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Re-operative parathyroidectomy: How many positive localization studies are required?

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Background: Re-operative parathyroidectomy in patients with recurrent or persistent hyperparathyroidism can be challenging. We review our experience to determine the optimal number of localization studies prior to re-operation.

Methods: From 2001 to 2019, 251 patients underwent re-operative parathyroidectomy. Parathyroidectomies were stratified to 4 groups based upon the number of positive localization studies obtained: A) ZERO, B) 1-positive, C) 2-positive, D) 3-positive.

Results: The overall cure rate was 97%, where 201 single gland resections, 23 two-gland resections, 22 subtotal/total, and 5 forearm autograft resections were performed. Thirty-two patients had no positive studies (A), 172 patients had 1-positive (B), 42 patients had 2-positive (C), and 5 patients had 3-positive studies (D). There was no difference in surgical cure rates between groups ($p = 0.71$). The majority of patients had one or no positive imaging studies yet almost all still achieved cure.

Conclusion: Successful re-operative parathyroidectomy can be performed with minimal pre-operative scans in certain clinical contexts.

Introduction

Hyperparathyroidism (HPT) is a relatively common endocrine disease in the United States and is predominantly caused by an underlying single benign parathyroid adenoma. Multigland disease can occur as in cases of familial syndromes and has increased prevalence with “mild” primary hyperparathyroidism.[1,2] Surgical intervention is the only means to achieve a durable cure, however operative failure remains a relatively common complication following parathyroidectomy with 3–10% of patients requiring remedial operation of recurrent of persistent disease.[3] When performed by an experienced, high-volume endocrine surgeon, initial parathyroidectomy for primary hyperparathyroidism results in greater than 95% cure rate.[4,5] However, incomplete resection of 1 or more abnormal parathyroid glands results in persistent or, sometimes, recurrent primary hyperparathyroidism and requires reoperation.

Long-term, untreated primary hyperparathyroidism has significant detrimental multi-organ effects and warrants attempt for operative cure.[5,6] However, remedial parathyroid surgery is challenging. The operation is more technically difficult due to scarring from previous operation(s) and therein lies an inherently greater risk of injury to the recurrent and superior laryngeal nerves as well as to the residual normal parathyroid tissue.[7] Additionally, aberrant parathyroid glands are more commonly ectopic in the remedial population, often necessitating a more extensive, and thus more challenging, operation.[7] Thus, many surgeons obtain multiple parathyroid studies with the hope of localization prior to proceeding with a re-operation. Due to the limitations in accuracy of parathyroid localization studies in the setting of persistent or recurrent disease, this may dissuade some surgeons from reintervention. Additionally, since cure rates are lower (82%–98%) and risks are higher, many surgeons use stricter indications for subsequent operation than for initial surgery.[8–10] Because there are no consensus guidelines for optimal imaging studies in the re-operative parathyroid setting, we reviewed our 18-year re-operative parathyroidectomy experience.

Materials and methods

A retrospective review of all patients from 2001 through 2019 who underwent re-operative parathyroidectomy consecutively

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across two academic institutions for biochemically proven recurrent or persistent hyperparathyroidism was performed. Data was prospectively collected, and all surgeries were performed by 2 high-volume endocrine surgeons (HC and BL.) Medical records were reviewed; demographic and medical information including laboratory results, pathology, and operative reports, was acquired. Of the 251 patients included in our study, 204 were from a single institution during the years 2001–2015. The remaining 47 patients were from the second institution during the years 2015–2019 when one of the operating surgeons moved institutions. All reoperations from each site that occurred during these respective time periods were included in the analysis.

Preoperative parathyroid localization imaging modalities that were utilized include neck ultrasound (US), 99mTc-sestamibi scintigraphy ("sestamibi scan"), and intravenous-contrasted high-resolution four-dimensional computed tomography of the neck (4D CT neck.) Final imaging reports read by board-certified radiologist were reviewed and compared to intraoperative findings documented by the operating surgeon. Images and reports from studies that were performed at referring institutions were uploaded into our institutions electronic medical record. Findings from surgeon-performed neck US were documented in clinic notes at time of initial consultation. A positive localization study was defined as concordant preoperative imaging results and intraoperative pathologic findings. In the event that additional diseased glands were found intraoperatively and preoperative imaging localized fewer focus of disease, albeit correctly, this was still considered a negative study due to discordance.

