those with negative preoperative imag-
ing), and limited long-term follow-up.

Conclusions
As compared with classic PHPT patients, NCHPT patients
have higher rates of multigland hyperplasia with smaller
parathyroid glands resected. NCHPT patients may be treated
with a targeted approach with IOPTH, but surgeons should
have a low threshold to convert to bilateral exploration if
only a small abnormal gland is discovered or if IOPTH does
not drop by >50% within 10 minutes.

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significant contribution to manuscript revisions, final approval of
manuscript; Salem I. Noureldine, study design, data analysis,
manuscript drafting, manuscript critical revisions, final approval of
manuscript; Jonathon O. Russell, patient contribution, data inter-
pretation, manuscript drafting, manuscript critical revisions, final
approval of manuscript; Aarti Mathur, patient contribution, manuscript
critical revisions, final approval of manuscript; Jason D. Prescott,
patient contribution, manuscript critical revisions, final approval of
manuscript; Ralph P. Tufano, study design, manuscript
drafting, manuscript critical revisions, final approval of manuscript.

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Supplemental Material
Additional supporting information is available in the online version
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