

# Reoperative Parathyroid Surgery in the Era of Sestamibi Scanning and Intraoperative Parathyroid Hormone Monitoring

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**Hypothesis:** Results of reoperative parathyroid surgery (RPS) have improved with the advent of sestamibi parathyroid subtraction scanning and intraoperative parathyroid hormone (IOPTH) monitoring.

**Design:** Retrospective review of patient histories, preoperative localization studies, operative data, including IOPTH monitoring, and outcomes for patients undergoing recent RPS at a single institution. Follow-up was complete (mean, 20 months).

**Setting:** Tertiary care referral center.

**Patients:** All patients undergoing RPS for benign persistent or recurrent primary hyperparathyroidism during the period 1989 to 1997.

**Main Outcome Measures:** Overall cure rate and operative morbidity from RPS; sensitivity and accuracy of preoperative localization studies; and prediction of cure from IOPTH monitoring.

**Results:** The study group included 124 patients (87 women and 37 men). Hypercalcemia was corrected in 109 patients (88%). Permanent recurrent laryngeal nerve in-

jury occurred in 0.8% and permanent hypoparathyroidism in 13% of patients. Test sensitivities and accuracies, respectively, were as follows: ultrasound with biopsy, 90% and 82%; sestamibi parathyroid subtraction scanning, 82% and 67%; and ultrasound alone, 75% and 65%. Level of IOPTH was predictive of cure in all patients with a 70% or greater fall from baseline at 20 minutes after excision. Persistent multigland disease was the major cause for reoperative failure (73%).

**Conclusions:** Neither cure rates nor operative morbidity have changed appreciably over the past 2 decades, despite the introduction of sestamibi parathyroid subtraction scanning and IOPTH monitoring. Multigland disease continues to represent the principal cause of failure in RPS despite the routine use of preoperative localization studies. Thus far, increasing the stringency of IOPTH monitoring from a 50% to 70% decline from baseline levels has been predictive of cure, even in multigland disease. Most missed abnormal glands reside in normal anatomic locations, and the need for multiple operations, not just the reoperation, results in the increased morbidity seen with RPS.

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**I**N 1991, A 2-YEAR institutional experience from the Mayo Clinic<sup>1</sup> was published reporting the results of 384 consecutive patients undergoing first-time operations for benign primary hyperparathyroidism. Of these patients, 99.5% were cured, with permanent morbidity in less than 1%. The same group<sup>2</sup> in 1986 published the results of reoperative parathyroid surgery (RPS) for persistent or recurrent hyperparathyroidism and, in sharp contrast, the cure rate was only 89%, with permanent morbidity noted in 17%. A comparable cure rate of 90% was reported by the National Institutes of Health group. In their group, 35% to 43% of patients left the hospital taking cholecalciferol (vitamin D) or calcium, and 6% experienced vocal cord paralysis.<sup>3</sup> The in-

roduction of sestamibi parathyroid subtraction scanning (SPS)<sup>4</sup> and intraoperative parathyroid hormone (IOPTH)<sup>5</sup> monitoring during the most recent decade raised hopes that these tests would reduce the number of operative failures. Therefore, we sought to determine whether SPS and IOPTH monitoring might affect outcomes and morbidity in patients having recently undergone RPS at a single endocrine referral center.

## RESULTS

Of the 124 patients, 37 were men and 87 were women. Ages ranged from 10 to 87 years (mean, 53 years). One hundred one patients were diagnosed as having sporadic disease; 15, multiple endocrine neo-

## PATIENTS AND METHODS

### OVERVIEW

This retrospective review involved all nonmalignant cases of RPS performed at Mayo Clinic, Rochester, Minn, from 1989 through 1997. Outcomes were evaluated (alleviation of hypercalcemia, permanent laryngeal nerve injury, and permanent hypoparathyroidism), along with the results of preoperative localization studies and IOPTH monitoring.