It is our practice to use a radio-guided technique for all parathyroidectomies, except in those for which it is contraindicated (i.e. pregnancy, lactation). Technique for radioguided parathyroidectomy has been previously published.[11] Briefly, a nuclear medicine technician peripherally injects 10 miC of Tc 99m-sestimibi 1–2 h preoperatively. Preoperative films are not obtained. Background counts of the thyroid isthmus are performed using a handheld 14 mm gamma probe (Neoprobe, Devicor Medical Products, Inc) followed by ex-vivo counts of resected specimen(s). A value of >20% of background count is used as a diagnostic threshold for confirming hyperplastic parathyroid tissue. We routinely use intraoperative PTH (ioPTH) samples drawn at 5, 10, and 15 min following parathyroid resection and use a >50% decline as threshold for surgical cure. Planned bilateral neck exploration (BNE) was performed when MGD was suspected by preoperative imaging, a planned concomitant thyroid procedure, or indicated by prior operative note findings. Conversion to a BNE from a directed approach was performed if there was not an appropriate drop in ioPTH after resection of the parathyroid tissue identified as hyperfunctional by ex-vivo gamma counts.

Patients were stratified into 4 groups based upon the number of positive preoperative localization studies obtained: Group A) zero positive preoperative studies, Group B) 1-positive preoperative study, Group C) 2-positive preoperative studies, and Group D) 3-positive preoperative studies. Operative success was defined as normocalcemia (serum calcium level $\leq$ 10.4 mg/dL) 6-months postoperatively[12] and pathologic confirmation of parathyroid tissue on intraoperative specimen.

To compare the association between patient characteristics, imaging modalities, and surgical outcomes amongst patient groups, the Wilcoxon rank-sum test, the Fisher exact test, and the chi-squared test were used, as appropriate. Significance was defined as $p < 0.05$. IRB approval was obtained at the University of Alabama at Birmingham.

Table 1
Patient demographics and summative results.

Demographics	N = 251 patients (%)
Age, years	57 ± 1
Gender, % female	78%
Diagnosis	
Primary HPT	215 (86%)
Secondary/Tertiary HPT	36 (14%)
Biochemical Characteristics	
Ca levels, mean (mg/dL)	
Preoperative	10.6 ± 0.1 mg/dL
2-week postoperative	9.4 ± 0.9 mg/dL
6-month postoperative	9.3 ± 1.2 mg/dL
PTH levels, mean (pg/dL)	
Preoperative	248 ± 35 pg/mL
2-week postoperative	77 ± 176.4 pg/mL
6-month postoperative	80.8 ± 118.2 pg/dL
Gland weight (mg)	638 ± 102 mg
Initial operation performed	
No gland resected	119 (47%)
Single gland resection	73 (29%)
Two gland resection (double adenoma)	8 (3%)
Subtotal parathyroidectomy	51 (20%)
Remedial operation performed	
Single gland resection	201 (80%)
Two gland resection	23 (9%)
Subtotal parathyroidectomy	22 (9%)
Forearm autograph resection	5 (2%)
Ectopic Glands on Remedial Operation	96 (38%)
Carotid sheath	4 (4.2%)
Intrathyroidal	30 (31.2%)
Mediastinal	32 (33.3%)
Retroesophageal	18 (18.8)
Undescended	12 (12.5%)
Complications	30 (12%)
Transient hoarseness	4 (1.6%)
Transient hypocalcemia	21 (8.4%)
Permanent hoarseness	0 (0%)
Permanent hypocalcemia	6 (2.4%)
Cure	241 (96%)

