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Radioguided Parathyroidectomy for Hyperparathyroidism in the Reoperative Neck

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Abstract

Background—The purpose of this study was to determine if radioguided parathyroidectomy (RGP) is effective for hyperparathyroidism (HPT) in the reoperative neck.

Methods—We retrospectively reviewed all patients with HPT and a history of neck surgery who underwent RGP over a 7-year period. Data are reported as mean ± SEM.

Results—We identified 110 patients with primary (n=94), secondary (n=7), or tertiary (n=9) HPT who underwent 138 previous neck operations. The average hospital stay was 0.6 ± 0.1 days. The in and ex vivo counts obtained with the gamma probe were 310 ± 26 and 130 ± 13, respectively. The ex vivo percentage of background was 69 ± 9%, and virtually all resected parathyroids had ex vivo counts ≥ 20%. Following RGP, 96% of patients were cured, and 4.5% experienced complications (all transient). Cure rates after RGP significantly decreased as the number of previous neck surgeries increased (P=0.002). Additionally, reoperative neck patients with single adenomas were more likely to experience cure than patients with hyperplasia (P=0.02).

Conclusions—These results illustrate that RGP is valuable adjunct in the reoperative neck. In addition, RGP allows similar lengths of stay, efficacy, and complication rates as those reported for patients undergoing initial parathyroidectomy.

Hyperparathyroidism (HPT) results from the excess secretion of parathyroid hormone (PTH) by at least one hyperfunctioning parathyroid gland usually leading to hypercalcemia. In patients with HPT who meet the indications for parathyroidectomy, initial surgery is associated with high cure rates and minimal morbidity for primary, secondary, and tertiary HPT (1–3). Nonetheless, persistent or recurrent disease develops in a subset of these patients and requires re-exploration. Failure of initial surgery is frequently due to an incomplete or inadequate resection because the diseased parathyroid gland(s) was not identified or a supernumerary gland was present (4, 5). These missed glands are often in an ectopic location or in the normal anatomic position. Failure to identify multiple abnormal glands in patients with a presumed adenoma also occurs and leads to persistent HPT. In addition, patients may present for an initial parathyroidectomy with a history of prior neck surgery related to thyroid, carotid, spine, malignant, or tracheal disease.

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In these patients who have undergone previous parathyroidectomy or other neck operations, resection of diseased parathyroids can be difficult due to dense scar tissue as well as anatomic distortion and loss of tissue planes. Such challenges have led to higher rates of failure and morbidity in this setting, especially recurrent laryngeal nerve injury and permanent hypoparathyroidism (5, 6). Redo cases also have been associated with an increased length of stay and total hospital costs (3). The use of a radioguided probe and ^{99m}Tc-sestamibi injection in initial minimally invasive parathyroidectomies has been associated with decreased operative times, length of stay, hospital costs, and complications, but the role of radioguided surgery in the reoperative setting is less clear (7–9).

The literature definitively supports the use of preoperative localization with ^{99m}Tc-sestamibi scanning, ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), or selective venous sampling (SVS) in patients with persistent or recurrent HPT (2, 10–13). In these reoperative cases, however, multiple imaging studies are often necessary and may be difficult to interpret or even misleading (14). Intraoperative localization with radioguided surgery has been shown to facilitate initial parathyroidectomy in patients with HPT, though few studies have examined this adjunct in patients who have undergone prior neck surgery (15–18). Despite the advances in parathyroid surgery, room for progress exists in the setting of the reoperative neck. The purpose of this study was to determine if the radioguided technique is an effective adjunct during parathyroidectomy for HPT in the reoperative neck.

METHODS

We performed a retrospective review of a prospectively collected database that included all patients who underwent parathyroid surgery at the University of Wisconsin from March 2001 to September 2008 by 2 endocrine surgeons. Inclusion criteria for this study were: (1) a confirmed diagnosis of primary, secondary, or tertiary HPT, (2) a radioguided parathyroidectomy (RGP) was performed, and (3) a history of prior neck surgery. Patients with mediastinal parathyroids requiring any form of thoracotomy were excluded. Of the 1021 consecutive parathyroid surgeries performed, 110 (11%) patients met these criteria and were included in this study. We evaluated patient demographics, imaging, anesthetic method, gland weight, lengths of stay, radioguided probe use, and outcomes. The duration of surgery was collected retrospectively from anesthetic records and encompasses the entire time period where the patient was in the OR.

