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RADIOGUIDED PARATHYROIDECTOMY FOR TERTIARY HYPERPARATHYROIDISM

Yash R. Somnay, BS, Eric Weinlander, BA, Amal Alfhefdi, MD, David Schneider, MD, MS, Rebecca S. Sippel, MD, and Herbert Chen, MD

Section of Endocrine Surgery, Division of General Surgery, Department of Surgery, University of Wisconsin, Madison, WI

Abstract

Background—Tertiary hyperparathyroidism (3HPT) is defined as the persistent hyperproduction of parathyroid hormone (PTH) and resulting hypercalcemia following renal transplantation. Here, we examine the utility of radioguided parathyroidectomy (RGP) in patients with 3HPT.

Materials and Methods—We reviewed a prospective surgery database containing 80 3HPT patients who underwent RGP from January 2001 to July 2014 at our institution. We evaluated patient demographics, operative management, radioguided neoprobe utilization and operative outcomes. Data are reported as mean $\pm$ SEM.

Results—The mean age of the patients was 52 ± 1 years, and 46% were male. 69 patients had hyperplasia and received subtotal parathyroidectomy, while 5 patients had double adenomas and 6 patients had single adenomas. The average calcium level among 3HPT patients was 10.8 ± 0.1 mg/dl preoperatively and 8.7 ± 0.1 mg/dl postoperatively. *In vivo* radioguided counts normalized to background counts averaged $145 \pm 4\%$, while *ex vivo* counts normalized to background counts averaged $69 \pm 5\%$. All but one *ex vivo* count was $>20\%$. Ectopically located glands were successfully localized in 38 patients using the gamma probe. *Ex vivo* percentage did not correlate with parathyroid gland weight, preoperative PTH or preoperative calcium. Our radioguided approach achieved normocalcemia in 96% of 3HPT patients undergoing radioguided parathyroidectomy; 2 patients developed recurrent disease.

Conclusions—In this series, all enlarged parathyroid glands were localized and resected using the gamma probe. Thus, RGP reliably localizes adenomatous, hyperplastic and ectopically located glands in patients with 3HPT, resulting in high cure rate following resection.

Corresponding author: Herbert Chen, MD, K3/705 Clinical Science Center, 600 Highland Avenue, Madison, WI 53792, USA, Tel: +1 608-263-1387, Fax: +1 608-252-0912, chen@surgery.wisc.edu.

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DISCLOSURES

The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

Keywords

radioguided parathyroidectomy; tertiary hyperparathyroidism; gamma probe; technetium (99mTc) sestamibi

INTRODUCTION

Tertiary hyperparathyroidism (3HPT) is the state of excessive parathyroid hormone (PTH) secretion from hyperfunctioning parathyroid tissue that has failed to reset after successful renal allograft placement^{1, 2}. This phenomenon occurs subsequent to prolonged hyperparathyroidism that is secondary to renal failure³. While most successful renal transplant patients experience stabilization of parathyroid hormone regulation, 8% of them will carry autonomously hyperfunctioning parathyroid tissue⁴⁻⁶. Significant morbidity occurs from elevated PTH in over 50% of these patients, and includes symptoms such as osteopenia/osteoporosis, pancreatitis, formation of renal calculi, and mental status changes^{4, 6}.

Surgery remains the only curative therapy for patients with 3HPT². The recommended operative approach is resection by either a total parathyroidectomy with forearm allograft transplant, or a subtotal removal⁷. In select cases, a less than subtotal resection may be appropriate, especially when disease is limited to single or double adenomas^{8, 9}. Surgical innovations have introduced new ways to accurately locate abnormal parathyroid glands for resection using sestamibi parathyroid scintigraphy. Patients are injected with the radiotracer technetium (99mTc) sestamibi prior to their operation, and a gamma probe is then used to identify abnormal parathyroid glands for excision^{7, 10, 11}. When *ex vivo* counts are >20% background, this finding confirms the identity of a hypercellular parathyroid and averts the need for an intraoperative frozen section according to Norman's "20% rule". Thus, advantages of a successfully executed radioguided approach include reduced operative time, more effective localization of ectopic glands and more favorable cosmetic results^{2, 12}.

