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Use of the gamma probe to identify multigland disease in primary hyperparathyroidism

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Abstract

Aim—The purpose of this study was to determine threshold gamma probe counts to distinguish single adenoma (SA) from multigland disease (MGD) during radioguided parathyroidectomy.

Methods—A retrospective analysis of 1656 patients was performed. *Ex vivo* counts of the first excised gland were taken and recorded as a percentage of background counts.

Results—69.4% of MGD patients had counts below the 50% threshold. The 50% threshold correctly grouped 72.8% of our cohort. Counts of more than 100% were accurate for grouping SA, with only 6.8% of patients with counts more than 100% having MGD.

Conclusions—The gamma probe can aid surgeons in deciding to continue neck exploration if MGD is suspected or wait for labs to confirm cure if SA is suspected.

Keywords

gamma probe; multigland disease; primary hyperparathyroidism; radioguided parathyroidectomy; radionuclide counts; single adenoma; threshold

Background

Primary hyperparathyroidism (PHPT) is a condition in which one or more parathyroid glands become overactive, resulting in hypersecretion of parathyroid hormone (PTH) causing elevation in serum calcium levels [1,2]. Common symptoms include bone and joint pain, muscle weakness, fatigue, kidney stones, abdominal pain and neuropsychiatric illness [3–6]. PHPT affects about 1% of the population with 80–85% of cases due to a single

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Ethical conduct of research
The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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adenoma (SA) [1,7]. The other 10–15% of cases are caused by more than one hyperactive gland, known as multigland disease (MGD) [8]. Surgical removal of the overactive gland(s) is the sole curative treatment for PHPT, and it has greater than a 98% success rate when performed by an experienced surgeon [9–11]. Surgeries for PHPT can potentially fail if not all hyperactive parathyroid glands are removed. This can occur if the patient suffers from MGD that goes unrecognized or if the true culprit gland is not located.

One underutilized surgical technique to treat PHPT is radioguided parathyroidectomy. In this procedure, the patient receives an injection of technetium (Tc-99m) sestamibi (MIBI) several hours prior to surgery. MIBI is a lipophilic monovalent cation that has an increased uptake in epithelial cells rich in mitochondria, such as parathyroid adenomas. The gamma probe used in radioguided parathyroidectomy measures the relative uptake of MIBI in the excised tissue by providing a radionuclide count. Immediately following the initial incision, the surgeon uses the gamma probe to measure background radionuclide counts over the isthmus of the thyroid. When a suspected hyperactive parathyroid gland is excised, the surgeon takes the *ex vivo* radionuclide count. Previous studies have shown that *ex vivo* counts above 20% of background indicate that the excised tissue is a hyperactive parathyroid [12]. With smaller incisions and increased experience with the gamma probe, the utility of the gamma probe at our institution has shifted toward confirmation that excised tissue is indeed parathyroid tissue and its relative activity rather than location of overactive parathyroid gland(s). Therefore, the gamma probe does not replace preoperative imaging or localization studies. In addition, the gamma probe cannot replace sound surgical judgment and knowledge of parathyroid anatomy and development. Rather, it serves as an adjunct tool, along with intraoperative PTH (IoPTH) measurement, to determine the proper extent of exploration.

A study by Chen *et al.* [13] has shown that both SA and MGD present with *ex vivo* counts more than 20% of background. When examining these results carefully, it appeared that SA presented with a higher mean percent of background radionuclide counts compared with MGD. Therefore, the purpose of this study is to investigate whether probe counts can suggest if PHPT is due to a SA or MGD. Such a threshold would prompt surgeons to continue neck exploration or wait for IoPTH levels.

Methods

A retrospective analysis was performed by using a prospectively collected database of patients who underwent parathyroidectomy at a single, large tertiary referral center from January 2001 to May 2014. Included in the study were adult patients with PHPT who underwent an initial radioguided parathyroidectomy. Familial disease, secondary, tertiary or reoperative cases were excluded. Additionally, we excluded patients who underwent a concurrent thyroid operation. Lastly, due to lithium's association with hyperparathyroidism, patients with prior lithium exposure were not included in the study. Patients were stratified into two groups, SA and MGD based on intraoperative findings.

