Guidelines for Radioguided Parathyroid Surgery

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Objective: To confirm or refute the notion that only parathyroid adenomas have radioactivity higher than 20% of background.

Design: Retrospective analysis of a prospective patient data set.

Setting: Tertiary care referral center.

Patients: Forty-six patients (9 men and 37 women; mean ± SD age, 53.7 ± 12.1 years) underwent thyroid and parathyroid surgery between December 2005 and December 2006 to collect data on ex vivo radioactivity percentages on a variety of tissues.

Interventions: Patients were injected with 296 to 925 MBq of technetium Tc 99m sestamibi 1½ to 3½ hours before surgery. Biopsy specimens were taken of normal parathyroid glands, normal thyroid tissue, and lymph nodes and ex vivo radioactivity was recorded. Hyperplastic parathyroid glands and adenomatous glands were excised. Finally, some enlarged glands were cut into segments, and radioactivity counts were recorded and compared with the weight of the tissue.

Main Outcome Measures: All counts were compared with radioactivity percentages in the surrounding tissues, and results were expressed as a function of these background radioactive counts.

Results: The mean ± SD ex vivo background radioactivity of parathyroid adenomas was 148.5%±83.1% of background activity (range, 40.1%-388.9% but never less than 40%). The mean ± SD ex vivo background radioactivity of hyperplastic parathyroid glands was 74.6%±18.0% (range, 49.5%-109.1% but never less than 40%). A significant difference was found in ex vivo background radioactivity between pathologic parathyroid tissue and the other tissue specimens studied (normal parathyroid glands [2.4%±1.8%], thyroid tissue [4.5%±2.8%], lymph nodes [1.6%±0.8%], and fat [0.4%±0.3%]).

Conclusions: Ex vivo radioactivity percentages can differentiate hyperactive parathyroid tissue from any other tissue, but they cannot differentiate adenoma from hyperplasia and thus are not helpful in ruling out multiglandular disease. Interpretation of ex vivo radioactivity percentages should take into consideration the size of the specimen.

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Radioguided surgery for the treatment of parathyroid adenoma has been popularized as a new, more efficient, less morbid, and even safer operative strategy. The underlying principle of radioguided surgery is that radioactivity percentages of diseased, hyperactive parathyroid tissue, whether it be hyperplastic or adenomatous, are clearly higher and different than any other surrounding tissue and are therefore an easily detectable marker for the identification of abnormal parathyroid tissue. In addition, proponents believe that radioactivity percentages are significantly different in parathyroid hyperplasia than they are in parathyroid adenoma, thus making them a substitute for intraoperative frozen section analysis, eliminating the need for intraoperative intact parathyroid hormone (iPTH) level assays or even frozen sections. The opponents of the radioguided technology, on the other hand, claim that an experienced surgeon can visually identify abnormal parathyroid tissue with accuracy that is as good as any kind of radioactive detection procedure. Disagreement surrounds the statement that the levels are precise enough to eliminate the need for intraoperative iPTH levels and frozen sections.

A study by Murphy and Norman of 1290 specimens from 345 patients reported specific radioactivity cutoff levels that can differentiate among thyroid tissue, lymph nodes, normal parathyroid tissue, parathyroid hyperplasia, and parathyroid adenoma. Clear-cut levels of radioactivity in tissue specimens could significantly simplify and expedite parathyroid surgery, since both frozen sections and iPTH analysis add considerable time and cost to a relatively short procedure. According to Murphy and Norman, lymph nodes, normal parathyroid tissue, and fat never have a background radioactivity of higher than 2.2%, whereas thyroid tissue radioactivity is higher than 5.5%. On the basis of the data of Murphy and Norman, hyperplastic parathyroid glands have a
Primary objective of this study was to confirm or refute the notion that only parathyroid adenomas had radioactivity higher than 20% of background. The second objective was to assess the significance of percentage of radioactivity in a patient with a positive sestamibi scan. A hand-held gamma probe with a built-in detector and Geiger-Müller tube (RMD Instruments LLC, Watertown, Massachusetts) was used to measure the activities of tissues and pathologic diagnosis.

Other authors, however, have attempted to reproduce these data, with variable results. Most studies, additionally, were based on the percentage of radioactivity of excised tissue without attention to the volume of tissue being measured. The assumption must have been that the percentage of radioactivity is not dependent on the mass of the excised tissue.

The primary objective of this study was to confirm or refute the notion that only parathyroid adenomas had radioactivity higher than 20% of background. The secondary objective of the study was to assess the significance of specimen mass in the actual ex vivo radioactivity percentages, in addition to histopathologic diagnosis.