Radioguided parathyroidectomy has been described most extensively among patients with primary hyperparathyroidism, the majority of whom present with single adenomas, and for which this approach has been reportedly most feasible^{10, 12, 13}. While subsequent reports have determined that a radioguided approach is equally effective for both adenomatous and hyperplastic glands, an examination of its utility in 3HPT has been restricted to cohorts that were combined with secondary hyperparathyroidism patients and that had limited sample size^{2, 14}. Because 3HPT presents most commonly as multiglandular disease, it is important to establish the utility of using radioguidance for operative management in this disease setting as well. Additionally, given the presumed advantages of a radioguided approach, which include reduced operative time and a more sensitive localization of abnormal glands relative to preoperative ultrasound, the 3HPT patient population may be more justly served with this operative approach¹⁵. This study presents the largest exclusive series of 3HPT patients undergoing radioguided parathyroidectomy in an effort to determine its efficacy in this patient population.

MATERIALS AND METHODS

Between January 2001 and April 2014, 80 3HPT patients underwent initial bilateral neck exploration using radioguidance at our institution. These were patients who previously had hyperparathyroidism secondary to chronic kidney disease and had received successful renal allografts. Patients were excluded if they were undergoing reoperative parathyroidectomy for recurrent or persistent hyperparathyroidism. The University of Wisconsin Institutional Review Board approved this study. Our institution is biased towards performing a subtotal parathyroidectomy in all cases of hyperplasia for 3HPT patients, while those with single or double adenomas have their according number of enlarged glands removed. Fragments of glands are sent for cryopreservation in instances when three or more glands were removed.

All patients received intravenous injections of 10mCi of technetium^{99m}-sestamibi for a median time of 67 minutes (range, 30–450 minutes) prior to parathyroidectomy. Prior to incision, background counts were obtained by placing the 11-mm collimated gamma probe (Neoprobe 2000, Ethicon Endo-Surgery Breast Care, Cincinnati, OH) against the skin covering the thyroid isthmus. Radioguided localization of hyperfunctioning parathyroid glands was performed after the incision was made. The probe was used to scan the area and identify radionuclide counts that were higher than the background counts, signifying areas of abnormal parathyroid tissue. These *in situ* counts, referred to as “*in vivo*”, were recorded as a percentage of the background counts. Once excised, the tissue was placed atop the gamma probe away from the patient, and this “*ex vivo*” count was recorded and expressed as a percentage of background counts as well. The highest (“hottest”) *in vivo* and *ex vivo* count were used in this study. In all cases, intraoperative PTH (ioPTH) monitoring was used to determine the endpoint of surgery, defined by a greater than 50% drop in serially drawn PTH levels indicating that the adequate number of hyperfunctioning glands have been excised.

Patient data was collected prospectively and reviewed retrospectively. Surgical cure was defined as having a postoperative serum calcium <10.2 mg/dL at 6 months. Recurrence was defined as a return of serum calcium levels >10.2 mg/dL beyond 6 months after surgery while maintaining normal kidney function. Hypocalcemia was defined as having a calcium level <8.5 mg/dL within one week after surgery. Those whose hypocalcemia resolved by 6 months were considered transient cases of hypocalcemia. Those whose hypocalcemia persisted beyond 6 months in the background of low PTH levels were classified as having permanent hypocalcemia due to hypoparathyroidism. Data was analyzed using SPSS software (version 10.0, SPSS Inc, Chicago, IL). Statistical significance was assigned with P-values of less than 0.01. All data are recorded as mean $\pm$ SEM.

RESULTS

Patients and demographics

There were thirty-seven males (46%) and forty three females (54%) comprising the cohort of 3HPT patients undergoing radioguided parathyroidectomy. The average age of patients undergoing radioguided parathyroidectomy was 52 ± 1 years. Preoperatively, patients had an average calcium level of 10.8 ± 0.1 mg/dL and an average PTH level of 271 ± 25 pg/mL.

(Table 1). Following parathyroidectomy, the mean calcium was reduced to 8.7 ± 0.1 mg/dL and the mean PTH was reduced to 88 ± 13 pg/mL. Patients had a mean vitamin D level that was within the normal range while creatinine levels lied in the upper end of normal before surgery, indicating normal renal function (Table 1).

