Reoperative parathyroidectomy: An algorithm for imaging and monitoring of intraoperative parathyroid hormone levels that results in a successful focused approach

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Background. *Advances in preoperative imaging and use of intraoperative parathyroid hormone (IOPTH) levels are changing the approach to reoperative parathyroidectomy (ReopPTX). We sought to develop a protocol for imaging and IOPTH monitoring that allows for a focused, successful operative approach.*

Methods. *We reviewed our prospective database of consecutive patients with primary hyperparathyroidism who underwent ReopPTX with IOPTH monitoring between December 1999 and June 2007.*

Results. *Thirty-nine patients underwent 43 ReopPTXs for persistent (79%)/recurrent (21%) disease. All underwent ultrasonography and sestamibi imaging; 24 cases (56%) underwent additional imaging studies. Sensitivity of ultrasonography was 56%, sestamibi 53%, both studies 67%, computed tomography (CT) 48%, magnetic resonance imaging (MRI) 67%, and selective venous sampling (SVS) 50%. IOPTH monitoring predicted accurately cure in 100% and failure in 78%. A focused/unilateral approach was performed in 60%; median operative time was 45 minutes (range, 12–127). At last follow-up, 36 (92%) patients were normocalcemic.*

Conclusions. *We propose that ultrasonography and sestamibi studies should be done before all ReopPTXs; failure to localize should prompt sequential CT, MRI, and SVS until localization is achieved. IOPTH monitoring defines cure and is recommended for all ReopPTXs. This algorithm allows for a focused operative approach in >50% of ReopPTXs with operative times comparable with first-time, minimally invasive parathyroidectomy. (Surgery 2008;144:611-21.)*

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Initial operation for primary hyperparathyroidism (pHPT) has a cure rate of >95%, whether performed via a bilateral cervical exploration or a minimally invasive approach.[1-5] Despite these success rates, pHPT persists or recurs in 5% to 10% of patients.[6-8] Patients with persistent hyperparathyroidism (HPT) have an increased serum calcium concentration within 6 months postoperatively owing to inadequate initial parathyroidectomy (PTX); those with recurrent HPT are normocalcemic for ≥6 months after operation and then develop hypercalcemia, usually due to newly developed pathology. Compared with initial PTX, reoperative parathyroidectomy (ReopPTX) for persistent or recurrent disease is associated with decreased success rates and increased complication rates, specifically recurrent laryngeal nerve injury and postoperative hypocalcemia.[6,7,9,10] These results can be explained by the obliteration of normal tissue planes owing to scarring from previous operations, making it difficult to identify abnormal parathyroid glands in eutopic and ectopic locations as well as to locate and preserve the recurrent laryngeal nerves and normal parathyroid glands.

With technologic advances in radiology, options for preoperative localization continue to increase and improve. Noninvasive imaging modalities include ultrasonography (US), sestamibi/technetium-99m scintigraphy, computed tomography (CT), and magnetic resonance imaging (MRI);

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invasive methods include selective arteriography, selective venous sampling (SVS) with parathyroid hormone (PTH) measurements, and image-guided fine-needle aspiration for PTH levels. Despite these advances and options in radiologic imaging, no common algorithm for preoperative localization before ReopPTX has been proposed. Furthermore, the use of IOPTH monitoring has been demonstrated to be an excellent predictor of cure and has proved helpful in reoperations for recurrent or persistent HPT.[4,5,11-14] By analyzing our contemporary series of ReopPTXs using modern imaging modalities and IOPTH monitoring, we sought to develop a protocol for imaging and IOPTH monitoring that allows for a focused and successful approach for ReopPTX.

METHODS

After Institutional Review Board approval was obtained, we reviewed the medical records of all 706 patients in our prospective database who underwent PTX at 1 institution between December 1999 and June 2007. Inclusion criteria for this study were patients with pHPT who underwent reoperations for recurrent or persistent disease with complete IOPTH monitoring information. Persistent HPT was defined as hypercalcemia within 6 months of the initial PTX; recurrent HPT was defined as hypercalcemia that occurred after ≥6 months of normocalcemia. The study cohort was composed of 39 patients who underwent 43 reoperations.

Before reoperation, all patients completed our preoperative localization protocol consisting of neck US and 99m technetium-labeled sestamibi scan, as described previously.[15] We do not perform routinely sestamibi scans with single-photon emission CT. Selected patients underwent CT, MRI, and/or parathyroid angiography with SVS. Cervical CT with intravenous contrast was performed using helical acquisition with 2.5 mm image thickness. Multiplanar, multisequence neck MRI was performed with and without intravenous contrast. Parathyroid angiography and SVS with provocative angiography were performed with selective catheterization and sampling of the internal jugular veins bilaterally, subclavian veins bilaterally, left brachiocephalic vein, superior vena cava, right atrium, and suprarenal and infrarenal inferior vena cavae. A 2-fold gradient between the PTH levels in the selective venous sample compared with that in peripheral blood establishes the site of venous drainage of the neoplasm. Interpretation of imaging results (i.e., true positive [TP], false negative) were determined as described previously.[15]

The planned and actual operative approaches were recorded prospectively. Operations included minimally invasive or focused PTX (removal of 1 parathyroid gland through a small incision); a unilateral cervical approach, involving identification of both ipsilateral parathyroid glands; a standard, bilateral cervical exploration with 4-gland identification; or a mediastinal approach via a median sternotomy or videoassisted thoracoscopic approach. Four of the 43 reoperations were performed with a radioguided approach. Intraoperative US was not performed in any patients. All operations were performed under general anesthesia.

