Reexamining Normative Radiation Data for Radioguided Parathyroid Surgery

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Objectives: To reexamine the “Norman rule” (affected parathyroid gland would contain at least 20% radioactivity compared with background), report normative radiation data, offer alternative ratios, and explore the effect of lapsed time on minimally invasive parathyroidectomy (MIRP).

Design: Retrospective analysis.

Setting: Tertiary care academic medical center.

Patients: A total of 116 consecutive patients who had a diagnosis of primary hyperparathyroidism, positive findings on sestamibi scan, and complete study data from 2000 to 2005 at a single institution.

Interventions: Minimally invasive radio-guided parathyroidectomy (MIRP) for primary hyperparathyroidism.

Main Outcome Measures: Ten-second gamma radiation counts at key procedural steps. Various ratios of measured radioactivity counts were studied.

Results: A total of 116 patients who underwent MIRP had complete data; 91 patients waited 4 or more hours until surgery (78%), with some waiting 8 or more hours. Every patient had a successful surgery and was observed for 1 year thereafter. The Norman ratio of radiation counts (ex vivo to background) was compared with other radiation ratios using Spearman correlation; the comparisons included skin to background ($r=0.579$), in vivo to background ($r=0.770$), basin to background ($r=0.525$), and in vivo–basin to background ($r=0.788$). Regression analysis indicated that the Norman ratio decreased over time at 11% per hour ($P=0.31$).

Conclusions: Alternative ratios to the Norman ratio are reported. An ex vivo to background ratio greater than 20% as a rule of successful parathyroid adenoma excision was observed in all but 2 cases in our series.


Primary hyperparathyroidism (HPT) is defined by a hypercalcemic state that results from an excessive secretion of parathyroid hormone (PTH).1 It results in significant symptoms, comorbidities, and end organ damage.2 Most cases are caused by a solitary adenoma.3 Although less common, 4-gland hyperplasia, carcinoma, and multiple adenomas have been associated with HPT.3,4 The incidence of HPT is approximately 1 in 1000, with most patients being middle-aged women.5,7

The traditional surgical approach involves either unilateral or bilateral neck dissection in which 2 or 4 glands are examined, respectively. Glands that appear large are excised and compared with normal gland biopsy specimens by frozen section analysis to confirm hypercellular parathyroid tissue.4,8 Although cure rates with exploration are reported as high as 98%, this traditional surgical approach is associated with morbidities such as a large cervical incision, carotid injury, dysphagia, pneumonia, deep venous thrombosis, and aspiration pneumonia.9

When compared with conventional neck exploration, either bilateral or unilateral, minimally invasive radioguided parathyroidectomy (MIRP) is superior in terms of cost, operative time, length of hospital stay, and patient acceptance, and it has equal cure rates.3,4,10-14 The MIRP procedure uses technetium Tc 99m (Tc-99m) sestamibi to help the surgeon localize the parathyroid adenoma with the aid of a gamma detector. Technetium Tc 99m sestamibi binds to the inner mitochondrial membrane where adenosine triphosphate is produced. As the parathyroid adenoma is a highly metabolically active gland, it is rich in mitochondria. The Tc-99m sestamibi will wash out of adjacent normal tissue leaving the adenoma still with increased radiation levels for surgery.15

A Tc-99m sestamibi injection performed on the day of the surgery will help the surgeon localize the adenoma. With the aid of the gamma detector, the surgeon can localize the adenoma based on the radioactive counts. Murphy and Nor-
man\textsuperscript{16} developed a simple method (the Norman ratio) of evaluating excised tissue by calculating the ratio of the ex vivo radiation count (from the parathyroid sample after it has been excised) to the background radiation count (from the patient’s right shoulder).\textsuperscript{16} They concluded that if the ex vivo counts are greater than 20\% of the background counts, then the excised tissue is a parathyroid adenoma.

The goal of the present study was to report normative radiation count data from a series of consecutive MIRP cases collected prospectively; evaluate the effectiveness of the Norman ratio in our series; compare the Norman ratio to alternative ratios; and study the effect of elapsed time (time from injection to excision) on the recorded radioactive counts and feasibility to perform the MIRP. Our hypothesis was that alternative ratios of radioactive count data might provide a method to diagnose the affected parathyroid gland(s).

**METHODS**

This was a prospective, nonrandomized study of 135 consecutive patients who underwent MIRP performed by a single surgeon (B.C.S.) from July 2000 to May 2005 at The Penn State Milton S. Hershey Medical Center. The internal review board approved the study. The patients were initially selected on the basis that they had elevated serum calcium and PTH levels. Parathyroid lesions were found on the left (n=70), right (n=44), inferior (n=99), and superior (n=25), and 1 gland’s location was missing from the record. There were 37 right inferior lesions, 62 left inferior lesions, 14 right superior lesions, 15 left superior lesions, and 3 midline lesions. One patient had a right lesion without indication as to superior or inferior. Likewise, another patient had a left lesion the orientation of which was not recorded. One patient had a double adenoma. Eleven patients had ectopic adenomas. A total of 135 patients were treated, including 97 women, 34 men, and 4 patients with no sex recorded. The median age of our population was 58.5 years (range, 36–87 years). Our study population (n=116) was limited to those with complete data sets.