The etiologies for hyperparathyroidism among the 3HPT cohort undergoing radioguided parathyroidectomy included 69 of whom had hyperplasia and were treated with subtotal parathyroidectomy, 5 with double adenomas, and 6 with single adenomas, which were removed accordingly. (Table 2).

Radioguided Data

A summary of intraoperative findings pertaining to radioguided gland detection is shown in Table 3. The mean radionuclide background count was 182 ± 8 . *In vivo* counts of the largest resected gland in each patient averaged to $145 \pm 4\%$ of background while *ex vivo* counts averaged $69 \pm 5\%$ of background. Notably, of the 80 patients, 79 had *ex vivo* counts that were higher than 20% of background. Consequently, intraoperative frozen section was avoided in these cases. The one remaining patient had an *ex vivo* percentage of 18.8% and, in fact, underwent reoperation parathyroidectomy. Importantly, the average raw *in vivo* count was significantly greater than background ($p=0.0000001$), underscoring the sensitivity of intraoperative radioguidance. The mean weight of the heaviest parathyroid gland resected was 954 ± 88 mg.

Intraoperative gamma detection of ectopic glands

Radioguidance was used to identify and excise ectopically located glands. These were identified and located using the gamma probe in a total of 38 patients from whom 54 glands were removed (Table 4). These glands came most commonly from the thymus ($n=29$), with the second highest location being intrathyroidal ($n=11$). This was followed by glands detected retroesophageally ($n=10$) followed by those outside of the thymus mediastinally ($n=2$). Finally, 1 undescended ectopic gland and 1 carotid ectopic gland were located and removed. Of the 38 patients, 24 had single ectopic glands, 12 had two ectopic glands, and 2 had three ectopic glands. Interestingly, upon stratifying patients by the number of ectopic glands they carried, we found that the mean hottest *ex vivo* count as a percentage of background were lowest among patients with no ectopically located glands, and increased as the number of ectopic glands discovered in a patient increased (Table 5). Those who had no ectopic glands ($n=42$) had an average *ex vivo* percentage of $61 \pm 5\%$. Those who had one ectopic gland ($n=24$) averaged an *ex vivo* percentage of $71 \pm 9\%$ while those with two ectopic glands averaged an *ex vivo* percentage of $88 \pm 13\%$. Only 2 patients had three ectopically located glands, and their mean *ex vivo* percentage was the highest at $96 \pm 18\%$. We next performed linear regression analysis to determine if *ex vivo* percentage correlated with other such parameters as parathyroid gland weight, preoperative PTH and preoperative calcium. Neither preoperative PTH nor calcium correlated with *ex vivo* percentage. Interestingly, heavier parathyroid gland weights tended to yield higher *ex vivo* percentages than smaller glands. However, the correlation between gland weight and *ex vivo* percentage was only weakly positive ($R^2=0.22$), and did not reach statistical significance.

Rate of cure and complications

Radioguided parathyroidectomy was an effective operative approach for our 3HPT cohort (Table 6). Following surgery, 77 of the 80 patients (96%) were cured while only 2 patients recurred (3%). Of the 3 patients who failed, 2 underwent reoperation and were subsequently cured. The two patients with recurring disease were found to have their first instance of abnormally elevated serum PTH and calcium subsequent to their 6-month follow-up assessment. The mean operative time was 105 ± 8 minutes (Table 6).

Radioguided parathyroidectomy resulted in a low rate of complications. Transient hypocalcemia was observed in 9 patients (11%) who underwent radioguided parathyroidectomy, of who 6 experienced hungry bones (8%). These patients were promptly placed on calcium with subsequent symptom resolution. Permanent hypocalcemia due to hypoparathyroidism following parathyroidectomy was only observed in 3 patients who underwent radioguided parathyroidectomy. These patients were placed on calcium, with eventual normalization of calcium levels and remission of symptoms upon their latest follow-up. Other complications such as transient hoarseness and parasthesias resolved upon calcium supplementation and close observation.