Our protocol for IOPTH monitoring has been described previously.[16] Before July 18, 2005, IOPTH values were determined in the operating room per protocol using the Quick-IntraOperative Intact PTH assay, a 2-site immunochemiluminometric assay (Nichols Institute Diagnostics, San Juan Capistrano, Calif); the Immulite 1000 Turbo Intact PTH system, a 2-site chemiluminescent immunometric assay (Diagnostic Products Corporation, Los Angeles, Calif), has been used since this date. A PTH value is determined at "baseline" (after anesthesia induction and before incision) and at "time zero" (at the time of parathyroid gland removal). Blood samples for PTH levels are then drawn at 5 and 10 minutes after resection of each adenoma or enlarged parathyroid gland. Our criteria for concluding an operation is an IOPTH value at 10 minutes postresection of the last parathyroid gland that is (1) ≥50% less than either the "baseline" or "time zero" value, whichever was greatest, and (2) within the normal range of the IOPTH assay.

For this study, operative success or curative PTX was defined as (1) normocalcemia with ≥6 months follow-up or (2) meeting IOPTH criteria and being normocalcemic within 6 months of follow-up, if ≥6 month follow-up information was not available. Patients not meeting this standard were considered as having failed the operations.

Data on demographic, imaging, operative, intraoperative findings and IOPTH values, parathyroid gland weight and pathology, and complications were collected prospectively, as were postoperative PTH and calcium levels at 1 week and 3, 6, and 12 months. Patients were classified as having single gland disease (SGD) when only a single abnormal gland was removed, or as having multiple gland disease (MGD) when >1 abnormal gland was removed. Complications included recurrent laryngeal nerve injury (defined as vocal cord paralysis documented by laryngoscopy) and permanent hypoparathyroidism (defined as persistent

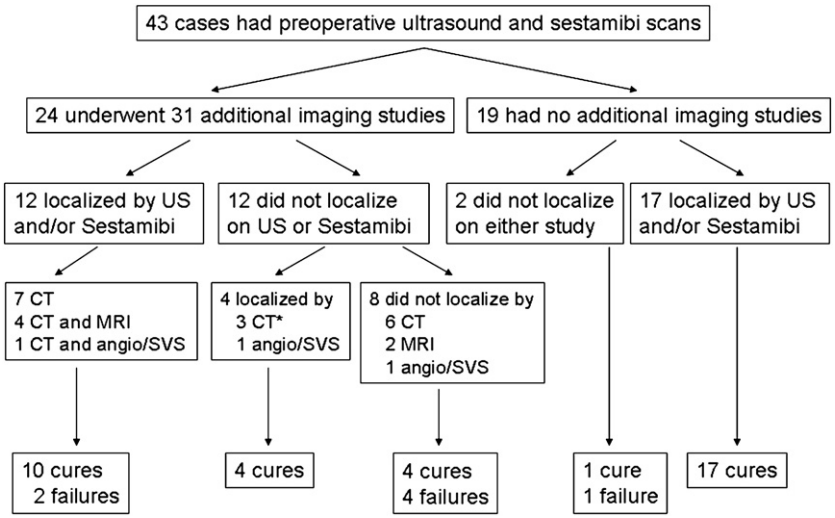

Fig 1. Preoperative localization studies performed before all 43 reoperations. *CT*, Computed tomography; *MRI*, magnetic resonance imaging; *SVS*, selective venous sampling; *US*, ultrasonography. *One patient who localized by CT also had a false-negative angiography/SVS.

hypocalcemia >6 months postoperatively that required calcium and calcitriol supplementation). Routine follow-up calcium and PTH values were not available for all patients.

RESULTS

Thirty-nine pHPT patients underwent a total of 43 reoperations with IOPTH monitoring by 3 surgeons; 4 patients underwent a second reoperation at this institution for persistent disease. Before reoperation, 35 (90%) had undergone 1 initial operation, 3 had undergone 2 operations, and 1 with multiple endocrine neoplasia type I had undergone 4 previous operations. Of these 43 reoperations, 35 (82%) were performed for persistent disease and 8 (18%) for recurrent disease. Of the 39 pHPT patients studied, 26 (67%) were female and 13 (33%) were male. The median age at reoperation was 57 years (range, 30–83). The cause of pHPT was SGD in 18 (46%) and MGD in 20 (51%), including 4 with multiple endocrine neoplasia and 1 with parathyromatosis. The etiology of the 1 remaining patient is unknown because this patient has undergone 2 operations with no glands removed; an ectopic mediastinal gland is suspected. The median preoperative calcium concentration was 11.2 mg/dL (range, 9.9–13.7), PTH level was 120 pg/mL (range, 58.4–576), and creatinine concentration was 0.9 mg/dL (range, 0.5–2.1); for the 25 patients with preoperative, 24-hour urinary calcium values, the median was 362 mg (range, 53–1066). At last follow-up, 36 (92%) patients were normocalcemic; 3 have persistent disease.

