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A Prospective Trial Evaluating a Standard Approach to Reoperation for Missed Parathyroid Adenoma

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Objectives

The authors evaluate the results of preoperative imaging protocols and surgical re-exploration in a series of patients with missed parathyroid adenomas after failed initial procedures for primary hyperparathyroidism.

Background

The success rate is lower and the complication rate is increased in patients undergoing reoperation for primary hyperparathyroidism compared with initial procedures. Scarring and distortion of tissue planes plus the potential for ectopic gland location leads to this worsened outcome.

Methods

Two hundred eighty-eight consecutive patients with persistent/recurrent hyperparathyroidism were treated at a single institution after a failed procedure or procedures at outside institutions. Two hundred twenty-two of these patients (77%) were believed to have a missed single adenoma, and these patients underwent 228 operations and 227 preoperative work-ups. Preoperative evaluation consisted of a combination of four noninvasive imaging studies—neck ultrasound, nuclear medicine scan, neck and mediastinal computed tomography scan, and neck and mediastinal magnetic resonance imaging. Based on the noninvasive testing alone, 27% patients underwent surgery whereas the other patients underwent invasive studies, including selective angiography (58%), selective venous sampling for parathyroid hormone (43%), or percutaneous aspiration of suspicious lesions (15%).

Results

Abnormal parathyroid adenomas were found in 209 of 222 initial procedures and 6 of 6 second procedures, with an overall success rate in terms of resolution of hypercalcemia in 97% (215/222) of patients. The single most common site of missed adenoma glands was in the tracheal-esophageal groove in the posterior superior mediastinum (27%). The most common ectopic sites for parathyroid adenomas are thymus (17%), intrathyroidal (10%), undescended glands (8.6%), carotid sheath (3.6%), and the retroesophageal space (3.2%). The most sensitive and specific noninvasive imaging test is the sestamibi subtraction scan, with 67% true-positive and no false-positive results. The rate of true-positive and false-positive results for ultrasound, computed tomography, magnetic resonance imaging, and technetium thallium scans were 48%/21%, 52%/16%, 48%/14%, and 42%/8%, respectively. The incidence of injury to the recurrent laryngeal nerve was 1.3%.

Conclusions

A single missed parathyroid adenoma is the most common cause for a failed initial parathyroid operation. Appropriate use of preoperative imaging tests and knowledge of the potential location of parathyroid adenomas can lead to very high cure rates with minimal morbidity.

The most common etiology of primary hyperparathyroidism (HPT) is a solitary parathyroid adenoma found in 85% of patients with this diagnosis.[1] Surgical excision of the parathyroid adenoma is curative and, in experienced hands, can be accomplished in 90% to 97% of patients with almost no morbidity.[1,2] Initial studies of patients with persistent or recurrent elevated calcium levels after an initial parathyroid procedure suggested that the majority of patients in this category had multiglandular disease unappreciated at the initial operation.[3-5] However, these reports originated from institutional series with considerable experience in parathyroid surgery and are not representative of the general population after failed parathyroid procedures. A missed single abnormal parathyroid adenoma accounts for the majority of patients who fail initial procedures for the treatment of primary HPT.[2,6]

Scarring and distortion of normal tissue planes in the neck after a prior cervical exploration lead to decreased success rates and increased complications after reoperative parathyroid procedures.[6,7] The failure to identify an adenoma at an initial procedure suggests that it will not be an obvious lesion by either location or appearance. The features used to identify parathyroid adenomas such as color, shape, and tactile perception of gland may be much more difficult to appreciate because of fibrosis within the tissues from the previous procedure.[8] For these reasons, endocrine surgeons universally agree that preoperative imaging studies are an essential component of reoperative parathyroid surgery.[9-12] A variety of noninvasive and invasive techniques are available to image or localize abnormal parathyroid glands. This report is a large and current analysis of 222 consecutive patients believed to have a missed single parathyroid adenoma who underwent re-exploration for HPT. The patients were evaluated with a prospectively defined sequence of radiologic tests. Analysis of the results of preoperative imaging studies, the location of the missed adenomas and how that relates to the initial failed procedure, and the outcome and complications of the surgical procedures will be analyzed.

METHODS

Between July 1982 and July 1995, 288 consecutive patients referred from other institutions with a diagnosis of primary HPT underwent operation at the National Institutes of Health (NIH). Each patient had undergone at least one previous neck exploration for treatment of HPT at another institution before referral to the NIH. All patients had preoperative biochemical testing with elevated serum calcium levels, elevated parathyroid hormone (PTH) levels, and 24-hour urinary calcium levels that were either normal or elevated. Operative reports and pathology slides were obtained for each patient at the time of the referral. Nine patients in this series of 288 had a pathologic and clinical diagnosis of parathyroid cancer with unequivocal features of mitotic figures, fibrous trabeculae, or local invasion of the capsule and vascular structures.[13] Fifty-seven patients had multiglandular hyperplasia, either in the setting of multiple endocrine neoplasia, type I (n = 26) or nonfamilial multiglandular hyperplasia (n = 31; Fig. 1). The remaining 222 patients (77% of the total population) were believed to have single parathyroid adenomas, and this patient population is analyzed in this report.