Sestamibi parathyroid subtraction scanning using technetium Tc 99m sestamibi of the neck and chest with single photon emission computed tomography (SPECT) imaging was performed according to the protocol previously outlined from our institution.<sup>6</sup> The standard dose of sestamibi at the present time is 740 MBq. A true-positive scan is defined as one that delineates the location of a single abnormal gland to a single region (such as the right side of neck, left side of neck, mediastinum, or forearm), with subsequent surgical confirmation and biochemical cure. In the case of multigland disease, the scan is considered true-positive only if it displays all regions of overactivity. If the scan misses one region, it is considered a false-negative scan.

### IOPTH MONITORING METHODOLOGY

The rapid 15-minute PTH immunochemiluminometric assay was performed according to the protocol of Kao et al.<sup>7</sup> Variable thresholds for the decline in PTH levels have been used, ranging from 50% to 70%,<sup>8</sup> but we accepted a 50% or greater drop from the baseline PTH value at 20 minutes as indicative of cure.

### STATISTICAL METHODS

Sensitivity and accuracy were determined for preoperative localization tests, with 95% confidence intervals calculated for all estimates of sensitivity and accuracy. The  $\chi^2$  or Fisher exact test was used to compare rates of complications.  $P < .05$  was considered statistically significant.

All patients had at least 2 serum calcium determinations after operation. Serum calcium levels greater than 2.5 mmol/L, associated with inappropriate levels of serum PTH, were considered failures.

plasia; and 8, familial non-multiple endocrine neoplasia hyperparathyroidism. The number of prior neck explorations were as follows: one, 95 patients; two, 24 patients; and three or more, 5 patients. One hundred one patients (82%) had undergone surgery at other centers while 23 patients (18%) had undergone previous surgery at Mayo Clinic. This latter group of patients accounted for approximately 1.3% of our total parathyroid surgical practice during that same time. Single enlarged glands had been missed in 15% of the Mayo initial explorations compared with 82% of the referral cases.

All available operative and pathology reports, as well as slides from previously resected parathyroid tissue, were reviewed prior to each reexploration. Preoperative lo-

calization included cervical high-resolution real-time ultrasonography, ultrasonography with fine needle aspiration biopsy for cytologic confirmation and PTH assay, and SPS. Computed tomography, magnetic resonance imaging, and venous sampling were rarely used. The locations of the abnormal excised parathyroid glands were recorded. Follow-up ranged from 1 month to 8 years (mean, 20 months). Beginning in 1994, IOPTH monitoring was instituted at Mayo Clinic. Complete information was available on 16 patients in whom it was used.

### PREOPERATIVE CLINICAL DATA

Pertinent preoperative laboratory values prior to RPS were as follows: serum calcium, 2.43 to 3.45 mmol/L (mean, 2.78 mmol/L; reference range, 2.22-2.50 mmol/L); phosphorus, 0.48 to 1.39 mmol/L (mean, 0.81 mmol/L; reference range, 0.81-1.45 mmol/L); PTH, 2.1 to 20 pmol/L (mean, 9.4 pmol/L; reference range, 0-5.1 pmol/L); and urinary calcium, 2.55 to 21.15 mmol/d (reference, <6.88 mmol/d).

Indications to proceed with reoperation were varied. Most patients had had 1 or more of the following indications: nephrolithiasis (64 patients [52%]); significant bone disease based on bone mineral densitometry (44 patients [35%]); or symptoms of "feeling unwell," including malaise, depression, and musculoskeletal aches and pains (47 patients [38%]).

### LOCALIZATION STUDIES

All but 3 patients had preoperative localizing studies. These 3 patients had undergone minimal explorations elsewhere by inexperienced surgeons and were cured following our reexploration during the early postoperative period. High-resolution (10-MHz) real-time neck ultrasonography was used for 113 patients; an accuracy rate of 65% and sensitivity of 75% were achieved. When high-resolution real-time ultrasonography was combined with cytologic and biochemical (PTH) confirmation by fine needle aspiration of a suspected abnormal parathyroid, accuracy improved to 82% with a sensitivity of 90%. Sestamibi parathyroid subtraction scanning was used for 55 patients and had an accuracy rate of 67% and sensitivity of 82% (**Table**). Increasing numbers of concordant true-positive studies resulted in improved surgical success rates; however, this was not statistically significant (**Figure 1**).