Results

Two hundred and fifty-one patients with recurrent or persistent hyperparathyroidism underwent re-operative parathyroidectomy over a 19-year period. The majority of patients were female (78%) and the mean age was 57 ± 1 years. Eighty-six percent (215/251) patients had primary hyperparathyroidism and 14% (36/251) had either secondary or tertiary hyperparathyroidism. The mean preoperative serum calcium and parathyroid hormone (PTH) levels were 10.6 ± 0.1 mg/dL (normal 8.8–10.4 mg/dL) and 248 ± 35 pg/mL (normal 20–75 pg/dL), respectively. The mean 2-week post-op serum calcium and PTH were 9.4 ± 0.9 mg/dL and 77 ± 176.4 pg/mL, respectively. The average total parathyroid gland weight was 638 ± 102 mg and almost all surgeries were performed as outpatients with the average length of stay being 0.3 days. Ninety-six patients had ectopic glands identified on reoperation with 4 located within the carotid sheath, 30 intrathyroidal, 32 mediastinal, 18 retroesophageal and 12 undescended. Table 1 summarizes patient demographics and characteristics.

Of the 251 patients included in our study, all had previous parathyroid operations. In 119 (47%) of these previous operations, the initial surgeon failed to resect a parathyroid gland based on review of pathologic and operative reports when available from

Table 2
Group A-D stratification.

	Group A	Group B	Group C	Group D	p-value
+ Localization tests	Zero	1	2	3	–
N	32	172	42	5	–
Operative Success	97%	97%	93%	100%	0.710
Bilateral explorations	65%	8%	5%	0%	0.003

referring institution. Seventy-three (29%) patients underwent a single gland resection at their initial operation, 51 (20%) patients underwent subtotal/total parathyroidectomy and 8 (3%) had double adenomas and underwent resection of 2 parathyroid glands at their index operation. Amongst the 251 remedial operations performed at our institution, 201 (80%) were single gland resections, 23 (9%) were two-gland resections, 22 (9%) were subtotal/total parathyroidectomies, and 5 (2%) were resections of forearm autografts.

Overall the complication rate was 12% and this predominantly included transient complications. Transient hoarseness occurred in 4 patients (1.6%) but resolved in all patients within six-months after surgery and no patients had permanent hoarseness. Transient hypocalcemia occurred in 21 patients and 6 patients developed permanent hypocalcemia.

An overall success rate of 96% was achieved for all reoperations. The mean 6-month postoperative Ca and PTH levels were 9.3 ± 1.2 mg/dL and 80.8 ± 118.2 pg/dL, respectively. Six patients (2.4%) had hypocalcemia at the 6-month mark with a mean Ca level of 7.32 mg/dL among these six patients. Within 1 year postoperatively the mean Ca level of these patients was 8.32 mg/dL with only 1 patient having a Ca level below 7 mg/dL and requiring ongoing oral Ca supplementation greater than 1 year after reoperation.

We then stratified patients based on number of positive localization studies obtained. Group A included 32 patients who had no positive localization studies prior to undergoing reoperation. Amongst these 32 patients, 65% (21/32) underwent 4-gland bilateral neck exploration for hyperplasia. When comparing all 4 groups of patients, there was a significantly greater rate of 4-gland exploration performed in Group A ($p = 0.003$) due to a greater prevalence of hyperplasia in this cohort. Table 2 summarizes the number of studies, the operative success rates, and rate of bilateral neck explorations per group.

Group B included 172 patients who had 1-positive localization study prior to proceeding to re-operative parathyroidectomy. Fourteen of these patients (8%) underwent bilateral neck explorations. Group C patients included those with 2-positive localization studies prior to undergoing re-operative intervention and accounted for 42 of the 251 patients (17%) within our study. Two patients (5%) in Group C underwent bilateral neck explorations. Group D patients were those with 3 positive localization studies prior to proceeding with re-operation and included only 5 patients or 2% of our entire cohort. All of the Group D patients underwent localized, unilateral parathyroidectomy, conversely stated no Group D patients were subjected to bilateral neck explorations. When comparing surgical cure rates, there was no difference between the 4 groups (A: 97%, B: 97%, C: 93% and D: 100%; p-value 0.71.)