On referral to the NIH, each patient underwent a prospectively determined series of imaging studies. The patients initially were evaluated by noninvasive imaging techniques consisting of neck ultrasonography, nuclear medicine scanning, computed tomography, and magnetic resonance imaging (MRI).[14] These imaging techniques have been described previously. Ultrasound is performed using a 10-mHz transducer to identify masses of relatively low echogenicity within the neck.[15] The

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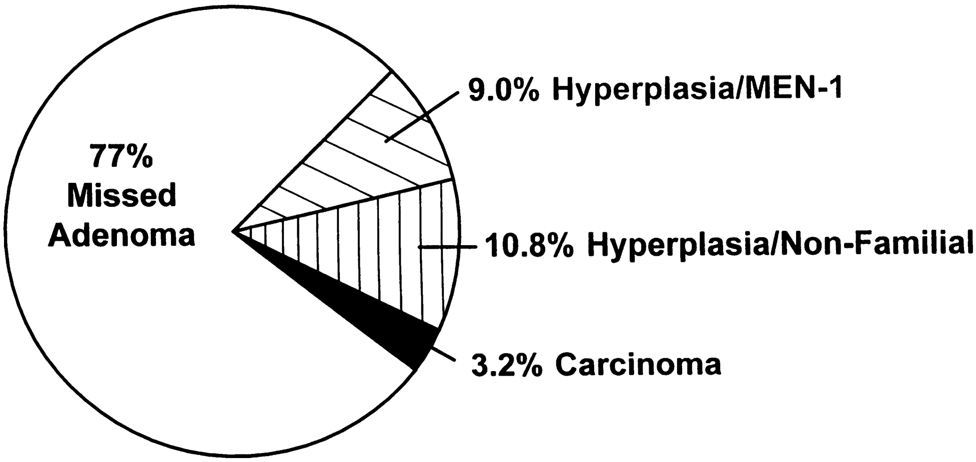

Figure 1. Distribution of patients according to diagnosis referred for reoperative parathyroid surgery to the National Institutes of Health from July 1982 to July 1995.

nuclear medicine scans initially were performed with a technetium thallium subtraction technique.[16,17] Since 1993, an iodine-123/sestamibi subtraction technique has been used.[18,19] Computed tomography scans were obtained with contrast using contiguous 5-mm sections in the neck and 10-mm sections in the mediastinum.[15] Magnetic resonance imaging was performed of both the neck and mediastinum in patients evaluated since 1986, when this technology became available.[15,20] All noninvasive imaging studies then were evaluated simultaneously by a senior radiologist (JLD). If the combined findings of these studies identified a nonequivocal lesion consistent with a parathyroid adenoma on two or more studies, the patients were taken to the operating room for surgical exploration. If the data from these noninvasive studies were negative, equivocal, or contradictory, the patients proceeded to invasive testing.

If potential parathyroid lesions were visualized on the noninvasive studies that were accessible to a percutaneous aspiration, but were not clearly parathyroid adenomas (*e.g.*, intrathyroidal lesions), then this was performed using either ultrasound or computed tomography guidance.[21,22] Aspirates were evaluated for PTH content by radioimmunoassay, and positive aspirations resulted in unequivocal gradients. For patients with negative or equivocal noninvasive imaging scans in which there was no potential lesion to aspirate for PTH, patients were referred for selective angiography, as described previously.[23] Positive lesions were identified as a hypervascular blush with this imaging technique. If a lesion was identified clearly by angiogram, patients were taken to the operating room for surgical exploration. If the angiogram results were negative, then patients underwent selective venous sampling for PTH. Selective venous catheterization of veins draining the neck and mediastinum were performed with simultaneous samples taken from systemic veins and multiple samples from all patent inferior, middle, and superior thyroid veins, thymic veins, and vertebral veins.[24] Parathyroid hormone levels were measured by a midregion or intact radioimmunoassay. A positive PTH gradient was defined as a step up of at least twice the peripheral PTH determined from the mean of iliac vein samples.[24] These results were used to localize the source of PTH to either the left neck, right neck, both sides of the neck, or thymus. A negative study was one in which no twofold gradient was achieved.