### GLANDS REMOVED, CRYOPRESERVATION, AND AUTOTRANSPLANTATION

Of the 124 patients who underwent reexploration, 108 had a single gland removed, 6 had 2 glands removed, and 3 had 3 glands removed. Two patients had tissue removed that was identified as containing ectopic parathyroid cells and 5 patients had no abnormal tissue removed.

The overwhelming majority of glands removed were in normal anatomic position (76%). Of glands not in normal positions, 8 were found in the mediastinum, 7 were intrathyroidal, 6 were within the carotid sheath, 3 were anterior to the trachea, and 2 were retroesophageal (**Figure 2**).

## Preoperative Localizing Studies\*

Test	No. of Patients Undergoing Test	Result, No.				Sensitivity, % (95% CI)†	Accuracy, % (95% CI)‡
		TP	FN	FP	TN		
Ultrasound	113	65	22	18	8	75 (64-83)	65 (56-73)
SPS	55	37	8	10	0	82 (68-92)	67 (53-79)
Ultrasound with biopsy	33	27	3	3	0	90 (73-98)	82 (65-93)
Technetium and thallium scan	33	18	13	2	0	58 (39-75)	55 (36-72)
CT of mediastinum	15	4	6	1	4	40 (12-79)	53 (27-79)
CT of neck	14	6	6	2	0	50 (21-79)	43 (18-71)

\*TP indicates true-positive; FP, false-positive; TN, true-negative; FN, false-negative; CI, confidence interval; SPS, sestamibi parathyroid subtraction scanning; and CT, computed tomography.

† $TP/(TP+FN)$ .

‡ $(TP+TN)/No. of tests$ .

Thirty-three patients had tissue cryopreserved. Of these, 8 patients became permanently hypocalcemic. Four of these 8 patients had reimplantation of cryopreserved tissue with only one presently eucalcemic (25%). Thirteen patients had immediate autotransplantation primarily to the forearm. Of these patients, 4 (32%) remain hypoparathyroid.

## IOPTH MONITORING

Of the 16 patients who had IOPTH monitoring, 15 (94%) were cured. All cured patients experienced a greater than 70% drop in IOPTH level at 20 minutes following excision. Intraoperative PTH was confirmatory in all 5 cases of suspected single-gland disease and was confirmatory in 9 of the 11 cases of multigland disease in which it was used. In 1 case of multigland disease, it directly influenced the course of the operation and prompted the need to explore the contralateral side. In the 1 failure with multigland disease, the IOPTH drop of 50% to 60% was misleading and resulted in premature termination of the operation. In another case of multigland disease, the IOPTH level did not fall below 50% of the baseline, yet the patient was cured.

## RESULTS OF SURGERY

Cure of hypercalcemia was achieved in 109 patients (88%). Cervical reexploration was performed in 106 patients (85%), mediastinal exploration alone in 9 patients (7%), and combined cervical-mediastinal exploration was performed in 9 patients (7%). Ninety-two patients had a unilateral cervical exploration and 32 patients had both sides explored. The mean operative time was 111 minutes (median, 102 minutes). There were no operative or perioperative deaths. Morbidity was incurred in 18 patients (15%), with permanent hypocalcemia accounting for 16 (89%) of the 18 cases and recurrent laryngeal nerve injury and hematoma each occurring in 1 patient. While cure rates and morbidity were not statistically different from those of our previous review,<sup>2</sup> morbid conditions directly related to the technical aspects of the operation were reduced.

## RPS FAILURES

Fifteen patients (12%) remained hypercalcemic following their RPS at Mayo Clinic and deserve careful review.

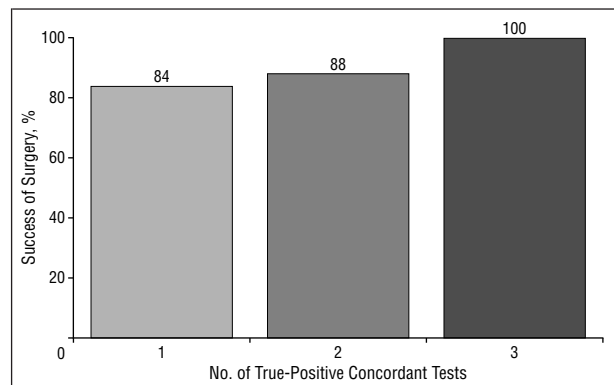


Figure 1. Operative success rate in relation to number of concordant true-positive localizing studies. Three patients had no preoperative localization studies.