**METHODS**

**PATIENT POPULATION**

The medical records of patients who underwent thyroid and parathyroid surgery between December 2005 and December 2006 were reviewed for data collected on ex vivo radioactivity percentages on a variety of tissues. Forty-six patients (9 men and 37 women; mean ± SD age, 53.7 ± 12.1 years) referred to a tertiary care referral center had data available for analysis. Ten patients underwent thyroidectomy for neoplasm, and 38 patients underwent parathyroidectomy for primary or tertiary hyperparathyroidism. The preoperative iPTH levels of all patients were reviewed. Three patients assumed to have normal parathyroid glands during thyroidectomy were excluded from the study because of an incidental diagnosis of hyperparathyroidism by preoperative iPTH levels. All other patients had preoperative iPTH levels consistent with their preoperative diagnosis.

**SESTAMIBI SCANNING**

All patients had preoperative iPTH and calcium measurements taken. Patients with hyperparathyroidism underwent administration of technetium Tc 99m sestamibi (296-925 MBq) before the day of surgery, and nuclear scanning images were taken 15, 90, and 180 minutes after injection to determine the washout rate of the thyroid gland. The last image taken at the third hour was used to determine parathyroid location and rule out any abnormalities.

**RESULTS**

Some patients with hyperparathyroidism underwent 4-gland exploration, and only enlarged glands were excised. In patients undergoing thyroidectomy for thyroid neoplasms, normal parathyroid glands were occasionally biopsied, whereas intracapsular parathyroid glands were excised, biopsied, and reimplanted into an incision pocket in the sternocleidomastoid muscle. A handheld GS-1 gamma probe (RMD Instruments LLC, Watertown, Massachusetts) was used to measure the radioactive counts of the excised tissue. The probe was held in contact with the tissue, and ex vivo counts were recorded. Similarly, the counts of excised fat tissue and lymph nodes were recorded. Finally, the background radioactivity of the neck was measured by holding the probe in contact with the skin of the neck over the lateral part of the incision. Diseased parathyroid glands were cut into 4 comparable size and weight segments, and the percentages of radioactivity were again measured for each segment.

Ex vivo radioactivity values were recorded as a function of what percentage of background radioactivity they corresponded to, with background radioactivity being 1 (100%). All parathyroid specimens were submitted as frozen sections for pathologic diagnosis. Intraoperative iPTH levels were measured 15 minutes after parathyroid excision. Finally, confirmed normal glands were reimplanted along the ipsilateral sternocleidomastoid muscle.

**STATISTICAL ANALYSIS**

Statistical analysis was performed with SPSS statistical software, version 15.0 (SPSS Inc, Chicago, Illinois). Continuous data were displayed as mean ± SD. Statistical significance was accepted when P < .05. The Levine test for equality of variances was used to determine statistically significant variances. The univariate (GLM model) analysis of variance and the Newman-Keuls tests were used to determine statistical significance for parathyroid background radioactivity percentages in parathyroid adenomas, hyperplastic parathyroid glands, and normal parathyroid specimens.
roid glands and other tissues ($P < .001$). Although the mean percentages of background radioactivity in parathyroid adenoma were statistically higher than in hyperplastic parathyroid glands ($P < .001$), the spread of individual values overlapped (Figure).

Ex vivo parathyroid glands from 15 patients with parathyroid adenoma were divided into 4 comparable weight segments, and the radioactivity of each segment was compared with the whole gland. In all cases, the ex vivo radioactivity percentage of each segment was lower than that of the original whole parathyroid gland ($P < .001$) (Table 2).

**COMMENT**

During the 1990s, minimally invasive, targeted parathyroidectomy gained attention among surgeons. This attention was the result of the use of a technetium-labeled myocardial perfusion agent, technetium Tc 99m hexakis 2-methoxyisobuthyl isonitrile (sestamibi), for parathyroid imaging by Coakley et al in 1989. Since then, sestamibi scanning has been used as the primary agent for parathyroid imaging. Intravenous sestamibi administration before surgery has often been used for radioguided parathyroidectomy. Sestamibi localizes non-specifically in the mitochondria and cytoplasm in response to elevated membrane potentials across the membrane bilayers. It is concentrated in tissues that have increased cell activity or higher numbers of mitochondria. In addition, sestamibi also tends to be taken up by thyroid tissue; however, it washes out faster in the thyroid than in the parathyroid glands, making it an ideal agent for parathyroid scanning when the appropriate protocol is used.