All patients undergoing parathyroidectomy get either an ultrasound and/or a sestamibi scan for preoperative localization, and this provides a starting point for exploration. Surgical cure of PHPT at our institution is confirmed by a 50% decrease in serum PTH from the baseline

PTH level measured preoperatively. When there is a spike in IoPTH at the 5-min time point due to manipulation of the gland, this becomes the new 'baseline' level and we define cure as a 50% drop from this new baseline [14]. These IoPTH levels are taken 5, 10 or 15 min postexcision and this determines operative cure. Using the background (initial count taken on the isthmus of the thyroid) and *ex vivo* radio-nuclide counts (count taken on the specimen after it is excised) from the gamma probe, this study investigated whether there was a percent of background radionuclide count, calculated as [(*ex vivo*/background) × 100], which would indicate to surgeons whether PHPT is due to a SA or MGD after the initial gland is excised. That is, the surgeon excises a suspected SA, and then uses the gamma probe counts to decide whether to continue exploration for suspected MGD, or to wait for IoPTH to confirm that this excised gland was truly the only hypersecreting gland.

Patient demographics and preoperative lab values were compared between the SA and MGD groups as was gland weight of the removed parathyroid gland(s). The threshold percentage was determined by the percent of background that optimized the correct percentage of both SA and MGD groups. We also investigated patients with radionuclide counts more than 100% background to determine if very high radionuclide counts could be used to differentiate SA from MGD. We compared probe counts by the following subgroups: mild hyperparathyroidism, defined as patients with normal serum PTH levels (15–65 pg/ml) or serum calcium levels (8.5–10.2 mg/dl) or, in some cases, both normal calcium and PTH. Patients with a vitamin D deficiency was defined as a preoperative vitamin D less than the upper limit of normal (30 ng/ml), independent of serum calcium and PTH levels.

The data were analyzed by using SPSS statistical software (IBM Corp 2013, Armonk, NY, USA). Continuous variables were compared by using Student t-tests or Wilcoxon rank sum tests where appropriate. Categorical variables were compared by using Chi-squared tests or Fischer's exact tests where appropriate. $p < 0.05$ was considered statistically significant.

Results

Patient demographics & preoperative labs

From January 2001 to May 2014, 1656 patients underwent radioguided parathyroidectomy and met our inclusion criteria for this study. Of these patients, 1300 had a SA while 356 had MGD. Patients in the SA and MGD groups were no different in terms of demographics (Table 1). SA patients had significantly higher baseline PTH ($p < 0.001$), calcium ($p < 0.001$), urine calcium ($p = 0.009$) and gland weight ($p < 0.001$) compared with MGD patients. In addition, SA patients had significantly lower phosphate ($p < 0.001$) and vitamin D ($p = 0.001$) levels compared with MGD patients (Table 1).

Gamma probe counts

The background radionuclide counts did not differ between the SA and MGD groups ($p = 0.936$); however, the SA group had significantly higher mean *ex vivo* counts compared with MGD patients (167.0 and 92.7, respectively, $p < 0.001$) and therefore significantly higher mean% background counts as well (91.7 and 49.7%, respectively, $p < 0.001$) (Table 2).

Larger glands generally had higher *ex vivo* counts with every 1 mg of gland weight predicting a 1.4% increase in *ex vivo* counts ($p < 0.001$).

Threshold

An *ex vivo* count of 50% of the first excised gland served as the best threshold to distinguish MGD from SA. The patients with *ex vivo* counts more than 50% and the patients with *ex vivo* counts less than 50% did not differ in age or gender. However, those with *ex vivo* counts more than 50% had significantly higher Ca and PTH ($p < 0.001$ for both) as expected. Importantly, 69.4% of MGD patients had *ex vivo* counts below the 50% threshold. Of all patients with *ex vivo* counts less than 50%, 42% of them had MGD (Figure 1). The 50% *ex vivo* count threshold was accurate for 72.8% of our entire cohort.