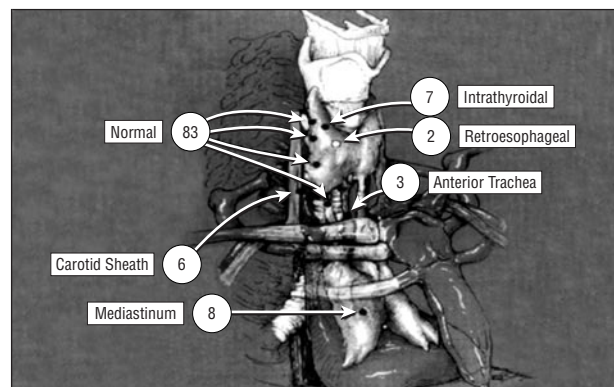


Figure 2. Anatomic location of abnormal glands removed at reoperative parathyroid surgery. The numbers represent number of glands removed at that site.

Even though 12 (80%) of these patients had sporadic disease, 11 (73%) had multigland disease based on previous records, histologic examination, and preoperative localization tests. No abnormal tissue was found in 5 of the 15 patients. One of these patients subsequently had a successful mediastinal exploration performed elsewhere, where a single adenoma was removed. Abnormal tissue was, however, excised and histologically verified in 10 (67%) of the 15 failures. Preoperative localization studies led to this abnormal parathyroid tissue in 8 of the 10 patients. Among the 15 failures, 8 patients had undergone preoperative SPS. All 8 tests, by the

criteria used, were either false-positive or false-negative. In all 4 sestamibi scans performed in patients where no tissue was found, all were false-positive. Intraoperative PTH monitoring was used in only 1 (7%) of these 15 failures. This patient had a 50% to 60% drop from baseline at 20 minutes after removing 1 abnormal parathyroid gland that was visualized by a preoperative sestamibi scan. However, this patient with multiple endocrine neoplasia type I remained hypercalcemic postoperatively.

#### COMMENT

Although success rates for first-time parathyroid operations remain high with very low morbidity when performed at centers with considerable experience,<sup>1</sup> reoperations for persistent or recurrent primary hyperparathyroidism (nonmalignant) remain a challenge to achieve similar results.<sup>2,3</sup> Morbidity, particularly permanent hypoparathyroidism, remains much more problematic in RPS than in first-time operations, even in very experienced hands. In the reoperative setting, tissue planes are scarred, making safe visualization and protection of normal structures more challenging. Because of this, the indications for reoperation must be more conservative than with first-time operations. Ongoing nephrolithiasis, impairment of renal function, or worsening osteopenia are clear indications for reoperation. Serum calcium levels greater than 3 mmol/L, severe aches and pain, fatigue, and depression may also warrant reoperation.

To reemphasize the disparities in primary parathyroid surgery vs RPS, initial exploration can produce a cure rate of 99.5% and operative morbidity of less than 0.8%.<sup>1</sup> The success rate for RPS by the same group in 1986 was only 89%, with 4% of patients experiencing recurrent laryngeal nerve paralysis; 13% were left with permanent hypoparathyroidism. During the past decade, we have seen the introduction of SPS with reported sensitivities greater than those achieved with prior nuclear medicine studies and other localization studies. Our own experience<sup>6</sup> confirmed this impression with reported sensitivities greater than 80%. In 1993, after the original report on IOPTH<sup>9</sup> and further substantiation by Irvin et al,<sup>5</sup> we developed our own rapid immunochemiluminometric assay, which has been used selectively since that time.<sup>7</sup> With the advent of this new technology, we wished to determine whether our operative success rate had improved along with diminished perioperative morbidity. The overall cure rate in this study was 88%, statistically no different from our previously published results.<sup>2</sup> Although the occurrence of permanent recurrent laryngeal nerve injury fell from 4% to 1% during the past 2 decades, the incidence of permanent hypoparathyroidism stayed the same at 13%. Whereas the course of the recurrent laryngeal nerve is virtually unaltered by prior neck exploration—albeit often obscured by dense scar—the ability to identify not only a normal parathyroid gland amidst the scar, but saving it and its blood supply while searching diligently for a missing hyperplastic gland can be extremely difficult. Moreover, permanent hypoparathyroidism cannot always be avoided in the reoperative setting despite extreme care, primarily because of the earlier

removal or devascularization of normal parathyroid tissue. Permanent hypoparathyroidism is a complication of the previous unsuccessful operation, and cannot be blamed solely on the most recent reoperation.