Preoperatively, all patients underwent localization with imaging of their neck unless one of 2 situations occurred: (1) a concomitant thyroid procedure was planned and the patient did not have a history of parathyroid surgery (n=2), or (2) the patient had secondary (n=2) or tertiary (n=2) HPT and had not been previously operated on for parathyroid disease. For patients who had no history of parathyroidectomy, ^{99m}Tc-sestamibi single photon emission computed tomography (SPECT) was routinely performed in all cases. If this study was positive, no further imaging was obtained; however, when negative, a cervical ultrasound also was performed. For these non-parathyroid reoperative neck patients, parathyroidectomy was performed even when both imaging studies were negative. Conversely, in patients with a history of parathyroidectomy, at least one positive localization study was required prior to reoperation. If ^{99m}Tc-sestimibi and ultrasound were both negative in these patients, magnetic resonance imaging (MRI) was performed. Early in our experience, thallium-technetium subtraction scintigraphy was performed prior to MRI.

The radioguided procedures were performed as previously described (16, 18). Briefly, patients were injected with 10mCi ^{99m}Tc-sestamibi 1 to 2 hours before surgery, and an 11-mm collimated gamma probe (Neoprobe 2000, Ethicon Endo-Surgery Breast-Care, Cincinnati, OH) was used to localize hyperfunctioning parathyroid tissue. Background counts were defined as the gamma readings measured prior to skin incision when the probe was placed perpendicular to the thyroid isthmus. In vivo counts were then obtained prior to gland excision when the gamma probe was directly over the enlarged parathyroid in situ and, typically, were about 150% of the background counts. Lastly, once the hyperfunctioning parathyroid was removed, the gland was positioned on the end of the gamma probe (directed away from the patient) to obtain the ex vivo counts. The “20% rule” described by Norman was used to confirm parathyroid identity (19).

The operative approaches depended upon the underlying etiology and number of diseased glands remaining in the neck. For patients with primary HPT and a single remaining gland, a focused, minimally invasive dissection was carried out. Patients with secondary or tertiary HPT and those with primary HPT suspected to have missed multiple gland disease underwent a radio-assisted open, bilateral neck exploration. Subsequent forearm autotransplantation was performed in patients who underwent previous subtotal parathyroidectomy for primary, secondary, or tertiary HPT. Surgical success was defined as a normocalcemia (serum calcium less than or equal to 10.2 mg/dl) at 6 months or greater follow-up. Recurrence was considered to be a confirmed serum calcium level greater than 10.2 mg/dl at any time after 6 months.

Statistical analysis was performed with SPSS software (version 10.0, SPSS Inc, Chicago, IL). Data are reported as mean ± standard error of the mean (SEM). The positive predictive value (PPV) of these studies was calculated as the number of patients with correct localization (corresponding to surgical specimen/true positives) divided by the number of patients with localizing studies (true positives + false positives. One-way analysis of variance (ANOVA) was used for comparisons among groups with Bonferroni post-hoc correction. A *P* value of less than 0.5 was considered statistically significant. This study was approved by the University of Wisconsin Institutional Review Board.