Characteristics of the initial 39 parathyroid operations. Of the patients' initial 39 operations, 28 (72%) were done at outside institutions and 11 (28%) were performed at this institution. The operative approach was bilateral in 27 (69%), unilateral in 9 (23%), minimally invasive PTX in 2 (5%), and mediastinal in 1 (3%). At the time of initial parathyroid operations, 20 (51%) had adenomas removed, 12 (31%) had no parathyroid glands resected, and 7 (18%) had only normal parathyroid glands removed. Twelve (31%) patients underwent with IOPTH monitoring and all 12 failed to meet IOPTH criteria to terminate an operation. In 11 patients, the IOPTH values did not decrease by 50% by the end of the case; in the remaining patient, the IOPTH values decreased by 50%, but the IOPTH values were still minimally increased at 10 and 30 minutes after removal of a single adenoma. For these 12 patients, 4 had missed MGD and 7 had SGD missed at initial exploration; the etiology of the last patient remains unknown, but is presumed mediastinal in origin.

Preoperative imaging studies for 43 reoperations. As shown in Fig 1, all patients completed our preoperative localization protocol of cervical US and sestamibi scan. No further imaging was performed in 19 (44%) patients. In 17 of these 19 patients, localization by 1 or both studies was achieved; all 17 had successful PTX. Twenty-four cases (56%) underwent 31 additional localization studies, totaling 21 CTs, 6 MRIs, and 4 angiography/SVS studies. Of these 24 cases, 12 abnormal glands localized by US and/or sestamibi, 10

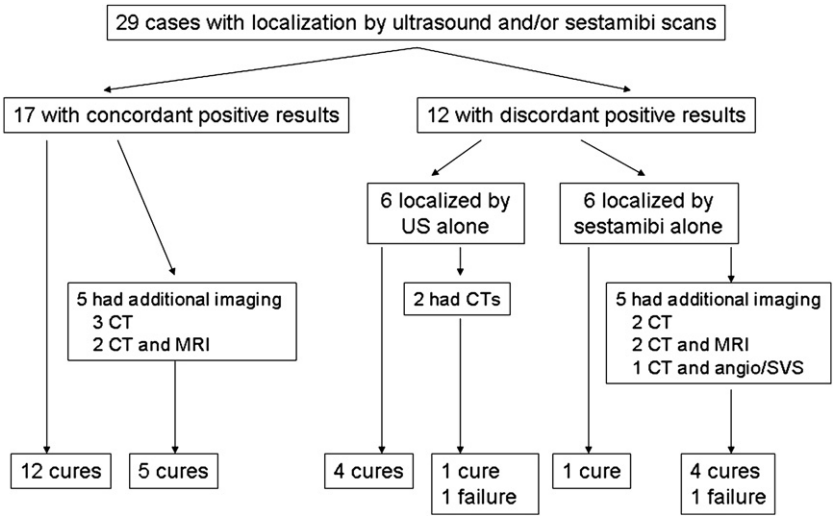

Fig 2. Outcome of 29 cases with dieases that localized by US and/or sestamibi scans. Concordant results were defined as true positive on both studies; discordant results were defined as true positive on 1 study but false negative on the other. *CT*, Computed tomography; *MRI*, magnetic resonance imaging; *SVS*, selective venous sampling; *US*, ultrasonography.

patients had curative reoperations and 2 were failures (1 with parathyromatosis and 1 with a mediastinal adenoma that was removed on subsequent reoperation).

Fourteen cases did not have a gland localize on US or sestamibi; 12 underwent 14 additional studies. Four patients had adenomas that localized on additional imaging and underwent curative PTX. The remaining 8 patients had no glands that localized on further imaging; 4 had failed reoperations secondary to MGD (2 reoperations in 1 patient), 1 has parathyromatosis, and 1 had mediastinal disease that was removed during a subsequent operation. Two patients had no glands that localized on initial imaging and did not undergo additional studies; the etiology of the 1 failure remains unknown because this patient has declined reoperation. In this subgroup of 10 reoperations that had no positive localization studies, 5 involved removal of a single adenoma in a eutopic position and were cured.

As shown in Fig 2, 29 cases had disease that localized by US and/or sestamibi studies. There were 17 patients who had concordant positive results (both studies were TP); 5 underwent further imaging studies and all 17 patients were curative. The remaining 12 cases had discordant, positive US and sestamibi results (TP on 1 study but false negative on the other); 7 underwent additional imaging studies. Ten (83%) proved to be curative reoperations; the 2 failures were due to parathyromatosis and a mediastinal adenoma that was removed at subsequent reoperation. For these 29 cases with disease that localized by US and/or sestamibi, additional imaging (MRI and angiography/SVS) was helpful in only 2 patients who had mediastinal adenomas requiring thoracoscopic removal.

Table I. Sensitivity of preoperative localization studies

Localization Study	*Sensitivity (TP cases/TP + FN cases)*
US	56% (24/43)
Sestamibi	53% (23/43)
US and sestamibi	67% (29/43)
CT	48% (10/21)
MRI	67% (4/6)
Angiography/SVS	50% (2/4)

CT, Computed tomography; *FN*, false negative; *MRI*, magnetic resonance imaging; *SVS*, selective venous sampling; *TP*, true positive; *US*, ultrasonography.

The sensitivity of all preoperative localization studies is summarized in Table I. The greatest sensitivity was achieved when the results of both US and sestamibi were interpreted together (TP on either or both studies). The sensitivity of MRI was also high; however, the sensitivities for CT, MRI, and angiography/SVS are limited by the small number of patients undergoing each study.