We also examined glands with extremely high *ex vivo* counts (>100%). A percentage of background less than 100% almost always predicted SA. Of patients with *ex vivo* counts more than 100%, only 6.8% had MGD (Figure 2).

The positive predictive value for the 50% cutoff in relation to MGD was 42.1%, but the negative predictive value of the 50% cutoff with respect to MGD was 89.9%. The 50% cutoff was ultimately correct at classifying 72% of the entire cohort. We also found that the 100% cutoff had a positive predictive value of 93.2% for SA.

Mild hyperparathyroidism

Of our cohort of 1656, 411 were classified as having mild hyperparathyroidism. We found that a higher percentage of mild HPT patients had MGD compared with the entire cohort (44.3 and 21.5%, respectively). We also found that patients with mild HPT and nonmild PHPT had similar mean background radionuclide counts ($p = 0.897$), but patients with mild HPT had significantly lower *ex vivo* radionuclide counts compared with nonmild patients ($p < 0.001$). Of the 411 patients with mild HPT, 229 were SA and 182 were MGD. The 50% threshold correctly grouped 62.9% of the SA patients with mild HPT and 79.7% of the MGD patients. Therefore, the threshold correctly grouped 70.3% of the entire mild HPT subset.

Vitamin D deficiency

Vitamin D deficiency did not independently affect *ex vivo* counts ($p = 0.2$). Vitamin D deficiency was however associated with higher PTH levels and larger gland size. Of the 1142 patients in our cohort with vitamin D data, 542 were vitamin D deficient. The vitamin-D-deficient patients had mean PTH value of 123.9 pg/ml while vitamin D-sufficient patients had mean PTH value of 100.9 pg/ml ($p \leq 0.001$). Vitamin-D-deficient patients also had mean gland weight of 631.8 mg and vitamin D-sufficient patients had mean gland weight of 534.4 mg ($p = 0.0409$).

Discussion

This study describes the use of radioguided parathyroidectomy to treat PHPT and its utility in distinguishing SA from MGD. Here, we report that threshold *ex vivo* radionuclide count levels of the first gland excised can suggest to surgeons whether the patient has MGD or SA. Such a threshold would allow surgeons to feel confident about continuing neck exploration if MGD is suspected or if the *ex vivo* counts suggest SA, then waiting for IoPTH levels from the lab, instead of subjecting the patient to the risks of further exploration. The gamma probe serves as an adjunctive tool in the operating room to help decide on the extent of surgery with the goal of appropriating risk of additional exploration and effectively using operative time.

We found that the best threshold to distinguish MGD from SA was at least 50% of background. If the counts were above background, almost all of these patients had a SA. Previous studies reported that an *ex vivo* gamma probe count more than 20% of background confirms that the excised tissue is hyperactive parathyroid tissue [12,13]. This is the first study to our knowledge whose aim was to find a threshold using the gamma probe to identify etiology of PHPT.

Here, we report on an expanded use of the gamma probe to assist in distinguishing SA from MGD based on the activity of excised parathyroid tissue. Previous reports have described how the gamma probe can eliminate the need for frozen section to confirm that excised tissue is indeed parathyroid tissue versus thyroid, or lymphatic tissue [15]. The probe can also assist in locating parathyroid adenomas in ectopic or unusual locations by scanning the operative field for higher counts [16,17]. Although this remains a helpful use of the gamma probe in selected cases, it is not the most helpful aspect of the probe in routine cases. The real challenge for parathyroid surgeons remains how to best select patients who are best served by a four-gland exploration versus a minimally invasive approach [18,19]. The probe provides adjunctive information to help the surgeon make this decision in real-time in the operating room. As a result, valuable operating room time is utilized most efficiently. We have previously reported that when the surgeon identifies all four glands, IoPTH really does not change operative outcomes and only extends the operative time. Furthermore, parathyroid surgeons still struggle to identify the proper extent of surgery for this disease. Those who argue for a routine four-gland exploration argue that IoPTH potentially misses MGD [21,22], but more extensive dissection may lead to higher complication rates, especially hypoparathyroidism [23,24]. Rather than routinely undertaking bilateral exploration, the probe counts provide additional information to help the surgeon make this decision in the operating room after a suspected SA is excised.