Many conditions exist for false negativity and false positivity in parathyroid scanning. Sestamibi counts are related to (1) the baseline iPTH level, (2) the weight or mass of the tissue, and (3) the cell cycle phase. If the iPTH level is below 200 pg/mL (to convert to nanograms per liter, multiply by 0.1053), the accuracy of sestamibi scanning decreases to 81%. In contrast, when the iPTH level is above 400 pg/mL, 100% accuracy is usually obtained. Increases in perfusion and functional activity, as well as targeting of abundant mitochondria-rich oxyphil cells, seem to be key components in a successful uptake. A relationship has also been observed between the intensity of focal uptake in the parathyroid glands and the cell cycle phases for patients.

Radioguided parathyroidectomy is a frequently performed procedure. Although the value of radioguided surgery is somewhat controversial, it has become a popular technique. Proponents of radioguided parathyroidectomy affirm that this technology decreases operative time, cost of surgery, postoperative complications, and length of postoperative stay by allowing for smaller, more cosmetically appealing incisions and eliminating the need for 4-gland exploration. Critics of the technology believe that they can attain the same results without the use of radioguided technology. The purpose of this study was not to ascertain or deny the value of radioguided surgery but to further assess the value and accuracy of radioguided surgery for those surgeons who use it.

This technology is used in 2 ways. First, in all cases, preoperative technetium Tc 99m sestamibi is injected 1 to 3 hours before surgery. Many surgeons will use the probe to identify the quadrant of increased radioactivity level to localize the involved gland, which is complemented by the localization studies performed preoperatively. Radioguided surgery helps identify hyperactive parathyroid tissue in normal and abnormal locations in the neck and superior mediastinum.

The second use of radioguided technology is for measurement of ex vivo radioactivity percentages of excised tissues as a guide to their histopathologic diagnosis. On the basis of initial studies by Murphy and Norman in 1999, it was proposed that the ex vivo radioactivity percentage can differentiate the following tissues from each other: nonparathyroid tissue, normal parathyroid tissue, parathyroid hyperplasia, and parathyroid adenomas.

Data from their study of 1290 tissue specimens from 345 patients led to the conclusion that lymph nodes, normal parathyroid glands, and fat never had radioactivity that was above 2.2% of the background radioactivity percentage. Thyroid tissue radioactivity was never above 5.5% of the background radioactivity percentages. Hyperplastic parathyroid tissue always had radioactivity between 7.5% and 16%. Tissues that had radioactivity of 20% or higher of background radioactivity percentages were diagnosed as solitary parathyroid adenomas. These data are currently accepted and used as a guide to identify excised tissue in lieu of frozen section pathologic diagnoses. Ex vivo radioactivity has also been used as a substitute for intraoperative, postexcision iPTH measurements. Ex vivo radioactivity determination takes only a couple of seconds, as opposed to the 10 to 30 minutes required for histologic processing of frozen sections and/or blood sample processing for iPTH measurements.

In 2001, McGreal et al studied ex vivo radioactivity percentages in 75 cases of primary hyperparathyroidism and concluded that the cutoffs mentioned herein are accurate in confirming histopathologic diagnoses. Their data, however, revealed that normal parathyroid glands often have radioactivity of more than 2.2% above background radioactivity. In addition, 2 patients in their study...
were diagnosed as having a single adenoma by the cut-off of 20% above background radioactivity and were subsequently found to have either a second adenoma or hyperplasia.

Goldstein et al\(^4\) studied 40 cases of primary hyperparathyroidism. On the basis of clinical results (having based their surgical decision making on radioactivity measurements), they concluded that radioactivity percentages could substitute for histologic studies as an accurate method of tissue identification. They, however, reported no data on actual radioactivity percentages. A follow-up study\(^5\) in 2003 by the same group studied 127 patients. In this study, ex vivo radioactivity percentages of hyperplastic parathyroid glands and thyroid tissue were measured, and their clinical results were consistent with the cutoff of 20% above background radioactivity (also called the 20% rule).