Radioactive counts were obtained at different sites on each patient during surgery. The median counts were as follows: background, 3,469.0; skin, 6188.3; in vivo, 7277.0; ex vivo, 3977.7; and basin, 4332.0 (Figure 2). Various time intervals were recorded, including time from injection until the operative incision (median time, 312.5 minutes) and from incision to parathyroid adenoma identification (median time, 14 minutes).

To examine the effects of time between injection and surgery on the radioactive counts measured at the time of surgery, we analyzed the time intervals in the following categories: 3 hours or less (considered by most to be the optimal window in which to perform MIRP), more...
than 3 to 4 hours, more than 4 to 5 hours, more than 5 to 6 hours, more than 6 to 8 hours, and more than 8 hours. Our patient population was distributed across these intervals, with 91 patients waiting longer than 4 hours to receive their MIRP, which skewed our sample toward longer waiting periods (Figure 3). As time elapsed, ex vivo counts decreased. When ex vivo counts were normalized to the background counts, the rate of decline was not as dramatic (Figure 4).

In our series, the lowest percentage observed for the Norman ratio was 18.3% (median, 121.1%) (Figure 4). Regression analysis suggested that the Norman ratio decreased at a statistically insignificant average rate of 11.2 percentage points per hour from the time of injection ($P=.31$) over the nearly 10 hours of waiting time observed in our study. In spite of the ability to perform MIRP at delayed times following injection, our data suggest that the time it takes to excise the adenoma increases with increased delays from time of injection (Figure 5).

When all recorded counts were normalized to background, Spearman correlation studies were conducted on the various normalized counts compared with ex vivo to background ratio. Normalized skin compared with the Norman ratio had a Spearman correlation of 0.57875. Normalized in vivo compared with the Norman ratio had a Spearman correlation of 0.77015. Normalized basin compared with the Norman ratio had a Spearman correlation of 0.78765. Our ratio (in vivo–basin to background) compared with the Norman ratio had a Spearman correlation of 0.78765. Our ratio (in vivo–basin to background) compared with the Norman ratio had a Spearman correlation of 0.77015. Normalized skin compared with the background counts, the rate of decline was approximately an 11% decrease per hour. Even though performing MIRP within 3 hours from the time of injection is ideal, it is not always practical, and we have shown successful results in patients who have waited up to 10 hours before undergoing the procedure. These data may provide a rationale for administering injections late in the evening before the MIRP procedure, which might hasten an early “first” surgical start. This observation might also lessen the perceived impact of operative delays on successful execution of MIRP.

**TIME FROM INCISION TO IDENTIFICATION**

One advantage of MIRP is the speed with which it can be completed. Because the incision is small, the path to the affected gland more direct, and the closure less demanding, operative time (measured either as total minutes or time to discovery of the gland) is shorter with MIRP than with conventional exploratory surgery. The MIRP technique also does not rely on rapid parathormone assay or frozen section pathologic analysis, which also makes for shorter operating room time. Our average time from incision to gland identification was 14 minutes. This time grew longer as the time from injection to incision became longer ($P=.03$) (Figure 5). Although we demonstrate that long delays are not incompatible with successful MIRP, delays are not ideal and may prolong the procedure time. When faced with this dilemma, the surgeon can opt to reinject the patient and essentially move back the clock on the delay between injection and incision. This can be done in the preoperative holding area and presents a minimal radiation exposure risk.

**NORMAN RULE REPLICATED AND EFFECTIVE**

The Norman rule states that only a parathyroid adenoma will contain more than 20% of background radioactivity. In our patient population, 115 of 117 ex-vivo

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**COMMENT**

Technetium Tc 99m sestamibi is taken up into mitochondria-rich tissues by an unknown but likely multifactorial process. These tissues include cardiac muscle, salivary gland tissue, and enlarged parathyroid glands. Enlargement of parathyroid glands by mitochondria-rich oxyphil-cell hyperplasia makes these glands detectable by Tc-99m sestamibi scan. Our study included 116 patients with HPT, all of whom had positive findings on Tc-99m sestamibi scans for parathyroid adenoma. We have presented normative data for our standard counts taken during the MIRP procedure (Figure 2).

**TIME FROM INJECTION TO INCISION**

In our patient population, the time between injection and incision varied owing to scheduling and efficiency challenges in our institution. Only 10 of our patients underwent the procedure within the recommended window of 3 hours or less from time of injection (9%). In fact, the median time from injection to excision was 313 minutes: more than 50% of our patients were injected more than 5 hours before surgery (Table). When the ex vivo counts were normalized to background, little variation in counts was found as time elapsed. Since Tc-99m sestamibi is not metabolized, only the half-life decay and washout phenomenon affect the radioactive counts of the parathyroid adenoma. Our data indicate that by normalizing counts, the results reflect washout, which was approximately an 11% decrease per hour. Even though performing MIRP within 3 hours from the time of injection is ideal, it is not always practical, and we have shown successful results in patients who have waited up to 10 hours before undergoing the procedure. These data may provide a rationale for administering injections late in the evening before the MIRP procedure, which might hasten an early “first” surgical start. This observation might also lessen the perceived impact of operative delays on successful execution of MIRP.