Sestamibi parathyroid scanning was used in 55 (44%) of the patients undergoing preoperative localization. The overall sensitivity and accuracy rates for the present study were 82% and 67%, respectively, rates consistent with our previous findings and those of other centers.<sup>6,10-12</sup> Earlier in the course of our investigations with sestamibi, lower doses of the radionuclide were used that we now know resulted in lower sensitivity rates. With the use of higher doses (555-740 MBq), sensitivities have increased to between 80% and 90%. This study, however, continues to be plagued by significant false-positive studies, particularly in the setting of nodular thyroid disease, as well as false-negative studies in patients with multigland disease.<sup>6</sup> Studies using iodine 123 in place of technetium Tc 99m pertechnetate have shown more encouraging results with multigland disease but further confirmation is necessary.<sup>13,14</sup> Because fewer than half of the patients in this cohort underwent SPS, it may be unfair to say that sestamibi has had no effect on the outcome of RPS. Nonetheless, if we look at our 15 reoperative failures, 8 of those 15 patients had sestamibi scans performed, all of which were either false-positive or false-negative.

Intraoperative PTH monitoring has been used selectively at our institution over the past 4 years and was used in only 16 of these reoperations. It did, however, based on the original criteria, confirm a curative result in all 5 patients with suspected single-gland disease and in 9 of 11 patients with multigland disease. In 1 patient with multigland disease, it directly influenced the course of the operation and prompted the surgeon to explore the opposite side, where a second abnormal gland was identified, despite negative preoperative localization on that side. In one case of multigland disease, the patient was cured, based on calcium and PTH determinations postoperatively, despite the fact that the IOPTH level did not initially drop below 50%. In yet another patient with multigland disease, the operation was terminated prematurely, based on a 50% to 60% drop in the IOPTH level. This is the one failure (patient with multiple endocrine neoplasia type I) in the group of patients having undergone IOPTH monitoring. All patients with a greater than 70% drop in IOPTH at 20 minutes were cured.

The majority of missed abnormal parathyroid glands were found in usual anatomic locations (n = 83). A small number were intrathyroidal or were found within the carotid sheath, in locations well within the reach of a cervical collar incision. Only 6% of patients had parathyroid tumors within the mediastinum, out of the reach of the collar incision. Most referred patients requiring RPS had a missed single adenoma (82%) as opposed to our own first-time failures where missed single adenomas accounted for only 15%. This information underscores the importance of experience as well as a thorough understanding and knowledge of the anatomy and embryology of the cervical and mediastinal regions as it applies to the initial exploration.

Despite our 88% success rate overall in alleviating hypercalcemia, 12% of patients remained hypercalce-

mic and another 13% were rendered permanently hypocalcemic following reoperation; thus, 25% of the entire group ended up with either persistent hypercalcemia or hypocalcemia. We compared morbidity associated with RPS in 1998 vs 1986. The morbidity rate for vocal cord paralysis was 0.8% in 1998 and 4.0% in 1986 ( $P = .14$ , Fisher exact test); for hypoparathyroidism, it was 13% in both 1998 and 1986 ( $\chi^2 = 0.002$ ;  $P = .97$ ). Autotransplantation is by no means fail-safe. Although cryopreservation was often used, autotransplantation of cryopreserved tissue resulted in alleviation of hypocalcemia in only 25% of patients. Immediate forearm autotransplantation, used in select cases, was unsuccessful in 32% of patients in whom it was performed.