DISCUSSION

Intraoperative radioguidance has been established as a safe and effective adjunct to parathyroidectomy for patients with hyperparathyroidism^{14, 16–18}. Norman et al. initially pioneered the advent of this approach, reporting that nuclear mapping of parathyroid glands has extremely favorable outcomes and minimal complications in patients with primary hyperparathyroidism^{7, 10, 12}. He determined that all abnormal parathyroid glands should uniformly produce *ex vivo* counts >20% of background. Many initially questioned the merits of radioguided parathyroidectomy for primary hyperparathyroidism patients, arguing that they provide no appreciable advantages over traditional operative approaches¹⁹. However, a number of studies later have endorsed the value of radioguided parathyroid localization not only for detecting adenomatous glands from primary hyperparathyroidism patients, but for parathyroid hyperplasia as well. Early reports by Goldstein et al. and other groups first attested that radioguidance not only facilitates parathyroid gland localization in primary hyperparathyroidism patients, but also curtails hospital costs by reducing operative time, and obviates the need for frozen section^{20, 21}. It has even been shown that radioguidance can be utilized for successful reoperation in the setting of persistent primary hyperparathyroidism^{13, 22}. Our group has since reported outcomes on radioguided parathyroidectomy from cohorts that combine secondary and tertiary hyperparathyroidism patients with primary hyperparathyroidism patients¹⁴. However, because no disease group was individually examined in this study, it is not possible to determine the utility of a radioguided approach for any single disease classification. Although our subsequent study suggested that radioguided parathyroidectomy is effective for patients with secondary and tertiary hyperparathyroidism, this particular study combined these two disease groups, and was limited to only 18 3HPT patients². Thus, a thorough examination of a radioguided approach in patients with 3HPT is befitting. These patients suffer debilitating symptoms and are at increased risk of renal allograft failure if hypercalcemia is not promptly corrected².

Here, we report the largest to date series of exclusively 3HPT patients who underwent radioguided parathyroidectomy.

At our institution, radioguidance proved to be a safe and effective method for performing parathyroidectomy in 3HPT patients. In our study, 77 of the 80 patients who underwent radioguided exploration of their hyperfunctioning glands achieved cure at 6 months postoperatively (96%) (Table 6). Of the 3 patients who failed, one underwent 2-gland resection at initial operation. This patient underwent reoperation to remove 1.5 additional glands originally undiscovered by the gamma probe, in addition to an initially missed thymic supernumerary gland which was found the second time using radioguidance. This patient was cured as of latest follow-up. The other 2 failed patients initially underwent a subtotal parathyroidectomy. One underwent reoperation to remove the remaining partial gland that was causing residual disease using a radioguided approach, and achieved cure on latest follow-up. Of the two patients whose disease recurred 6 months after surgery, only one underwent reoperation to remove the remaining partial gland from the initial subtotal parathyroidectomy, and no ectopic glands were found. This patient underwent a non-radioguided, minimally invasive reoperation, and experienced remission based on most recent calcium and PTH levels.

Our study assesses the efficacy of radioguided parathyroidectomy in conjunction with bilateral neck exploration. Because radioguidance allows for more effective localization of abnormal glands and unnecessary neck dissection, a minimally invasive, unilateral approach to parathyroidectomy is permitted by effective radioguided localization if abnormal glands are limited and unilaterally confined. This is an operative approach which has been routine^{2, 23}. However, a more recent study of radioguided parathyroidectomy by Norman et al. concluded that a bilateral radioguided approach was in fact superior to unilateral radioguided exploration²³. In their cohort limited exclusively to patients with primary hyperparathyroidism, they reported a rate of cure which improved to nearly 99% from a previously 3–5% failure rate as unilateral exploration was slowly abandoned in favor of bilateral exploration. Cure rates from radioguided unilateral parathyroidectomies were still high, underscoring the very reason radioguided surgery originally took hold following Norman's earlier reports. Because our study focuses on tertiary hyperparathyroidism patients, who are more likely to have multiglandular disease, we routinely performed bilateral exploration assisted by gamma probe localization, and our findings support the conclusion of Norman et al. that radioguidance is a useful adjunct to a bilateral approach. Our study also uses ioPTH monitoring for establishing a surgical endpoint. All 80 patients experienced the 50% requisite drop in ioPTH to establish surgical cure. Among those whose disease persisted or recurred, we believe that their unidentified parathyroid tumors were present at the initial operation, but may have been producing low enough PTH to evade gamma probe detection, and their presence was masked by larger hypersecreting parathyroid glands that had a larger effect on ioPTH levels when removed. This study presents the utility of radioguidance as an adjunct to a described and commonplace surgical methodology.