The majority of patients underwent a standard surgical approach for re-exploration of the neck for HPT.[2,6] The transverse cervical scar from the previous incision was used, and after raising platysma flaps, the posterior lateral space of the neck was entered by dividing the deep fascia medial to the sternocleidomastoid muscle. In doing this, the structures of the carotid sheath are identified and retracted laterally, and the strap muscles are divided at their origin from the clavicle. This lateral approach avoids dissecting the plane between the strap muscles and the anterior surface of the thyroid gland where there are dense adhesions from the prior neck explorations. When indicated, intraoperative ultrasound was performed using a 10-mHz probe (Diasonics, San Francisco, CA).[25] Two alternative surgical approaches were used in patients who had glands that imaged preoperatively in ectopic locations in the mediastinum or undescended position. These techniques will be discussed in detail. All patients who had an abnormal parathyroid gland excised had a portion of it placed into chilled media on the operating room table and cryopreserved in an expeditious manner for possible future autotransplantation.[6] After surgery, all patients underwent sequential repetitive biochemical testing for serum calcium and PTH levels.

RESULTS

The demographic data in terms of sex and age of the study population are shown in Table 1. Twenty-two per-

Table 1. PATIENT DEMOGRAPHICS AND PRIOR PROCEDURES TO RESECT PARATHYROIDS IN PATIENTS WITH MISSED PARATHYROID ADENOMAS

Total patients	222
Male:female [no. (%)]	69:153 (31:69)
Age (yr)	
Mean	51.7
Range	16-86
No. (%) of prior surgeries	
1	174 (78)
2	38 (17)
3+	11 (5)
Persistent* [no. (%)]	205 (92)
Recurrent† [no. (%)]	17 (8)
History of neck radiation [no. (%)]	5 (2.2)

* Persistent disease defined as hypercalcemia documented within 6 months of surgery.
† Recurrent disease defined as normocalcemia for 6 months or more before development of hypercalcemia.

cent of patients had more than one prior exploration for primary HPT, with 11 patients (5%) having three or more neck or mediastinal procedures. The majority of patients (92%) had persistent primary HPT after their previous explorations. Persistent HPT is defined as documented elevated serum calcium levels within 6 months of the initial or prior surgical procedure. Seventeen patients (8%) had recurrent primary HPT with documented normalization of calcium levels for 6 months or more after their initial procedures.

The vast majority of patients had symptoms that clearly could be related to their primary HPT at some point during the course of their disease (Table 2). The most frequent symptoms were renal (48%) and bone symptoms (41%). There also was a high incidence of constitutional symptoms consisting of fatigue, neuropsychiatric symptoms or inability to concentrate, and muscle weakness in 28%, 21%, and 14% of patients, respectively. Nineteen percent of patients had gastrointestinal symptoms that typically were constipation or upper abdominal acid-related symptoms of gastritis or ulcer disease.

Table 2. INCIDENCE OF SYMPTOMS OR SIGNS RELATED TO PRIMARY HYPERPARATHYROIDISM AT ANY TIME DURING THEIR DISEASE IN PATIENTS WITH MISSED PARATHYROID ADENOMAS

Symptom	Total (%) (n = 222)
Nephrolithiasis	106 (48)
Bone symptoms (pain/decreased bone density)	91 (41)
Fatigue	61 (28)
Neuropsychiatric	46 (21)
Gastrointestinal symptoms	43 (19)
Muscle weakness	32 (14)
Nocturnal polyuria	19 (9)
Fractures	8 (4)
No symptoms	32 (14)

Table 3. OPERATIVE INCISIONS AND PROCEDURES PERFORMED AT INITIAL OPERATION AND REOPERATIONS AT OTHER INSTITUTIONS FOR PATIENTS WITH PRIMARY HYPERPARATHYROIDISM WITH MISSED ADENOMAS

	First Operation	Second Operation	Third Operation
Parathyroid excisions			
No PT tissue removed	23	20	10
One PT biopsied/excised	94	12	2
Two PTs biopsied/excised	64	1	0
Three or more PTs biopsied/excised	41	2	0
Additional incisions/resections			
Thyroid lobectomy	51	12	1
Thyroidectomy, total/subtotal	20	5	0
Cervical Thymectomy	14	8	0
Median sternotomy	5	10	4
Mediastinoscopy	0	1	0
Thoracotomy	0	1	0
Immediate autograft	1	2	1
Removal of autograft	0	0	3

* PT = parathyroid.