Despite their failings, the importance of preoperative localizing studies cannot be overemphasized in the reoperative setting. This has been well documented in earlier studies.<sup>2,10</sup> Ultrasound-guided fine needle aspiration and SPS were the 2 most sensitive studies in our experience. There appeared to be improved outcomes with increasing numbers of concordant tests, although this was not statistically significant because of small numbers ( $n = 3$ ) in the group with 3 concordant tests. We must not incriminate or imply a lack of benefit from SPS and IOPTH monitoring based on the results in this series. Sestamibi scanning was used in only 55 patients and IOPTH monitoring in 16 patients. Clearly, these tests were helpful and often complementary in several cases.

The following are concepts that have proved helpful in the management of patients with persistent and recurrent hyperparathyroidism at Mayo Clinic: (1) The diagnosis of primary hyperparathyroidism must be unequivocally reestablished biochemically. Benign familial hypocalciuric hypercalcemia should be ruled out. (2) Reasonable attempts should be made to review previous operative reports and pathology slides. (3) Localization studies should be used liberally. Every attempt should be made to obtain preoperative localization in all cases. It will reduce operative time in most cases. Sestamibi scanning and ultrasound-guided biopsy appear to be the best tests. Increasing numbers of concordant tests are comforting to the surgeon but are not essential in every case. (4) A preoperative vocal cord evaluation must be performed and the severity of the disease should be assessed, as both of these factors may influence the decision to reoperate. (5) The operation is more appropriately directed and limited than at initial exploration, based on preoperative localization. A lateral approach between the infrahyoid muscles and sternocleidomastoid muscle may offer easier access especially to expose superior glands. (6) Reasonable attempts should be made to identify the course of the recurrent laryngeal nerve, as this will greatly reduce the anxiety associated with tissue removal in a scarred plane. Once the abnormal gland or glands are removed, small biopsy specimens should be taken and submitted for frozen section histologic confirmation. The remainder should then be cryopreserved for possible reimplantation in the future. Despite somewhat limited success with reimplantation of cryopreserved tissue, the process offers some hope to the patient, who ends up hypoparathyroid, that at least some chance of eucalcemia still exists. Although IOPTH moni-

toring was confirmatory in every case of a missed single adenoma detected preoperatively by SPS, to predict which patient harbors a single adenoma as opposed to those with multigland disease often remains enigmatic. Ideally, virtually all reoperative patients with hyperparathyroidism should have immediately available IOPTH monitoring. Our data would support increasing the degree of decline in PTH level of 50% to 70% from baseline at 20 minutes as more accurate in patients with multigland disease. Further studies are needed to verify this. (8) In the absence of positive ultrasound or SPS results, further efforts at localization should be considered (eg, magnetic resonance imaging, venous sampling).<sup>15,16</sup> Although one needs to consider cost, further operative failures and morbidity outweigh financial concerns with regard to preoperative and perioperative tests.

Although radioguided surgery<sup>17</sup> has been used in patients undergoing RPS, we are not certain that this adds anything beyond good-quality preoperative SPS with SPECT in the hands of an experienced parathyroid surgeon.

The results of RPS at centers with considerable experience in parathyroid surgery underscore the importance of achieving success at the first operation.<sup>18-21</sup> The implications of these statements are far-reaching, particularly at the dawn of this new era of minimal access parathyroidectomy.

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## DISCUSSION

**Jay K. Harness, MD, Oakland, Calif:** This report by our colleagues at the Mayo Clinic brings into focus the consequences of failed initial exploration in patients with benign primary hyperparathyroidism. In the United States, failed initial neck explorations most commonly result from (1) explorations performed by surgeons with limited experience in parathyroid surgery, (2) multiple-gland disease, and (3) parathyroid adenomas located in the mediastinum out of reach through a low collar incision. Failure at initial parathyroid exploration subjects patients to increased risk of morbidity at subsequent operations. In this series from the Mayo Clinic, 13% of patients were rendered permanently hypocalcemic after reexploration, and 12% remained persistently hypercalcemic.