Operative approaches for the 43 reoperations. After reviewing all previous imaging studies, operative reports, and pathology reports, a preoperative planned approach was recorded. The actual operative approach performed was recorded postoperatively (Table II). For the 29 cases who had disease localized by US and/or sestamibi, a

Table II. Planned and actual operative approach for the 43 reoperative PTX

Operative approach	*Planned if localization by US and/or sestamibi* (n = *29*)	*Planned if localization by other study* (n = *4*)	*Planned if no localization* (n = *10*)	*Planned total* (n = *43*)	*Actual total* (n = *43*)
MIP/focused	8	1	0	9	9
Unilateral	13	2	1	16	17
Bilateral	6	0	9	15	14
Transthoracic	2	1	0	3	3

MIP, Minimally invasive parathyroidectomy; *US*, ultrasonography.

focused or unilateral cervical approach was planned in 21 (72%), a bilateral exploration in 6 (all had MGD except for 1 patient with SGD and 1 with a mediastinal adenoma), and a transthoracic approach in 2. For the 4 patients that did not localize by US and/or sestamibi but localized on subsequent imaging studies, a focused/unilateral cervical approach was planned in 3 and a sternotomy in 1. For the 10 patients that had no gland that localized on preoperative imaging studies, a bilateral cervical exploration was planned in 9 (90%); in 1 patient, a unilateral cervical approach was used during a second reoperation after having undergone an extensive 4-gland exploration and right thyroid lobectomy for MGD previously at our institution.

A focused or unilateral cervical approach was possible in 60% (26/43), whereas only 35% (14/43) required a standard, 4-gland exploration. The remaining 3 patients underwent operations for mediastinal adenomas, 2 undergoing median sternotomy and the other a thoracoscopic approach. The median time to gland removal was 45 minutes (range, 12–127) using a focused/unilateral approach and 60 minutes (range, 38–216) using a bilateral approach.

The IOPTH results influenced the extent of the actual operation in 4 patients. Two were planned bilateral explorations (owing to nonlocalizing preoperative studies), which were converted to unilateral explorations after single adenomas were removed and IOPTH values met criteria to conclude the operation. The remaining 2 operations were planned unilateral approaches (because both US and sestamibi scans localized to 1 side) that were converted to a 4-gland exploration. In 1 patient, IOPTH values failed to decrease appropriately after the removal of a 205-mg adenoma. Although no additional, hypercellular, parathyroid tissue was removed, the operation was concluded when a 90-minute postresection IOPTH value was 8 ng/mL. This patient was normocalcemic at 6 months of follow-up. In the fourth patient, no abnormal glands were identified and IOPTH values remained increased and unchanged after a bilateral exploration and thymectomy. It is presumed that, during the operation, the hyperplastic gland(s) became devascularized, because the patient became normocalcemic postoperatively and remains normocalcemic at 4 years of follow-up. In a fifth patient with known parathyromatosis, a planned bilateral approach was converted to a unilateral approach after multiple pieces of parathyroid tissue were removed; IOPTH values did not decrease during this operation, but the operation was terminated given the extent of disease, knowing this was a failed operation. Therefore, IOPTH values did not influence the extent of this fifth operation.

Location of the "missed" adenoma in 39 patients. At reoperation, an enlarged, hyperplastic parathyroid gland was located in a normal position in 25 patients (64%; including 5 in a retroesophageal location), an ectopic cervical location in 6 (15%; 3 undescended, 2 intrathyroidal, 1 in the carotid sheath), and a mediastinal position in 4; 1 patient had parathyromatosis. In the remaining 3 patients, the location of the adenoma is unknown but presumed to be ectopic/mediastinal. Of the 19 patients who had either no or only normal glands removed at the initial operation, 16 (84%) had SGD, 2 had MGD, and 1 is unknown. Of the 20 patients who had disease removed at the initial operation, 18 (90%) had MGD (residual disease left in situ after the first operation) and 2 had SGD with regrowth of a partially resected adenoma as the cause of persistent disease. Therefore, of the 39 patients, 18 (46%) had incomplete resection of multiple abnormal glands.

Outcome of 43 reoperative PTXs. Of the initial 39 reoperations, 34 (87%) were curative and 5 were known failures at the end of the operation, because the IOPTH values did not meet criteria to conclude an operation (Fig 3; Table III). Four of the 5 patients underwent repeat reoperation for persistent disease; 3 patients had no abnormal glands found at the time of the first reoperation (cases 1, 2, and 3A), and 1 patient had persistent disease due to parathyromatosis (case 4A). At the time of subsequent reoperation (Fig 3; Table III),

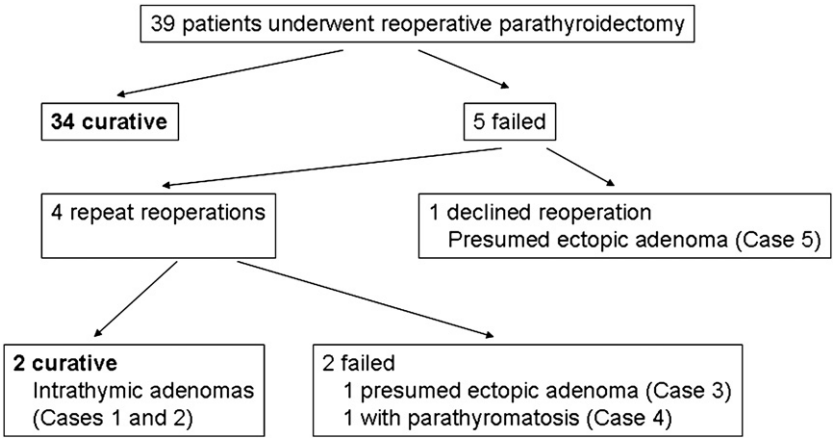

Fig 3. Outcome of 43 ReopPTX. Refer to text and Table III for a description of patients.