All patients were stratified into those with “mild disease” (normocalcemic hyperparathyroidism) or “moderate-severe disease” (elevated serum calcium and PTH levels). Thirty five percent of mild HPT patients had zero positive localizing studies compared to 11% in the moderate-severe HPT group ($p = 0.001$.)

Of the 32 patients in our study with zero positive preoperative localization modalities, only 4 of these patients proceeded to the operating room with zero attempted preoperative localization studies. Of the remaining 28 patients who had no positive preoperative localizing study, 14 of them underwent an attempt at localization with 1 imaging modality, 11 of them underwent an attempt at localization with 2 imaging modalities, and 3 patients had 3 attempted imaging modalities, all of which were non-localizing.

Due to the development and adoption of a new imaging techniques occurring during our study period, we re-stratified our data to assess the impact of high-resolution computed tomography on parathyroid imaging utilization. Based upon the data included in our database, both institutions adopted 4D CT neck for re-operative cases as early as 2009. Our original cohort of 251 patients was stratified into those who underwent re-operation between 2001-2008 and 2009–2018, the periods before and after adoption of 4D CT neck, respectively.

Between 2001 and 2008, 82 patients underwent re-operative parathyroidectomy. Seventy-eight of these patients (95%) also had a sestamibi scan performed preoperatively, 54 of which correctly localized (69%.) Thirty three of the 82 patients (40%) underwent neck ultrasound with only 14 of these correctly localizing (42%.) Of these 82 patients, 32 of them had both sestamibi and US performed (39%) and only 10 of these patients localized correctly on both studies. Thus, only 12% of the early cohort had “2-positive studies” prior to reoperation. Three patients had no imaging attempted prior to reoperation. One early cohort patient underwent a CT scan in 2004 prior to reoperation. This patient had no abnormal parathyroid tissue identified during initial operation per outside operative report.) Prior to reoperation, a 4D CT scan of the neck localized to the superior mediastinum and final pathology demonstrated parathyroid carcinoma.

The later cohort of patients underwent a reoperative parathyroidectomy between 2009 and 2018 and included 169 patients. Seventy-eight of these patients (46%) underwent CT neck before reoperation, of which 62% localized correctly. When looking at the number of patients in which 2-imaging modalities were attempted, 8 patients had both a neck US and 4D CT performed, 19 patients had sestamibi and neck US, and 22 patients had a sestamibi scan and CT scan performed. The frequency of 2-imaging-attempts in this later cohort was 28.9% (49/169) compared to 39% (32/82) in the earlier 2001–2008 cohort ($p = 0.06$.)

Among all 169 patients in the 2009–2018 cohort, the number of 2-positive localization studies were as follows: 11 patients correctly localized on both US and CT, 8 patients localized on sestamibi and CT, and 6 patients localized on sestamibi and US. Seventeen patients underwent all 3 modalities before surgery and only 3 patients had 3-positive localization studies prior to reoperation. Regarding patients within the later cohort who only underwent a single imaging modality attempt prior to reoperation, 106 patients had a sestamibi scan (44% correctly localized), 48 patients underwent neck US only (48% correctly localized) and 31 patients underwent CT neck only (58% correctly localized.)

We further analyzed the 91 patients who did not undergo CT scan during this 2009–2018 period to assess the frequency of dual imaging attempt despite availability of CT scans; 18.7% of patients (17/91) underwent both sestamibi and US compared to 39% in the earlier cohort. Among these 91 later cohort patients who did not undergo CT scan, only 6 of them had 2-positive localization studies (6.6%) prior to proceeding with reoperation. Overall, the cure rate for patients in the 2001–2008 cohort was 92% and 97% in the 2009–2018 cohort.

Discussion

Re-operative parathyroid surgery remains particularly challenging; as such there is no consensus statement regarding the number and type of optimal preoperative localization modalities.