We found that a 50% of background *ex vivo* radionuclide count served as the threshold that correctly grouped the highest percentage within both groups. The 50% threshold correctly classified nearly 73% of our entire cohort. We also found that extremely high counts (>100% of background) serve as an accurate indicator of SA. According to studies, the time to obtaining IoPTH that indicated a cure can take 20–50 min [21–27]. With operating room time costing $15.05 per minute [28], it would be more cost effective to complete exploration if MGD is suspected. If with continued exploration the surgeon identifies all four parathyroid glands, then there is minimal benefit for waiting for IoPTH [29], further using OR time more efficiently. Hence, the probe serves as a more immediate guide for the surgeon on whether to continue exploration if probe counts are lower and MGD is suspected or, if probe counts are high, then SA is more likely, and the surgeon can wait for IoPTH levels rather than subject the patient to increased risks of bilateral exploration, such as potential damage to the recurrent laryngeal nerves or hypoparathyroidism.

In addition to the retrospective nature of the study, another limitation is that the 50% threshold is not a perfect classifier. Although 70% of MGD patients fell below the 50% threshold, of all patients below the 50% threshold only 42% are MGD. Because operative cure cannot be definitively proven by using this threshold, surgeons still must use IoPTH to confirm surgical cure. A strength of the study, however, is that our results show the probe is highly accurate for predicting SA in patients with extremely high radionuclide counts, classified as counts more than 100% of background. Within the patients with counts more than 100% of background, only 6.8% had MGD. Another limitation of this study is that it requires the patient to get an injection of Tc-99m sestamibi, and therefore patients, the surgeon and staff undergo radiation exposure. However, a study by Oltmann *et al.* found that radiation exposure due to MIBI during radioguided parathyroidectomy is minimal for both surgeons, and staff [30]. Previous studies have shown that minimally invasive parathyroidectomy has significantly reduced operative times and total hospital costs when compared with traditional unilateral or bilateral neck exploration [31,32]. Our hope is that using this threshold will allow surgeons to use operating room time efficiently, thereby potentially reducing costs. Importantly, the cost of the probe must be weighed against any savings in OR time, and this will require further study.

Conclusion

In conclusion, although lower *ex vivo* counts cannot definitively distinguish MGD, the gamma probe can serve as an adjunct in helping the surgeon decide to wait for IoPTH or continue further exploration. Extremely high *ex vivo* counts can also indicate to surgeons that the presence of another adenoma is extremely unlikely. Therefore, the gamma probe serves as a useful adjunct to distinguish SA from MGD and allows surgeons to use OR time more efficiently.

Future perspective

The gamma probe is a useful adjunct for determining the etiology of PHPT (SA vs MGD) intraoperatively. Here, we have provided some guidelines for what probe counts may indicate the presence of MGD. This can assist the surgeon in deciding whether to undertake further exploration after excising a suspected SA. Future studies need to examine the exact cost of using the probe and whether this type of adjunct truly saves money in terms of operating room time. Similarly, the probe can potentially help surgeons undertake the proper extent of surgery based on the risk of MGD. A risk-adjusted use of bilateral exploration can potentially reduce complication rates. This too will require prospective evaluation.