RESULTS

We identified 110 patients with primary (n=94), secondary (n=7), or tertiary (n=9) HPT who underwent a total of 138 previous neck operations. Sixteen patients (15%) had a history of two prior neck surgeries, and 6 patients (6%) underwent 3 past neck procedures. The mean age of the patients was 59 ± 1 years, and 83 (77%) were female (Table 1). The types of previous neck operations included 73 (53%) open or minimally invasive parathyroidectomies (5 with thymectomy), 34 (25%) partial, completion, or total thyroidectomies, 10 (7%) carotid endarterectomies, 6 (4%) cervical spine surgeries with an anterior approach, 5 (4%) modified radical neck dissections, 4 (3%) tracheostomies, and 6 (4%) other procedures. These other procedures were a branchial cleft cyst excision, a tracheal web resection, a skin graft to the neck in a patient with 2 previous tracheostomies, multiple excisions of cervical skin cancer in a patient with a history of platysmaplasty, and an evacuation of a neck hematoma. Fifty-nine percent of the patients (65 of 110) were operated on for persistent or recurrent HPT. The reasons for reoperative parathyroidectomy in these 65 patients included missed adenoma (n=26), recurrent HPT (n=28), remnant hyperplasia (n=6), and a missed supernumerary gland (n=5). Eight of these 65 redo parathyroid patients had 2 prior parathyroid surgeries.

Preoperative data

The pre-operative laboratory data are illustrated in Table 1. Prior to surgery, seventy-seven percent of all patients were symptomatic including musculoskeletal complaints (n=44), fatigue (n=24), nephrolithiasis (n=12), mental status changes (n=2), and hypercalcemic crisis (n=3).

A total of 147 pre-operative localization studies were performed in the 110 patients. Thirty-seven percent of all patients (41 of 110) and 40% of redo parathyroid patients (26 of 65) had 2 imaging studies, and an additional 3 patients (3%; 2 for redo parathyroidectomy) had 3 studies. ^{99m}Tc-sestamibi and cervical ultrasonography were the primary pre-operative imaging modalities utilized. In patients with primary HPT, the respective sensitivities of ^{99m}Tc-sestamibi and cervical ultrasound were 85% (77 of 91) and 52% (16 of 31). The PPV of these pre-operative localization studies in the reoperative neck are summarized in Table 2. When these imaging modalities were combined in patients with primary HPT, 6 patients failed to localize and 16 were incorrectly localized. RGP was particularly useful in these cases (23%) where localization was not successful or was wrong. Six additional patients did not have any pre-operative localization performed. Four of these 6 patients had either secondary or tertiary HPT and were not reoperative parathyroid cases. The other 2 patients had primary HPT and underwent simultaneous total thyroidectomies for papillary thyroid cancer. Thus, 12 patients in this series had no localization studies that were positive. One patient each had an MRI and a CT scan after sestimibi and ultrasound were negative.

Operative data

The radioguided probe was used in all cases, and a unilateral exploration was performed in 70% of the reoperative neck surgeries. In addition, 9% of the RGPs were performed under local anesthesia. A single adenoma was the cause of HPT in 55 patients (60%) with primary HPT and 1 (11%) patient with tertiary HPT. Double adenomas were found in 14 patients (15%) with primary HPT. The underlying etiology of HPT was hyperplasia in all 7 patients (100%) with secondary HPT, 8 (89%) patients with tertiary HPT, and 25 (27%) patients with primary HPT. Thirty-nine percent of all patients had ectopic parathyroids. A thymectomy was performed during these reoperative neck cases in 17%, 14%, and 33% of patients with primary, secondary, and tertiary HPT, respectively. The other 86% of patients with secondary HPT had thymectomies performed during previous operations. The average total length of time spent in the operating room (including anesthesia) was 121 ± 4 minutes for all patients. We did not detect any differences in the length of time spent in the operating room among patients based on the etiology of their HPT (Table 3). In addition, the mean gland weight for the entire cohort was 676 ± 57 mg. Those patients with secondary and tertiary HPT did have significantly heavier gland weights when compared to patients with primary HPT (*P* < 0.03).

Radioguided probe data

The average time elapsed from injection of the ^{99m}Tc-sestamibi to the start of surgery was 110 ± 15 minutes and was similar among the 3 groups of patients (Table 3). The mean background, in vivo, and ex vivo gamma counts obtained with the radioguided probe in all patients were 216 ± 20, 310 ± 26 and 130 ± 13, respectively. We analyzed the ratio of ex vivo counts to the background counts (commonly expressed as a percentage) because a measurement of 20% or higher has previously been shown to confirm parathyroid pathology (19). The average ex vivo percentage of background for all patients was 69 ± 6%. Table 3 demonstrates that the mean background, in vivo, ex vivo, and ex vivo percentage of background gamma counts were similar among patients with primary, secondary, and tertiary HPT. Ninety-six percent of the resected parathyroids had ex vivo counts greater than or equal to 20%. Frozen section was not used in any of these reoperative neck cases.