Other studies have contradicted these conclusions. Burkey et al\(^8\) studied 150 patients with primary hyperparathyroidism and used the 20% rule to diagnose parathyroid adenoma. They described an 84% cure rate when using it as the only measure of confirmation of adenoma. Nichol et al\(^7\) studied patients with secondary or tertiary hyperparathyroidism; in their series, all hyperplastic parathyroid glands had radioactivity greater than 20% above background percentages. Chen et al\(^9\) found that all of their patients with hyperplastic glands had radioactivity values that exceeded 20% of the background activity. Olson et al\(^12\) studied 21 patients and concluded that ex vivo radioactivity values could not differentiate between adenoma and hyperplasia. Lal et al\(^10\) reported similar findings after studying 419 patients. Ugur et al\(^13\) evaluated 35 patients with primary hyperparathyroidism. They could not differentiate hyperplasia from adenoma by ex vivo radioactivity percentages. They found statistically significant differences in the in vivo radioactivity percentages between adenoma and hyperplastic glands.

All of these studies assessed radioactivity percentages of different tissues without taking into account the size of the specimen. It has been postulated that the likelihood of positive preoperative localization with a sestamibi scan could be related to the size of the involved gland. It is, therefore, logical that ex vivo radioactivity counts are related to the size of the tissue being measured. We, therefore, sought to determine if the size of the specimen affected the ex vivo radioactivity counts. This is the first study, to our knowledge, to assess the relationship between the size of the specimen and the ex vivo radioactivity counts. Radioactivity levels of lymph nodes, on the other hand, when measured to identify sentinel nodes have not been related to the size of the node according to any published studies.

The mean percentage of ex vivo background radioactivity of parathyroid adenomas, relative to background, was 148.5% (range, 40.1%-388.9%). Hyperplastic glands have similar values (mean, 74.6%; range, 49.5%-109.1%). A significant difference was found between adenomatous and hyperplastic parathyroid tissue when compared with other tissue specimens studied (mean, 2.4%, 4.5%, 1.6%, and 0.4% for normal parathyroid glands, thyroid tissue, lymph nodes, and fat, respectively). These tissues never had background radioactivity of more than 5% (Table 1).

The original 20% rule was based on primary hyperparathyroidism cases, compared with normal parathyroid glands. Biopsy specimens of normal parathyroid glands belonging to the same patients diagnosed as having an adenoma were studied. It is possible that normal parathyroid glands in patients with primary hyperparathyroidism were suppressed, perhaps not truly functioning as normal glands, and therefore had a decreased uptake of technetium Tc 99m sestamibi.

To clearly identify the parathyroid adenoma and the ex vivo background radioactivity percentage, we first measured the ex vivo radioactivity percentage of the gland. We then divided the gland into 4 comparable size and weight segments and repeated the counts again. We observed that the percentage of radioactivity above background of these segments was always less than the un-divided gland. The percentage of radioactivity above background is therefore proportional to the mass of the specimen, which has significant implications when decisions are being made based on radioactive counts ob-

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**Table 2. Comparison of Background Radioactivity Percentages of the Segments of the Parathyroid to the Entire Gland**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Background Radioactivity of the Segments of the Parathyroid (%)</th>
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<tbody>
<tr>
<td></td>
<td>Segment 1</td>
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<tr>
<td>1</td>
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<td>2</td>
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tained from whole excised parathyroid adenomas vs biopsy specimens of hyperplastic or normal glands.

Our preoperative technetium Tc 99m sestamibi dose was 740 MBq in most instances, but some variability occurred during the first couple of studies (range of doses, 296-925 MBq). Low doses such as 111 to 185 MBq or even 37 MBq can be used, and radioguided parathyroidectomy is still found to be safe and effective in patients with solitary parathyroid adenoma. Doses of radiation exposure can be reduced 20-fold, thus minimizing radioactive exposure to the patient and the operating room personnel. In our study, we administered doses between 296 and 925 MBq of technetium Tc 99m sestamibi. By expressing our results as percentages above background instead of absolute values, we minimized the potential impact this variability could have had in our results and conclusions.

Although the ex vivo radioactivity percentages greater than 20% above background clearly represent pathologic parathyroid tissue, no definitive conclusions can be made to differentiate single-gland disease from multigland disease (parathyroid hyperplasia or multiple adenoma). Radioactivity percentages are proportional to specimen size; therefore, the use of the ex vivo background radioactivity percentages for confirmation of the presence of parathyroid adenoma should incorporate the size of the specimen. Small biopsy specimens of tissue will not necessarily yield the expected high ex vivo radioactivity level diagnostic of hyperactive parathyroid glands. Excised tissue with radioactivity percentages greater than 40% above background are most likely hyperplastic or adenomatous parathyroid glands. Ex vivo radioguided surgery is not a substitute for intraoperative iPTH assay. It may replace frozen section diagnosis, since it can identify hyperparathyroid tissue.

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

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REFERENCES