In our surgeons' hands, the intraoperative gamma probe was capable of detecting all abnormal parathyroid glands for resection among the 80 3HPT patient cohort. The entirety of glands resected produced significantly more *in vivo* counts than background

($p=0.0000001$), underscoring the sensitivity of the gamma probe in detecting abnormal parathyroid glands (Table 3). Subsequently, the “20% rule” was applied to *ex vivo* counts. As stated, *ex vivo* percentages above 20% confirm excision of an adenomatous gland, and by omitting the need for frozen section analysis, reduce operative time as well^{12, 20}.

Furthermore, this approach may bypass time otherwise spent on unnecessary neck dissection. In our series of 3HPT patients who underwent parathyroidectomy using radioguidance according to the “20% rule”, all but one patient had *ex vivo* counts above 20% (Table 3). Hence, we avoided frozen section analysis in almost all patients during the operation. In the one patient who’s *ex vivo* percentage was less than 20% (18.8%) we proceeded with a frozen section and were able to determine that it was abnormal parathyroid tissue. We found that radioguidance among 3HPT patients allowed for a considerably brief operative time (105 ± 8 minutes) compared to the time traditionally required through nonradioguided means (151 ± 15 minutes), previously reported by Nichol et al. from our group² (Table 6). Altogether, these findings suggest that radioguidance is a sensitive tool for intraoperatively localizing abnormal parathyroid glands, and can effectively guide their excision in a time efficient manner.

Radioguided assistance is also a useful tool for identifying and resecting ectopically located glands. Previous studies have suggested that radioguided techniques facilitate the identification of ectopic glands in hyperparathyroidism patients, but these series were limited in their representation of 3HPT patients^{2, 14}. Ectopically located glands occur considerably among 3HPT patients, and because standard localization using ultrasonography, technetium^{99m}-sestamibi scans, and magnetic resonance imaging have been shown to be inadequate in identifying such glands in these patients, establishing the utility of gamma probe detection for this purpose is especially important²⁴. In our exclusively 3HPT cohort, we show that radioguidance was helpful in locating and resecting a total of 54 ectopic glands, all of which were hyperplastic. This frequency is normal in our experience with 3HPT patients, and coincides with past reports of ectopic gland incidence in this patient subset²⁴. Among these ectopic glands, 29 were thymic (Table 4). This is important because in traditional parathyroidectomies, routine cervical thymectomy is often advocated^{2, 8}. However, a radioguided approach may inform the surgeon whether thymic resection is necessary or not. Previous reports by our group have suggested abandoning routine bilateral cervical thymectomies in such patients with secondary and tertiary hyperparathyroidism if the gamma probe does not localize *in vivo* counts to the thymic vicinity. In our study, thymic resection was reserved for those with high ectopically located gamma probe counts around the thymus. Thus, we can conclude that radioguidance is a highly specific tool for determining when cervical thymectomy is appropriate, since those who underwent radioguided parathyroidectomy experienced a high rate of cure without routine thymic resection. Furthermore, in our cohort, 1 of the 3 persistent 3HPT patients had a thymic supernumerary gland that was localized by the gamma probe but overlooked by preoperative ultrasound. Similar to a previous report from our group, which demonstrated that radioguided localization is a more sensitive detector of hyperfunctioning glands than preoperative sestamibi scanning in primary hyperparathyroidism patients, our study may suggest the same phenomenon among 3HPT patients¹⁵.

Among other ectopically located glands, 11 were located intrathyroidally, 10 were retro- or paraesophageal, 2 were mediastinal, 1 was undescended, and was 1 carotid (Table 4). In two patients, the gamma probe was able to locate 3 ectopic glands. One of these patients had 3 intrathyroidal ectopic glands and the other patient had 1 thymic, 1 retroesophageal, and 1 paraesophageal gland. Interestingly, those patients with the most ectopic glands had a higher mean *ex vivo* radionuclide count as a percentage of background. Of note, we observed a decreasing trend in the mean *ex vivo* percentage across patients with decreasing numbers of ectopic glands (Table 5). This may suggest that the number of *ex vivo* radionuclide counts amassed by the resected glands is an indicator of the frequency of ectopic glands present. Interestingly, we found that patients' *ex vivo* percentages did not correlate with parathyroid gland weight. Although heavier parathyroid glands produced higher *ex vivo* counts creating a mildly positive trend between gland weight and *ex vivo* percentage, the majority of patients had smaller glands whose *ex vivo* counts varied broadly. This reduced the strength of linear association enough to preclude any distinct correlation between parathyroid gland weight and the *ex vivo* counts it generates.