Outcome data

The average duration of follow-up in this study was 17 ± 2 months. The mean post-operative serum calcium level for the entire cohort measured at 6 months was 9.4 ± 0.1 mg/dl. In addition, Table 4 demonstrates that the mean creatinine levels measured at 6 months were significantly different among all 3 groups ($P \leq 0.03$ for all comparisons).

Following RGP, 96% of all patients were eucalcemic at 6 months. There were no significant differences among patients with regard to the rate of eucalcemia in terms of their HPT type (Table 4). Four patients with primary HPT experienced a recurrence at 25 ± 12 months after their initial resection. Three of these patients had hyperplasia of their remnant following subtotal parathyroidectomy, and one developed a second adenoma. The average length of hospital stay for all patients was 0.6 ± 0.1 days. Patients with primary HPT had a significantly shorter mean length of stay compared to patients with secondary or tertiary HPT (P<0.02; Table 4). Five of these reoperative patients (4.5%) experienced complications which are outlined in Table 4. Both patients with transient recurrent laryngeal nerve injuries previously underwent at least one bilateral neck exploration with either a single or subtotal parathyroidectomy.

Additional analyses were performed to examine any potential risk factors for failure at reoperation. An analysis of the underlying pathology, showed that patients with single adenomas were significantly more likely to experience a cure at reoperation than patients with 4 gland hyperplasia (*P*=0.02). Patients with single adenomas, double adenomas, and hyperplasia had respective eucalcemia rates at 6 months after RGP reoperation of 100%, 93%, and 86% (*P*=0.03 by ANOVA). For this analysis, patients were considered to have a double adenoma if 2 glands were resected during an initial parathyroid operation in an otherwise reoperative neck or if the patient had a history of a parathyroidectomy for a single parathyroid adenoma and presented with persistent or recurrent HPT due to one hyperfunctioning gland. In addition, patients with 3 previous neck operations were significantly less likely to achieve a cure compared to patients with just 1 prior neck surgery.

The rates of euclacemia at 6 months for patients with 1, 2, or 3 previous neck surgeries were 98%, 87%, and 67%, respectively (P=0.002 by ANOVA). We also compared patients who had prior parathyroid operations to those who underwent a prior non-parathyroid neck surgery. Similar proportions of cure were observed among those patients who underwent previous parathyroidectomies when measured against those who underwent other past neck operations (90% vs. 98%, respectively, P=0.24).

DISCUSSION

Reoperation for persistent or recurrent HPT is often demanding because of scarring and distorted anatomy. Use of a radioguided probe in these situations has been proposed to facilitate dissection and localization of parathyroid tissue (16, 17). Studies that have examined reoperative parathyroid surgery have focused mainly on persistent or recurrent cases of HPT in patients with primary HPT. However, several additional neck surgeries result in similar fibrotic changes and alteration of tissue planes. Therefore, we report the utilization of a radioguided gamma probe in the reoperative neck in 110 patients with primary, secondary, or tertiary HPT.

In patients without a history of neck surgery who are undergoing initial parathyroidectomy, radioguided probe use has been shown to have multiple advantages over traditional approaches (20). One of these advantages is the omission of frozen section in patients who have ex vivo to background count ratios greater than 20%—the so-called “20% rule” for RGP described by Norman (19). This rule has been effectively utilized in patients undergoing initial parathyroidectomy for primary, secondary, and tertiary HPT (18, 20, 21). Our findings confirm the efficacy of the “20% rule” in reoperative neck patients. Frozen sections were not performed in any cases in this study. In addition, the counts obtained from the radioguided probe in these reoperative patients are similar to those previous published in patients with “virgin” necks (7, 18, 22). Therefore, the technical aspects of RGP appear to be the same for all patients regardless of previous neck surgery or HPT etiology. Furthermore, because limited dissection is possible, radioguided unilateral exploration can be undertaken in the majority of reoperative neck surgeries with select cases still performed under local anesthesia.