Choice of imaging technique depends largely on surgeon preference and technological availability, but imaging modalities can be expensive and often inaccurate. For non-remedial parathyroidectomy, the sensitivity of technetium-99 m (Tc-99 m) sestamibi scanning is 88% for solitary adenomas, 30% for double adenomas, and 44% for multigland disease with US being even less sensitive.[14]

In remedial parathyroid surgery, these localization accuracies are even lower. Mortenson et al. reported a localization accuracy of 80% for 4D CT neck, 51% for sestamibi scan, and 21% for neck US.[15] In this series of reoperative patients, 91% underwent 3 imaging modalities before remedial surgery. Studies investigating the cost of preoperative imaging modalities are limited. A 2013 study examining Medicare payments and institutional charges calculated the costs of 4DCT neck and sestamibi scans to be $1296 and $1112, respectively.[16]

In this review of complex re-operative parathyroidectomies, an important finding from our data is the lack of overall benefit to prescribing to a set minimum of concordant positive localization studies to achieve a durable cure. Positivity on imaging is not an indication for surgery in and of itself and conversely, lack of positivity on imaging is not strictly prohibitive of surgery.

In our series, patients belonging to Group A had a significantly greater rate of bilateral neck explorations compared to the other 3 groups, which can be attributed to the predominance of multigland hyperplasia, which has lower localization accuracies compared to adenomatous disease. This is demonstrated in groups with a lower number of positive localization studies and associated higher rate of bilateral neck explorations.

When our patients were stratified based on the timing of 4D CT neck adoption across our institutions, we can see that there was a decrease in frequency of sestamibi scan utilization as well as ultrasound albeit to a lesser extent. As might be expected, the frequency of attempting two imaging modalities prior to reoperative intervention decreased from 39% to 28.9% over the 2 decades of data as 4D CT neck has been shown to have superior sensitivity and specificity for localization of parathyroid adenomas compared to sestamibi and ultrasound, even though only 46% in the latter cohort underwent CT scan. This likely reflects the influence of evolution in practice patterns and acquired experience of the operating surgeons. Additionally, there was an increase in cure rate noted from 92% to 97% from patients who underwent reoperation between 2001-2008 and 2009–2018, respectively. While advancement in imaging techniques certainly may contribute to this, it is also, at least partly, a factor of the surgeons' skill acquisition and experience over time.

While this study examines a large cohort of re-operative parathyroidectomies spanning two decades and includes long-term follow-up, it is retrospective in design and there are several limitations that should be noted. The radiologists within our institutions have extensive experience in reviewing nuclear medicine uptake scans, neck ultrasonography, and CT imaging of neck soft tissue, but we acknowledge that there can certainly be human and technical error involved in the administration and interpretation of radiographic studies. Similarly, surgeon-performed neck US done in the clinic is subject to error and misinterpretation and is a notable limitation to include.

Additionally, our reoperative cure rate of 96% is slightly higher than other institutional experiences published.[12,13] This could also be attributed to individual surgeon experience and etiology of persistent or recurrent disease. All patients who were referred to the operating surgeons at our institutions with biochemical confirmation of disease recurrence (hypercalcemia more than 6 months after initial operation) or persistent disease after failed attempt at initial operation were offered re-operative parathyroidectomy and those who elected to proceed with surgery were included in our study. Thus, we did not include imaging results for non-operative patients in our study.

These results provide important insight into the pre-operative decision-making process of remedial parathyroidectomy and highlight the need to consider re-operating on persistent or recurrent hyperparathyroidism despite failure to preoperatively localize. It is important to note that these results are from a high-volume endocrine surgery practice with significant experience in reoperative and bilateral parathyroid exploration. Surgeon experience should factor into the decision to proceed with reoperating in the absence of preoperative imaging.

Conclusion

In summary, we found no difference in outcomes for re-operative parathyroidectomy based upon the number of positive localization studies obtained. We support that patients requiring remedial parathyroid surgery without positive localization remain surgical candidates and successful re-operative parathyroidectomy can be performed with minimal pre-operative imaging when performed by high-volume endocrine surgeons.

Declaration of competing interest

The authors have no conflicts of interest to disclose.

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