In the manuscript, the authors have suggested 8 concepts to be used in the evaluation and management of patients with recurrent or persistent hypercalcemia. I want to wholeheartedly endorse their recommendations. They encourage the liberal use of preoperative localization studies. High-resolution ultrasound with FNA [fine needle aspiration] biopsy and sestamibi parathyroid subtraction scanning have been found by the authors to be their most accurate preoperative studies. They also noted that an increasing number of true-positive tests increase the ultimate success at surgical exploration, but they do not suggest what the order or sequence of these studies should be. It is important to note that the false-positive rate for ultrasound with FNA biopsy was 10% and with sestamibi parathyroid scanning was 18%.

I have 3 questions for the authors. What were the reasons for the false-positive tests with ultrasound plus FNA biopsy and similarly for the false-positive results with sestamibi scanning? A small number of single and large glands were missed in patients initially operated upon at the Mayo Clinic. What were the reasons for these failures, particularly in the hands of such highly experienced surgeons? My final question is, what would the authors suggest as an algorithm for the type and sequence of perioperative localization studies in suspected single-gland and multiple-gland disease? I believe that this is particularly important since not all reoperative parathyroid surgery in the United States will be performed at the Mayo Clinic or other similarly highly experienced institutions.

**Orlo H. Clark, MD, San Francisco, Calif:** I would also like to congratulate the authors on an excellent paper and Dr Thompson on a superb presentation. I have several questions. (1) Why did the surgeons fail to find abnormal parathyroid glands in 5 patients? What were the localizing studies in these patients? (2) Why was the rate of hypoparathyroidism so high? As Prof Mathias Rothmund from Germany has stated, "one can almost always correct primary hyperparathyroidism, but one cannot usually correct hypoparathyroidism." How many of these patients received parathyroid autotransplants? Were the results different in patients who had already had 3 or 4 parathyroid glands removed? Did the authors autotransplant or cryopreserve parathyroid glands? What were the results in patients having parathyroid autotransplants or in those who received cryopreserved tissue? Hypoparathyroidism is a poor outcome after any parathyroid operation because these patients are sometimes difficult to manage metabolically.

I have one other question, Dr Thompson. How do you know if a patient has single-gland disease? A surgeon often has a good idea from the previous operative and histological findings, but is not certain. The only reason to use intraoperative PTH (IOPTH) is because the surgeon does not know whether the patient has single- or multiple-gland disease. This is true at the initial operation and at reoperation. Fortunately, a patient only has a single parathyroid tumor when the patient is cured after removing 1 tumor. The surgeon does not know the definite outcome until the next day when the blood calcium and PTH levels are normal.

**Richard A. Prinz, MD, Chicago, Ill:** I think there is a wealth of information for parathyroid surgeons in this paper. I have a number of questions. First, was there a difference in outcome based upon the number of prior operations? Second, do you use cryopreservation of parathyroid tissue in these patients, and, if so, have you had to utilize this tissue for patients who were hypoparathyroid after your reoperation? What are your results with autotransplantation of fresh and cryopreserved parathyroid tissue? Finally, some of your missed glands were in the mediastinum. What is your approach for mediastinal glands? Do you use thoracoscopic exploration for glands deep in the mediastinum?

**Dr Thompson:** Let me begin first with cryopreservation and autotransplantation. There were 33 patients who did indeed have tissue that was cryopreserved. Subsequent transplantation occurred in 4 of those patients, and in only 1 of those 4 was the patient rendered eucalcemic. There were 13 patients who had immediate autotransplantation and despite the immediate autotransplantation, only 9 of those patients ended up being eucalcemic. We still had 4 patients who were hypocalcemic. Our results for immediate autotransplantation were not as high as one might have expected.

Dr Harness raised a number of important points. He wanted to understand better how patients with an FNA biopsy could have a false-positive test. What we have learned from this experience is that you need to look at the PTH results and not just the cytology. There were some patients in whom only cytology was performed, and the cytology was said to demonstrate parathyroid cells. But as those of you know who do a lot of this type of surgery, it can be very difficult to differentiate the cytology of follicular cells of the thyroid and chief cells of the parathyroid. So it is critically important to go ahead and do an aspirate as well for the PTH assay.

The reasons for false-positive sestamibi scans primarily relate to patients with nodular thyroid disease, and in most of these patients we either found an adenomatous nodule, an inflammatory lymph node, or a follicular or Hürthle cell adenoma of the thyroid.