RGP in the reoperative setting also can be thought of as an additional localization procedure performed intraoperatively to facilitate parathyroidectomy. Preoperative localization with a combination of imaging modalities is recommended in patients with persistent or recurrent HPT (2, 10–13). In the current investigation, approximately 40% of patients had 2 or more preoperative imaging studies. However, 97% (63 of 65) of the reoperative parathyroid cases had at least one positive preoperative localization study. In the 2 patients who were not well-localized, intraoperative bilateral selective venous sampling for PTH was used to lateralize (one side PTH > 5% the opposite side) the exploration and the radioguided probe assisted in parathyroid localization. When pre-operative localization with imaging is not possible, we support the use of internal jugular localization to isolate the side of the neck that harbors the hyperfunctioning parathyroid, and typically perform this procedure intraoperatively by obtaining venous blood samples from both internal jugular veins and sending them for rapid PTH assay. Twenty-six patients in this study had this procedure performed intraoperatively, but we do not collect data on whether these samples were lateralizing in our prospectively collected database.

Additional previously reported benefits of RGP in patients without prior neck surgery are decreased operative times and lengths of stay (18, 20). In this study, the total time spent in the operating room as charted by anesthesia was approximately 2 hours, and 50% of patients were able to be operated on as an outpatient. While the total operating room time was similar among all patients, those with secondary and tertiary HPT stayed overnight. Our findings are consistent with a previous study that indicated short re-operative times with RGP in patients with primary HPT (16). Furthermore, these data indicate the total operating room time and length of stay may be decreased in the reoperative neck with RGP.

Previous analyses of patients undergoing repeat parathyroid surgery for persistent or recurrent HPT also have suggested that the rate of cure may be as low as 80% (4, 6, 16, 23–25). On the other hand, patients undergoing initial surgery for HPT have expected success rates of 95% or greater (1–3, 20). In our study, eucalcemia was achieved in 96% of all reoperative neck patients, a percentage similar to those reported in initial parathyroidectomies. However, success rates decreased as the number of previous neck operations increased. The proportion of patients achieving eucalcemia also decreased with increasing numbers of remaining diseased parathyroid glands. These observations confirm the findings of Richards and colleagues who showed that a single previous operation and solitary gland disease are associated with a higher likelihood of cure in reoperative parathyroidectomy (25). Our results expand these risk factors to patients with a history of any type of prior neck surgery, not just parathyroidectomy.

Traditionally, another downside to reoperative surgery has been a higher rate of complications. Permanent hypocalcemia and recurrent laryngeal nerve injury rates have been as high as 13% and 6.6%, respectively, in previously published series (6, 23). Though more recently, these rates have been reported to be as low as 3% and <1%, respectively, for reoperative cases and <1% for both complications in initial parathyroidectomies (3, 25). In the current study, no patients experienced permanent hypocalcemia or recurrent laryngeal nerve damage. These data suggest that reoperative neck surgery with a radioguided probe is as safe as initial minimally invasive parathyroidectomy.

In reoperative parathyroidectomies, preoperative localization with a combination of imaging modalities is clearly advantageous because the results can be used to guide dissection (2, 10–13). Even in patients who are undergoing reoperation in the neck, but an initial parathyroid surgery, this concept remains true. In these reoperative neck cases, radioguided probe use allows for additional intraoperative localization to facilitate minimal dissection in a field that may have dense scarring, fibrotic changes, and often friable tissue. Taken together, our results suggest that RGP is a safe and effective adjunct in the reoperative neck with cure rates that approach those seen in initial parathyroidectomies. Operative times, lengths of stay, and complication rates also are similar to the data reported for patients undergoing initial parathyroid surgery.