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**Table. Time From Technetium Tc 99m Sestamibi Injection to Skin Incision for Minimally Invasive Parathyroidectomy Stratified in Lapsed Hours**

<table>
<thead>
<tr>
<th>Hours, No.</th>
<th>Frequency</th>
<th>Cumulative Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤3</td>
<td>10 (8.9)</td>
<td>10 (8.9)</td>
</tr>
<tr>
<td>&gt;3-4</td>
<td>11 (9.8)</td>
<td>21 (18.8)</td>
</tr>
<tr>
<td>&gt;4-5</td>
<td>27 (24.1)</td>
<td>48 (42.9)</td>
</tr>
<tr>
<td>&gt;5-6</td>
<td>27 (24.1)</td>
<td>75 (67.0)</td>
</tr>
<tr>
<td>&gt;6-8</td>
<td>27 (24.1)</td>
<td>102 (91.1)</td>
</tr>
<tr>
<td>&gt;8</td>
<td>10 (8.9)</td>
<td>112 (100)</td>
</tr>
</tbody>
</table>

*a All data are reported as number (percentage) of procedures.

*b Data regarding either injection time or incision time were missing for 4 patients; these 4 patients were excluded from the present analysis.
cised adenomas satisfied the Norman rule by exhibiting radiation counts at a level more than 20% above background. The 2 excised glands that did not demonstrate values that met the Norman criteria (18.3% and 19.5%) were, nevertheless, very close to that threshold. It is not clear why these 2 adenomas did not meet the threshold as a result of their size or timing of their removal following Tc-99m sestamibi injection. One of these 2 excised adenomas was a second adenoma, and its counterpart gland exceeded the 20% threshold. As with any standard at its maximum sensitivity and specificity, established norms will not always be 100% correct.

The median value for the Norman ratio in our study was 121.1%, indicating that more than half the excised adenomas yielded ex vivo counts greater than 100% of background counts. While this seems a dramatic excess relative to the 20% threshold specified by the Norman rule, a high ratio is quite common and demonstrates that the rule’s threshold is set low enough to be sensitive for subtle adenomas and yet specific enough to make a robust identification of the affected parathyroid gland and distinguish it from a normal parathyroid gland, multiple parathyroid gland disease, and nonparathyroid tissue. In the present study, the Norman rule held true through excessive delays in time of injection to time of incision, and although the ratio decreases over time, the decrease was not significant.

ALTERNATIVE COUNT ANALYSIS

We evaluated 3 alternative ratios of radioactivity (in counts per second over 10 seconds) for surgeon interpretation similar to those of the Norman ratio (Figure 4). These ratios offer advantages in that they can be used at different points in the sequence of the operation. The skin to background ratio can be performed while the patient is on the table prior to the start of the MIRP. This might be
advantageous for surgeons who have their patients routinely marked by nuclear medicine preoperatively to plan the location of the incision and wish to confirm it.

The in vivo to background ratio can be calculated on identification of the gland in situ but prior to its vigorous dissection, interruption of its blood supply, or excision. This allows determination of the role of the gland in question and could prevent injury of, or disruption to, a healthy parathyroid gland discovered during surgery.

The basin to background ratio is calculated after excision of the suspected gland and gives real-time confirmation that the excised adenoma is the appropriate target. It also allows for the detection of a second ipsilateral adenoma and may reduce the likelihood of a surgical failure from double adenomas.

Correlation analysis demonstrated that the in vivo to background and in vivo–basin to background ratios had the best agreement with the Norman ratio and might be suitable proxies for it.

The use of radionuclide-guided parathyroid surgery is a time- and cost-effective alternative to exploratory surgery. The interpretation of radiation counts during surgery provides precise and reliable identification of affected parathyroid gland(s) and allows expedited excision. The Tc-99m sestamibi tracer allows gland localization based on its hyperfunctional status, not by virtue of its location. This approach can eliminate dependence on intraoperative frozen section or rapid parathormone assays and reduces costs and operative time waiting for these results. While this conclusion is disputed, we have demonstrated our hypothesis that alternative ratios can identify parathyroid adenomas during different steps of the MIRP procedure. However, none was superior to the Norman ratio.

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Author Contributions: Dr Stack had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Stack. Acquisition of data: Stack. Analysis and interpretation of data: Wineland, Siegel, and Stack. Drafting of the manuscript: Wineland and Stack. Critical revision of the manuscript for important intellectual content: Wineland, Siegel, and Stack. Statistical analysis: Siegel. Administrative, technical, and material support: Wineland and Stack. Study supervision: Stack.

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References