We conclude that radioguidance can reliably locate abnormal parathyroid glands for surgical removal in 3HPT patients undergoing parathyroidectomy. All abnormal parathyroid glands resected were intraoperatively detected using the gamma detector and all but one exceeded the 20% *ex vivo* threshold. Importantly, this method leads to a very high rate of cure with minimal rates of recurrence and complications. The use of the gamma detector for gland localization allows for an efficient use of operative time in part by avoiding nonessential surgical neck dissection and delays from acquiring frozen sections, which may help to avert unnecessary costs^{2, 10}. Finally, radioguidance is a sensitive tool for identifying supernumerary glands and allows for a much more careful deliberation before performing cervical thymectomy. This report now affirms that radioguided parathyroidectomy is a highly safe and effective approach for managing 3HPT patients.

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TABLE 1**Patient Demographics and Preoperative Findings**

	Radioguided N=80 (%)
Age (y)	52 ± 1
Male patients (%)	37 (46)
Vitamin D (ng/mL)	29.0 ± 1.2
Creatinine (mg/dL)	1.6 ± 0.1
Preoperative Ca (mg/dL)	10.8 ± 0.1
Preoperative PTH (pg/mL)	271 ± 25
Postoperative Ca (mg/dL)	8.7 ± 0.1
Postoperative PTH (pg/mL)	88 ± 13

Mean ± SEM

TABLE 2

Etiology of Disease

	Radioguided N=80
Etiology	
<i>Single</i>	6
<i>Double</i>	5
<i>Hyperplasia</i>	69

Mean $\pm$ SEM

TABLE 3**Radioguided Excision Data**

N	80
Mean background counts	182 ± 8
Mean <i>in vivo</i> counts	266 ± 11
Mean <i>in vivo</i> counts as % of background	145 ± 4
<i>in vivo</i> counts > background	80/80 (100%)
P-value of <i>in vivo</i> vs. background count	0.0000001 *
Mean <i>ex vivo</i> counts	127 ± 10
Mean <i>ex vivo</i> counts as % background	69 ± 5
<i>ex vivo</i> counts >20% background	79/80 (99%)
<i>ex vivo</i> <20% background, N	1 ^a
Mean gland weight (mg)	954 ± 88

Mean ± SEM

* Statistically significant (P<0.01)

^a 18.8% of background (underwent reoperation)

TABLE 4

Number of Ectopic Glands Excised Among Radioguided Parathyroidectomy Patients

Number of Patients w/ectopic glands		38
	<i>Location</i>	<i>Number Removed</i>
	Thymus	29
	Intrathyroidal	11
	Retro- or paraesophageal	10
	Mediastinal	2
	Undescended	1
	Carotoid	1
	Total glands resected	54

TABLE 5Ectopic Glands and Mean *ex vivo* % in Patients Undergoing Radioguided Parathyroidectomy (N=80)

Number of Ectopic Glands Discovered	N	Mean ex vivo count (% background)
0	42	61 ± 5
1	24	71 ± 9
2	12	88 ± 13
3	2	96 ± 18

Mean ± SEM

TABLE 6

Incidence of Cure, Recurrence and Complications

	Radioguided n=80 (%)
Cure, n (%)	77 (96)
Recurrence, n (%)	2 (3)
Operative time (minutes)	105 ± 8
Complications	
<i>Transient hypocalcemia n (%)</i>	9 (11)
<i>Permanent hypoparathyroidism, n (%)</i>	3 (4)
<i>Transient hoarseness, n (%)</i>	4 (5)
<i>Hungry bone syndrome, n (%)</i>	6 (8)
<i>Parasthesias, n (%)</i>	7 (9)

Mean ± SEM