Parathyroid surgeons continue to debate the proper extent of exploration. In order to move the field forward, surgeons need to be able to make patient-specific treatment decisions in the operating room. The probe is another intra-operative adjunct to help the surgeon decide to undertake further exploration or wait for IoPTH levels. Not only can this lead to more efficient use of operating room time, but could also reduce complication rates. Therefore, the probe along with the specific threshold values put forth in this study is certainly worthy of further evaluation.

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EXECUTIVE SUMMARY

Background

- Radioguided parathyroidectomy is one surgical technique involving the patient receiving an injection of Technetium (Tc-99m) sestamibi (MIBI), which is taken up by mitochondrial-rich cells.
- The gamma probe can be used to measure the relative uptake of MIBI in any given tissue.
- Comparing *ex vivo* counts of excised tissue to background radionuclide counts taken at the isthmus of the thyroid can lead to insight into what tissue was excised.
- Counts above 20% of background can be confirmed as hyperactive parathyroid tissue.
- The purpose of this study was to find a gamma probe threshold to assist surgeons in determining the proper extent of surgery after the initial gland is excised.

Methods

- A retrospective analysis was performed by using a prospectively collected endocrine surgery database.
- Patients were stratified into single adenoma (SA) and multigland disease (MGD) groups based on intraoperative findings.
- Threshold was determined by the percent of background, which optimized the correct percentage of both groups.
- Examined patients had counts greater than 100% of background.
- Subgroups examined include patients with mild hyperparathyroidism and patients with a vitamin D deficiency.

Results

- 1656 patients met inclusion criteria with 1300 SA and 356 MGD.
- Mean background counts did not significantly differ between the groups, but SA had significantly higher mean *ex vivo* counts compared with MGD.
- *Ex vivo* counts of 50% of background served as the best threshold to optimize the percent correct within both groups, correctly grouping 72.8% of our cohort.
- Counts more than 100% of background may serve as a more helpful cutoff as only 6.8% of patients with counts above this cutoff have MGD.

Discussion

- The threshold is to allow surgeons to feel comfortable continuing exploration if MGD is thought to be present rather than waiting for intraoperative parathyroid hormone (IoPTH) values.
- It has been shown that it can take 20–50 min to get IoPTH values back from lab.
- Operating room time can cost upward of US$15 per hour, so a threshold that can help surgeons feel comfortable continuing exploration before getting IoPTH values could save operative costs.
- This threshold cannot alone distinguish between SA and MGD but when used along with preoperative imaging and IoPTH values, we believe the gamma probe can be a useful tool to help surgeons reduce operative time and cost.

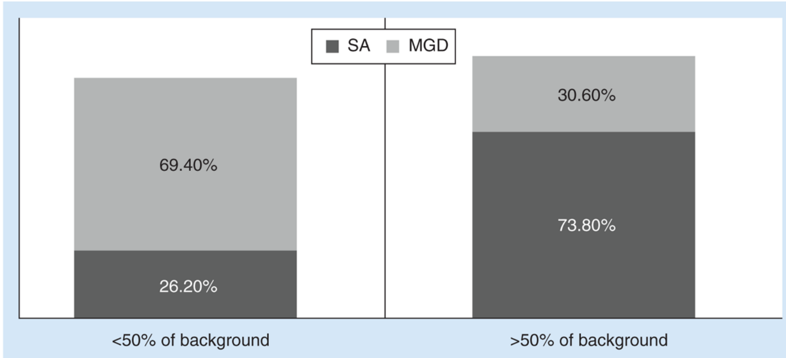

Figure 1. 50% threshold for distinguishing single adenoma from multigland disease

Light color: <50% threshold.

Dark color:>50% threshold.

Percentages represent the percent of the respective etiology (SA or MGD) that fall into each group of the threshold.

MGD: Multigland disease; SA: Single adenoma.