Table III. Characteristics of the 7 failed reoperations

Case	*Age at operation/gender*	*Operative approach*	*IOPTH criteria met*	*Operative findings/comments*
1	40/F	Bilateral	No	No parathyroid tissue identified.
2	53/M	Bilateral	No	Subtotal thyroidectomy and bilateral thymectomies performed. No abnormal parathyroid tissue identified.
3A*	42/M	Bilateral	No	Total removal of 3 glands (200, 490, and 200 mg) and right thyroid lobectomy.
3B*	45/M	Unilateral	No	Left thyroid lobectomy performed. No parathyroid tissue identified. Sestamibi and angiography/SVS localized possibly to left side.
4A†	63/F	Unilateral	No	Parathyromatosis.
4B†	66/F	Bilateral	No	Parathyromatosis.
5	56/F	Bilateral	No	Thymectomy performed. No parathyroid tissue identified.

IOPTH, Intraoperative parathyroid hormone; *SVS*, selective venous sampling.
*Cases 3A and 3B represent the same patient.
†Cases 4A and 4B represent the same patient.

2 had ectopic adenomas in the thymus localized by angiography/SVS requiring sternotomy; IOPTH criteria to conclude an operation was met, and both patients are normocalcemic at last follow-up (cases 1 and 2). In the remaining 2 patients, 1 (case 3B) had no abnormal glands removed (presumed mediastinal adenoma), and the fourth (case 4B) underwent "debulking" for parathyromatosis. Neither patient met IOPTH criteria to conclude an operation; both were known failures at the end of the case. The 1 patient (case 5) who has opted to not undergo a reoperation is presumed to have a mediastinal adenoma.

Therefore, at a median follow-up of 12 months (range, 1 week to 82 months), a total of 36 (92%) patients have undergone curative PTX: 28 were normocalcemic at ≥6 months follow-up and 8 were normocalcemic at 1 week ($n = 3$) or 3 months ($n = 5$) of follow-up with IOPTH values that met our criteria to conclude an operation. The remaining 3 patients, including 1 with parathyromatosis, have persistent disease.

IOPTH monitoring for reoperative PTX. The sensitivity, specificity, and accuracy of the IOPTH criteria were 94% (34/36), 100% (7/7), and 95% (41/43), respectively. The ability of the IOPTH criteria to predict accurately a curative operation (positive predictive value) was 100% (34/34), whereas its ability to predict a failed operation (negative predictive value) was 78% (7/9).

Complications of 43 reoperative PTX. One patient had a bilateral, recurrent laryngeal nerve injury after bilateral neck exploration; her vocal cord function returned to normal and her tracheostomy was removed 6 months postoperatively. Seven patients required both calcium and Rocaltrol supplementation for hypocalcemia; 1 required calcitriol only transiently during hospitalization,

and 2 were on calcitriol for <6 months. Therefore, the rate of permanent hypoparathyroidism was 9% (4/43). For these 4 patients, 3 met our IOPTH criteria. The 1 patient who did not had mildly increased IOPTH values after the removal of a 205-mg adenoma. No additional parathyroid tissue was identified after a bilateral neck exploration and the operation was concluded when a 90-minute postadenoma resection value was 8 ng/mL. Therefore, IOPTH values did not predict permanent hypoparathyroidism. No patients underwent parathyroid autotransplantation.

DISCUSSION

The operative management of patients with persistent and recurrent HPT remains a challenge despite advances in radiologic imaging and the use of other adjuncts, such as IOPTH monitoring. This study evaluated a contemporary cohort of 39 patients undergoing 43 ReopPTXs by 3 different surgeons using modern imaging modalities and IOPTH monitoring. Consistent with previous studies, we found that the majority of patients had missed glands that were located in the eutopic position (64%) and that a major reason for the initial failed PTX was incomplete resection of all abnormal glands (46%), supporting the notion that the initial failed PTXs were due to inadequate initial exploration and/or resection owing to surgeon inexperience.[7,8,10,12,17,18]

Our findings confirm those of previously published studies on persistent and recurrent HPT with respect to operative approach, cure rate, and complication rates. In our study, a cervical approach was possible in 93% (40/43) of patients; 60% underwent a focused or unilateral approach, 35% required a standard 4-gland exploration, and 3 required a transthoracic approach for mediastinal adenomas. These findings are consistent with previous studies that also demonstrate that all reoperations do not need to be performed with a bilateral neck exploration.[7,8,17,18] Of the initial 39 reoperations, 34 were curative (87% cure rate); 4 of the 5 failed operations underwent a second reoperation, resulting in 2 additional curative procedures (Fig 3). Therefore, our overall cure rate for ReopPTX was 92% (36/39 patients), which is similar to cure rates reported by recent studies and slightly greater than earlier studies that reported cure rates of 70% to 80%.[7,8,10,12,17,18] Our complications included 1 recurrent laryngeal nerve injury (2%) and a 9% rate for permanent hypoparathyroidism, which are also in the range of complication rates for prior studies investigating persistent/recurrent HPT.[7,8,10,12,13,17,18] The reported range of complication rates is quite wide, likely owing to the variable definitions of recurrent laryngeal nerve injury and permanent hypoparathyroidism.