Why did we at Mayo miss single adenomas? All of those cases were mediastinal glands and they were subsequently cured following mediastinal exploration.

As far as an algorithm for localization, I think this is still ongoing as far as the concept is concerned. My own personal preference is to get a sestamibi scan first. Even experienced ultrasonographers now say that we should get a sestamibi scan first. Number one, it shows you the mediastinum as well as the neck. Ultrasound cannot do that. I think that the sensitivity and accuracy of sestamibi alone is superior to ultrasound alone. If you are dealing with a very difficult case in which there have been multiple reoperations and both you and the patient cannot afford to have another failure, it would be very reasonable to then go ahead and get one of your expert ultrasonographers and insist that they biopsy any and all suspicious areas and aspirate the effluent for PTH.

**Dr Clark:** What were your results when all of the localization studies were negative or did it make any difference?

**Dr Thompson:** In this series there were only 3 patients who were explored without preoperative localization. The reason those patients were explored is because it was very evident that those patients had been operated on by a very inexperienced surgeon who didn't find any parathyroid tissue, the patient was within the first week of their first operation, and

the decision was made to go in and reexplore all those patients. In none of the other patients did we go in without a positive preoperative localization study. We have had a couple of patients where we had negative preoperative localizing studies (ultrasound, sestamibi) and we have then gone to venous sampling. In both of those cases it did lateralize to one side of the neck. What we found in each case was an intrathyroidal parathyroid adenoma. Having that information encouraged us to go ahead and remove that thyroid lobe before exploring anywhere else.

Dr Prinz, I can't really comment on the relationship of outcome to the number of prior operations. The vast majority had only 1 prior operation, although there were some who had 2 and some who had 3 or more prior procedures. As far as the approach to the mediastinal gland, we have approached these in a number of different ways. Occasionally thoracoscopic, occasionally via a Chamberlain procedure. The majority of these patients going back to 1989 underwent exploration through a classical median sternotomy. Certainly these other avenues of minimal access surgery need to be explored further.

#### IN OTHER AMA JOURNALS

##### JAMA

##### Resource Utilization in Liver Transplantation: Effects of Patient Characteristics and Clinical Practice

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**Context:** Liver transplantation is among the most costly of medical services, yet few studies have addressed the relationship between the resources utilized for this procedure and specific patient characteristics and clinical practices.

**Objective:** To assess the association of pretransplant patient characteristics and clinical practices with hospital resource utilization.

**Design:** Prospective cohort of patients who received liver transplants between January 1991 and July 1994.

**Setting:** University of California, San Francisco; Mayo Clinic, Rochester, Minn; and the University of Nebraska, Omaha.

**Patients:** Seven hundred eleven patients who received single-organ liver transplants, were at least 16 years old, and had non-fulminant liver disease.

**Main Outcome Measure:** Standardized resource utilization derived from a database created by matching all services to a single price list.

**Results:** Higher adjusted resource utilization was associated with donor age of 60 years or older (28% [\$53 813] greater mean resource utilization;  $P = .005$ ); recipient age of 60 years or older (17% [\$32 795];  $P = .01$ ); alcoholic liver disease (26% [\$49 596];  $P = .002$ ); Child-Pugh class C (41% [\$67 658];  $P < .001$ ); care from the intensive care unit at time of transplant (42% [\$77 833];  $P < .001$ ); death in the hospital (35% [\$67 076];  $P < .001$ ); and having multiple liver transplants during the index hospitalization (154% increase [\$474 740 vs \$186 726 for 1 transplant];  $P < .001$ ). Adjusted length of stay and resource utilization also differed significantly among transplant centers.

**Conclusions:** Clinical, economic, and ethical dilemmas in liver transplantation are highlighted by these findings. Recipients who were older, had alcoholic liver disease, or were severely ill were the most expensive to treat; this suggests that organ allocation criteria may affect transplant costs. Clinical practices and resource utilization varied considerably among transplant centers; methods to reduce variation in practice patterns, such as clinical guidelines, might lower costs while maintaining quality of care. (1999;281:1381-1386) www.jama.com

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