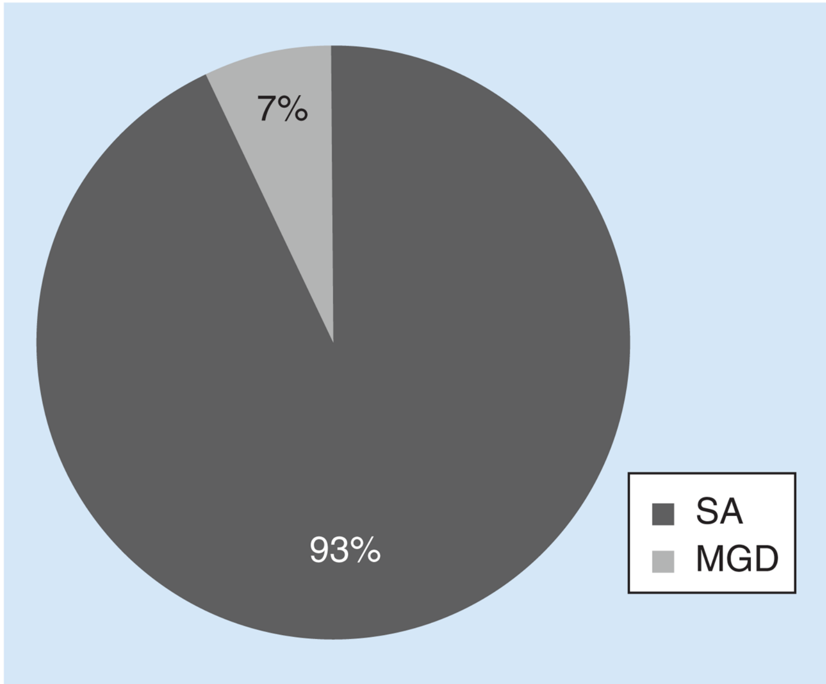

Figure 2. 100% threshold for distinguishing single adenoma from multigland disease

Percentages are the percent of the entire population with counts >100% of background represented by each etiology.

MGD: Multigland disease; SA: Single adenoma.

Table 1

Patient demographics and baseline lab values.

	Patients with SA (n = 1300)	Patients with MGD (n = 356)	p-value
Age (years)	60.99 ± 0.38	60.99 ± 0.67	0.952
Gender (female)	994 (76.5%)	284 (79.8%)	0.259
BMI (kg/m^2)	31.08 ± 0.22	30.81 ± 0.46	0.586
Preoperative PTH (pg/ml)	123.5 ± 2.27	99.6 ± 3.54	<0.001
Preoperative calcium (mg/dl)	11.03 ± 0.02	10.59 ± 0.04	<0.001
Preoperative phosphate (mg/dl)	2.84 ± 0.02	3.31 ± 0.18	<0.001
Urine calcium (mg/24 h)	327.62 ± 7.06	295.96 ± 15.22	0.061
Vitamin D (ng/dl)	30.62 ± 0.47	33.51 ± 0.92	0.004
Creatinine (mg/dl)	1.07 ± 0.08	1.18 ± 0.18	0.539
Gland weight (mg)	709.24 ± 25.75	411.57 ± 41.78	<0.001

Data are represented as the number with the percentage in parentheses for categorical data and the mean ± the standard error of the mean for continuous variables.

Normal preoperative PTH is 15–65 pg/ml.

Normal preoperative calcium is 8.5–10.2 mg/dl.

BMI: Body mass index; MGD: Multigland disease; PTH: Parathyroid hormone; SA: Single adenoma.

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Table 2

Gamma probe counts.

	SA	MGD	p-value
Background radionuclide counts	190.59 ± 3.51	191.12 ± 5.86	0.943
Ex vivo radionuclide counts	166.99 ± 3.75	92.66 ± 4.55	<0.001
% of Background counts	91.73 ± 1.61	49.70 ± 1.99	<0.001

Background counts taken at isthmus of thyroid at initial incision.

Ex vivo counts taken after excision of first suspected hyperactive gland.

% of background = (ex vivo radionuclide counts/background radionuclide counts) × 100.

MGD: Multigland disease; SA: Single adenoma.