Preoperative localization studies included US and sestamibi before all 43 reoperations. Of these 43 cases, localization by US and/or sestamibi was achieved in 29 (67%); 12 underwent further imaging studies (Fig 2). Additional imaging proved to be helpful in only 2 patients who localized correctly by sestamibi but underwent MRI and angiography/SVS before removal of mediastinal adenomas that required a transthoracic approach. Of these 29 cases, only 2 were failed reoperations (93% cure rate), including 1 patient with parathyromatosis and 1 patient who underwent median sternotomy subsequently for removal of a mediastinal adenoma. Given these findings, we agree with the recommendations proposed by Feingold et al[19] that all patients undergo both US and sestamibi scans before ReopPTX (Fig 4). If localization is achieved by either study or both studies, additional imaging should be performed only if a mediastinal adenoma is suspected. In these situations, we recommend either a preoperative CT or MRI to define better the size and location of the lesion relative to other structures, which assists in determining the transthoracic operative approach (median sternotomy or thoracoscopic). These recommendations are less stringent than those proposed by Jaskowiak et al,[8] who advocate proceeding to a reoperation only after 2 imaging studies are both positive and concordant.

As summarized in Fig 1, 14 cases did not have disease localized by either US or sestamibi; additional imaging localized disease in 4 patients in whom PTX was curative. The cure rate of the remaining 10 cases who had disease that did not localize on any imaging studies was 50%. Given these findings, if localization is not achieved by either US or sestamibi, we recommend proceeding with CT and/or MRI (Fig 4). If localization is not achieved with these studies, the more invasive option of angiography/SVS should be considered. We have limited experience with image-guided fine-needle aspiration of parathyroid tissue. If localization is not achieved by any study and a reoperation is performed, our cure rate is 50%. Therefore, in patients who do not localize by any imaging modality, we may consider conservative, nonoperative management.

In our series, the highest sensitivity (67%) was achieved when both US and sestamibi scans were interpreted together (TP on either or both

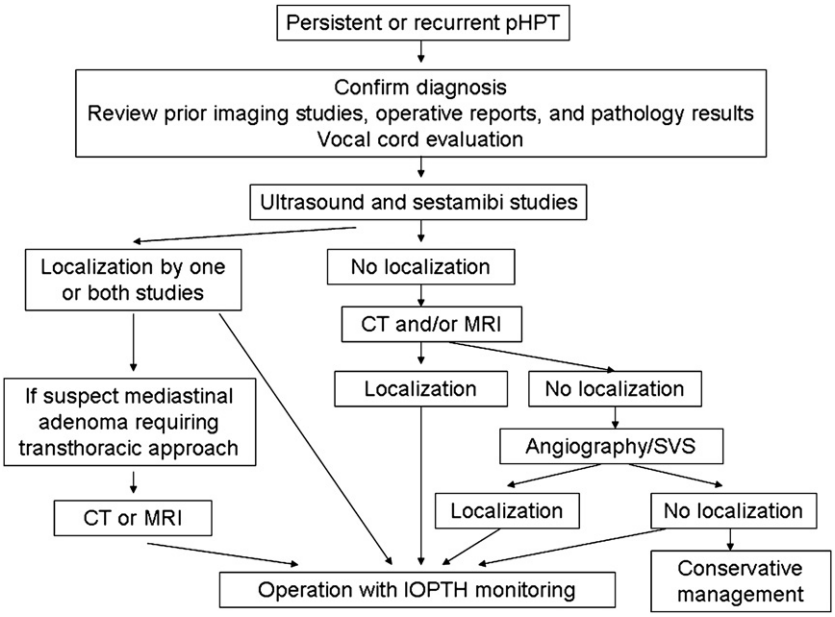

Fig 4. Proposed algorithm for the evaluation of patients with persistent and recurrent primary hyperparathyroidism. *CT*, Computed tomography; *IOPTH*, intraoperative parathyroid hormone; *MRI*, magnetic resonance imaging; *pHPT*, primary hyperparathyroidism; *SVS*, selective venous sampling.

studies). Although the numbers per imaging study are limited, our sensitivities for all imaging modalities are in the range of those reported by previous studies evaluating patients with persistent and recurrent HPT.[8,10,12,13,17,18] The reported wide range of sensitivities for each imaging modality is likely explained by the varying number of studies performed, operator-dependent nature of some studies (US, angiography/SVS), institutional preference of certain studies, and differences in quality and performance of studies within institutions and over time.

IOPTH monitoring was performed in all 43 ReopPTXs. The sensitivity, specificity, and accuracy of our IOPTH criteria were 94%, 100%, and 95%, respectively. The ability of the IOPTH criteria to predict accurately a curative operation (positive predictive value) was 100%, whereas its ability to predict a failed operation (negative predictive value) was 78%. These values are similar to those reported by 2 previous studies[13,14] and demonstrate that IOPTH monitoring can predict a curative ReopPTX by confirming the removal of all hyperplastic parathyroid tissue. Furthermore, IOPTH monitoring changed the operative approach in 4 patients. In 2 patients in whom the disease did not localize preoperatively, a bilateral cervical approach was planned and was converted to a unilateral approach after a single adenoma was removed and IOPTH values met criteria to conclude the operation. In the 2 other patients, IOPTH criteria were not met after an initial unilateral approach; subsequent 4-gland exploration was performed and both patients are normocalcemic at last follow-up. The studies by Udelsman et al[12] and Irvin et al[14] report that 35% to 47% of their patients undergoing ReopPTX benefited from the use of IOPTH monitoring, which suggested additional occult disease after the initial removal of hyperplastic tissue and/or assisted with localization of the abnormal parathyroid gland(s). We also recommend that IOPTH monitoring be performed during all ReopPTXs. We do not use other intraoperative adjuncts routinely, such as intraoperative US or radioguided techniques.