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Table 1

Pre-operative Characteristics

	Total	Primary HPT	Secondary HPT	Tertiary HPT	P value
N	110	94	7	9	
Age (years)	58 ± 1	60 ± 1	55 ± 6	55 ± 5	0.53
Serum calcium (mg/dL)	11.1 ± 0.1	11.1 ± 0.1	10.5 ± 1.0	11.0 ± 0.3	0.27
Serum PTH (pg/mL) *	234 ± 46	133 ± 13	1323 ± 535	440 ± 167	< 0.001
Serum creatinine (mg/dL)†	1.5 ± 0.2	1.0 ± 0.03	5.6 ± 1.3	2.1 ± 0.8	< 0.001

Data are given as mean ± standard error of the mean. *P* values determined by one-way ANOVA.

* $P \leq 0.03$ for pairwise comparisons between all 3 groups with Bonferroni post hoc correction.

† $P < 0.001$ for Primary HPT vs Secondary HPT and Secondary HPT vs Tertiary HPT; $P = 0.07$ for Primary HPT vs. Secondary HPT.

HPT, Hyperparathyroidism. *PTH*, Parathyroid hormone.

Table 2

PPV of preoperative localization studies

HPT Type Localization Study	*PPV* (TP/TP+FP)
Primary HPT	
^{99m}Tc-sestamibi	77% (58/75)
Ultrasound	60% (9/15)
Secondary HPT	
^{99m}Tc-sestamibi	67% (2/3)
Ultrasound	100% (3/3)
Tertiary HPT	
^{99m}Tc-sestamibi	100% (7/7)
Ultrasound	100% (1/1)

HPT, Hyperparathyroidism; *PPV*, Positive predictive value; *TP*, True positive; *FP*, False positive.

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Table 3

Operative Details and Radioguided Probe Utilization

	Total (n=110)	Primary HPT (n=94)	Secondary HPT (n=7)	Tertiary HPT (n=9)	P value
Operative data					
Total time spent in OR (min)	121 ± 4	118 ± 4	125 ± 16	144 ± 11	0.17
Gland weight (mg) *	676 ± 55	600 ± 50	1196 ± 300	1115 ± 302	0.002
Injection time (min)	110 ± 15	109 ± 18	83 ± 13	133 ± 45	0.84
Gamma counts					
Background	216 ± 20	220 ± 22	205 ± 40	183 ± 24	0.87
In vivo counts	310 ± 26	315 ± 30	276 ± 46	281 ± 44	0.88
Ex vivo counts	130 ± 13	142 ± 15	131 ± 20	114 ± 29	0.81
Ex vivo : background (%)	69 ± 6	70 ± 7	74 ± 18	64 ± 19	0.95

Data are given as mean ± standard error of the mean. One-way ANOVA used to compare groups.

* $P < 0.03$ for comparisons between Primary HPT and the 2 other groups with Bonferroni post hoc correction.

HPT, Hyperparathyroidism. *OR*, Operating room.

Table 4

Outcomes and Follow-up Data

	Total (n=110)	Primary HPT (n=94)	Secondary HPT (n=7)	Tertiary HPT (n=9)	P value
Post-operative Laboratory Values					
Serum Calcium (mg/dL)	9.4 ± 0.1	9.5 ± 0.1	8.5 ± 0.4	9.0 ± 0.3	0.003
Serum Creatinine (mg/dL)	1.6 ± 0.3	1.0 ± 0.04	5.6 ± 1.6	3.0 ± 1.7	<0.001
Ouctomes					
Eucalcemia at 6 mos (%)	106 (96)	91 (97)	6 (86)	9 (100)	0.46
Recurrence after 6 mos (%)	4 (4)	4 (4)	--	--	--
Length of stay (days)	0.6 ± 0.1	0.5 ± 0.1	1.1 ± 0.1	1.6 ± 0.1	<0.001
Complications					
Transient hypocalcemia	3	1	--	2	--
Transient RLN injury	2	1	--	1	--

Data are given as mean ± standard error of the mean. One-way ANOVA used to compare groups.

HPT, Hyperparathyroidism. *RLN*, Recurrent laryngeal nerve.