There are inherent limitations to any study evaluating a single institution's experience. We believe that our findings are generalizable because, at our institution, >1 surgeon performs PTX routinely and our imaging studies are not performed and interpreted routinely by 1 dedicated radiologist (except for angiography/SVS procedures). Another limitation is our relatively short follow-up for the majority of patients.

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DISCUSSION

Dr Christopher R. McHenry (Cleveland, Ohio): Patients with persistent or recurrent parathyroidism, as you have identified, are very challenging.

I think it is important to emphasize that you need to first confirm the diagnosis of pHPT. Once this has been done, the operative and pathology reports from prior operations should be reviewed and, if possible, the previous surgeon be contacted to try and determine how many and which parathyroid glands remain.

The goal is to identify the abnormal parathyroid glands and limit your exploration to removal of the abnormal glands to help minimize the potential complications. I have the following questions.

Would you clarify why you obtained additional localization tests in patients with a concordant positive US examination and sestamibi scan? I understand why you might do this in a patient who you suspect has a mediastinal parathyroid gland, but are there other reasons?

Can you tell us what you do when you have a >50% decline in intraoperative PTH but the level is not in the normal range?

Eleven of the 39 patients who underwent ReopPTX had their initial operations performed at your own institution. Did the intraoperative PTH measurements accurately predict the failure of the initial operation in this group of patients?

Finally, you described 1 patient with parathyromatosis, which is a particularly difficult problem to manage. This usually presents with multiple implants of parathyroid tissue that often do not image on localization studies. Can you specifically address the results of your localization studies and intraoperative PTH monitoring in this patient?

Dr Tina W. Yen (Milwaukee, Wis): With respect to the first question, why did we do additional imaging if we had concordant imaging results by US and sestamibi. Five of 17 patients who had concordant US and sestamibi scans went on to additional imaging; 3 had CT scans and 2 had CT and MRI scans.

Because this was a retrospective review of our prospectively collected data I cannot specifically say why we got additional imaging in these 5 with concordant imaging results. As I recall, at least some of these patients came with outside CT and MRI studies already performed. From my review of things, those patients that should definitely get additional imaging, specifically CT or MRI, are those with mediastinal adenomas who we think will require a transthoracic approach for removal.

With respect to the question of those patients that drop by 50% intraoperatively but do not fall into the normal range of the assay, there were a total of 3 patients. All 3 patients started out with very high baseline PTH levels, all >300. As you know, because the PTH half-life is 3 to 5 minutes, they are not going to fall appropriately into the normal range by 10 minutes. So oftentimes if we are pretty confident it is SGD, we will get additional PTH values at 15, 20, or 30 minutes post-resection and do not do further exploration. If those then fall into the normal range, we are pretty confident that we have removed all hyperfunctioning parathyroid tissue. If you think you might have MGD, are leaving behind occult disease, we usually go ahead and explore while we wait for further PTH values.

Your third question, yes, 11 patients had initial failed operations at our institution. Ten had IOPTH

monitoring and all 10 did not meet our IOPTH criteria to terminate an operation, so they were all known failures at the end of the case.

And then your last question regarding our patient with parathyromatosis, I probably should have excluded her from our analysis to make our results look better but I did not. In any case, she has undergone a total 4 different operations, two 4-gland explorations, and then with us most recently 2 reoperations, of which on reoperative imaging she never really localized on US, sestamibi, or CT scans at all. Intraoperatively after multiple pieces of hyperplastic tissue were removed, her IOPTH levels never fell either. So she was always a known failure at the end of all of her cases.

Dr L. Michael Brunt (St. Louis, Mo): Dr Yen, I have a couple of questions. In my own practice, the reoperative setting is one in which I will often use imaging adjuncts intraoperatively to help facilitate a focused exploration. So in the 29 patients who had positive US and/or sestamibi-positive localization preoperatively, did you use any of those, either a gamma probe or intraoperative US, to help facilitate the focused exploration in those patients?

And then a related operable approach question is, I would presume that most of the patients at the initial operation had an anterior approach through the midline straps. Did you alter your surgical approach and approach them through a lateral back door to stay out of a lot of the scar tissue in the central neck?

Dr Tina W. Yen (Milwaukee, Wis): Of the 29 cases that localized by US and/or sestamibi, we did not use the gamma probe or intraoperative ultrasounds. In all 43 reoperative cases, we used a radioguided approach in 4.

With respect to the lateral approach to reoperation, we actually did not record how many of those undergoing cervical reexploration had a lateral approach. As you state, it is a commonly used option for neck reoperations to avoid scar tissue.

Dr Michael S. Nussbaum (Cincinnati, Ohio): Just a quick question. In patients that you have had to do angiographic localization, do you have any experience with angiographic ablation?

Dr Tina W. Yen (Milwaukee, Wis): A total of 4 patients underwent angiography with venous sampling. None of them had ablation.

Dr Katharine Yao (Maywood, Ill): What do you define as cure rate? I know there is a definition for operative cure, and I do not do these surgeries on a regular basis, but you follow these patients' calcium levels 5, 10, or 15 years out and do you see that sometimes there are failures 15 years out where they may have had an operative cure?

Dr Tina W. Yen (Milwaukee, Wis): Yes. The cure rate for this study was defined as normocalcemic, ideally for ≥6 months or longer follow-up. If they did not have follow-up >6 months, as was the case for 8 patients, cure was defined as meeting OPTH criteria and being normocalcemic within that 6-month time frame. Our protocol is routinely to try to follow patients for ≥1 year postoperatively. But you are absolutely right, 1 of the limitations of our study is short follow-up. Our median follow-up was 12 months.

Dr Richard A. Prinz (Chicago, Ill): I would like to first focus on the 11 patients who were operated on at your own center and who had persistent or recurrent disease. I think the parathyroid surgeon really has 2 obligations to a patient when you are exploring the neck. The first, of course, is to cure the patient. And short of curing that patient, to try to be as convinced as you possibly can that the disease is not in the neck. So can you tell me what things you do when you have not accomplished the first goal to accomplish the second goal?

Second, with regard to these patients, I think I approach them differently. In other words, my failures, I really want to study anything, everything, and whatever imaging test is out there we will get before going back on them; whereas we approach someone who has been operated elsewhere, we do an US in the office and it shows us a lesion, we would be willing to operate on that. So I think there is a very different approach, in my mind, when you are working with your own failures. And I would like you to comment on that.

Intraoperatively, the PTH monitoring I think directs you that you have not cured the patient. The bulk of the disease is not in the neck. In my experience, when it is in the chest PTH levels during the operation do not change; they just pretty much stay at the same level no matter what you do. Has that been your experience?

Finally, you had 3 patients where you did a sternal split for a mediastinal lesion. I wonder if that is actually necessary when we have such excellent thoracoscopic surgeons around.

Dr Tina W. Yen (Milwaukee, Wis): At the time of reoperative exploration and central neck dissection, we do a bilateral neck exploration exploring all the places where an ectopic gland should be. If that entire exploration is unremarkable, there are several options. Should you do thyroid lobectomies in these patients if you think they might have an intrathyroidal adenoma? Should you do a lobectomy, if you do intraoperative US and they may localize something within the thyroid gland? Or, if you perform an intraoperative FNA and your PTH level is high, should you therefore then do a thyroid lobectomy on that patient at the time of your reoperation? All of these options can be considered.

Another option to consider is tying off vessels on the side you think the adenoma may be on. People who have IOPTH monitoring can entertain doing PTH sampling in the internal jugular veins to see if they can localize the adenoma on 1 side of the neck. Others advocate massaging 1 side of the neck and checking PTH levels to see if they rise, thereby localizing the adenoma to that side of the neck. These are all possibilities.

I think the majority of us would not favor going into the mediastinum unless we have imageable disease. If all of these maneuvers above failed and we still have not cured the patient at the time of the operation, I think the majority of us would not go into the mediastinum right then and there. We would close the patient, know

that they are a known failure, and then image them appropriately to see if we can localize a mediastinal adenoma.

I agree that, of our patients who had a mediastinal adenoma intraoperatively, none of them had PTH levels that fell significantly during their cervical exploration. For the 3 patients who required a transthoracic approach, 2 underwent median sternotomies for thymic adenomas and 1 underwent a VATS procedure for an adenoma that was located in the anteroposterior window. The question, could they all have been done thoracoscopically? Perhaps. But this again was a retrospective study.

Dr Janice L. Pasieka (Calgary, Alberta, Canada): Three questions: If I got your data right, 51% of the failed initial operations were for MGD. I am wondering if you can then comment, is this related to the paradigm shift in parathyroid surgery of a more focused approach? In other words, who did this? Were these focused minimal PTX that were misled by their initial imaging and were they being done by experienced hands, or did they have a 4-gland exploration and could not find anything?

The second question is related to the 10 patients in whom you had no localization, and it sort of alludes to what Dr McHenry and Dr Prinz are talking about—that the preoperative workup, the operative report, and the pathology on the initial operation in my mind is the first localization technique, because you can sometimes get an idea of what was missed or what they did not see. How much did that influence you in these 10 patients where you had no localization? And really, what was your plan? And then the last question was about the 9% chance of hypoparathyroidism. Have you considered cryopreserving tissue when you go into a reoperative setting?

Dr Tina W. Yen (Milwaukee, Wis): Thank you, Dr Pasieka. With respect to your first question, of the 51% with MGD, what were the initial approaches to these failed operations? Twenty patients had MDG, of which 16 were persistent cases and 4 (all MEN-1) had recurrent disease. Twelve underwent their initial operation at an outside institution (4 unilateral and 8 bilateral explorations). Eight underwent their initial operation at our institution. All underwent a bilateral neck exploration except one who had a minimally invasive parathyroidectomy. In some cases, it was difficult to interpret what was actually done at the initial operation, as operative reports and pathology reports varied in detail regarding location, size, weight, and microscopic findings of parathyroid glands.

The initial work-up and operation and review of all previous imaging studies certainly influenced our reoperative approach. I did not have time to show the data, but in the manuscript I go over the planned operation for each patient, which is dependent on the review of all records (operative and pathology reports) and all their preoperative imaging and compare that planned approach with the actual operative approach. Of the 10 patients who did not localize on any imaging study, 9 were planned bilateral neck explorations. One was a planned unilateral because he had had extensive multiple operations in the past at our institution and basically everything had been exonerated on 1 side of the neck so the goal was just to look at the other side on reoperation.

Our rate of hypoparathyroidism is about 10%. At our institution we do not cryopreserve for several reasons, but it is definitely something to consider.