Results of Parathyroid Surgery Performed Elsewhere

The details of the initial parathyroid procedure and the reoperations at outside institutions are shown in Table 3. Almost 90% of patients had biopsies or excisions taken of normal parathyroid lesions during their initial procedures. The ability to identify and perform a biopsy of normal parathyroid tissue in the reoperative setting at the second or third operations was diminished greatly. Several different procedures or resections were performed in conjunction with these outside explorations in an attempt to identify the missing abnormal parathyroid adenoma. The most common additional procedure was a thyroidectomy done in 71 of the 222 initial operations. Also, in approximately one third of the second and third explorations, a thyroid resection was performed as well (17/49 and 4/11). Mediastinal explorations to identify missed glands in the thymus were performed infre-

Table 4. UTILIZATION OF VARIOUS IMAGING TESTS OR PROCEDURES AND PERCENTAGE TRUE POSITIVE AND FALSE POSITIVE IN IDENTIFYING THE ABNORMAL MISSED PARATHYROID ADENOMA

Test	No. Done (%)*	%True Positive	%False Positive
Nuclear medicine	194/227 (85)		
Technetium-thallium	155/187 (68)	42	8
Iodine-Sestamibi	39/40 (17)	67	0
US, neck	225/227 (99)	48	21
CT, neck/chest	218/227 (96)	52	16
MRI, neck/chest	155/227 (68)	48	14
CT or US directed FNA	35/227 (15)	69	0
Angiogram	150/227 (66)	59	9
Venous sampling for PTH	98/227 (43)	76	4

US = ultrasound; CT = computed tomography, MRI = magnetic resonance imaging; FNA = fine needle aspiration; PTH = parathyroid hormone.
* Total 227 workups in 222 patients.

quently during the initial surgery but were more common in the initial reoperation or the second procedure, in which 25% of patients had some sort of thoracic exploration—most commonly via a median sternotomy (Table 3).

Preoperative Imaging Studies

Almost all patients underwent preoperative evaluation with an ultrasound of the neck and a computed tomography scan of the neck and chest (99% and 96% of patients, respectively). The use of nuclear medicine imaging[16] and MRI was not as complete as technologies developed after the initiation of these studies in 1982.[15] Specifically, during the time interval in which technetium thallium tests were used, 83% of patients were studied with this modality. Since sestamibi scans were introduced in the last 2 to 3 years, 98% of all patients evaluated have been studied. A similar phenomenon is noted for the use of MRI, in which only 68% of the total patient population has been evaluated because use of this imaging technique was not initiated until 1986.

The sensitivity and specificity of the noninvasive imaging studies are rather limited in this previously operated on patient population, as shown in Table 4. Only between 42% and 52% of patients studied had true-positive test results in which lesions that were visualized on all these noninvasive scans were parathyroid adenomas before the use of iodine-sestamibi. Also, there was a considerable degree of false-positive results reflecting a decreased specificity, particularly with ultrasound of the neck, in which there were 21% false-positive lesions and 16% and 14% false-positive results with the computed tomography and MRI scans, respectively. The majority of these false-positive ultrasound or scan results are related to identification of lymph nodes within the neck and jugular chain anywhere from the angle of the jaw to the root of the neck for ultrasonography and extending into the mediastinum for the cross-sectional imaging studies. A second site for false-positive results are lesions of thyroid origin. There was an 8% false-positive rate for the technetium thallium nuclear medicine scans primarily because of intrathyroid lesions. The single best noninvasive imaging study in terms of percent of true-positive results and percent of false-positive results is the iodine-sestamibi subtraction scan.[19] With this test, in 39 patients, two thirds of the lesions were identified, with no false-positive results. Only 27% of the total patient population had lesions definitively identified without conflicting results by the noninvasive studies and went directly to surgical resection. The remaining 73% of patients underwent some type of invasive localization procedure (Fig. 2).

Almost two thirds of the patients underwent selective angiography, and 35 patients (15%) of the total patient population had lesions that were visualized by noninvasive images confirmed to be a source of elevated PTH by fine-needle aspiration for hormone content. A blush was identified that turned out to be a parathyroid adenoma in 59% of cases, and there was a 9% false-positive rate with this study. Selective venous sampling was used in 98 of the 227 work-ups (Fig. 2). This modality had the highest rate of true-positive study results, with 76% of analyses performed showing a gradient in the region of the eventually identified parathyroid adenoma.

Operative Procedures

Two-hundred twenty-two patients underwent 228 surgical procedures for primary HPT at the NIH. Seventy-eight percent of the procedures were done through a transverse cervical incision (Table 5). Despite the extensive use of preoperative imaging studies, 31 of these 175 patients (14%) required a bilateral neck exploration for identification of a single parathyroid adenoma. Two additional surgical approaches commonly were used for a more directed excision of the parathyroid adenoma based on the preoperative radiologic studies. Twenty percent of patients were explored via a median sternotomy for a mediastinal gland in the thymus or elsewhere in the chest.[26] Twelve patients (5% of the total population) had a high oblique neck incision for directed resection of an undescended parathyroid adenoma.[27] One patient each had a posterolateral thoracotomy and a mandibular swing for very unusual ectopic glands in the

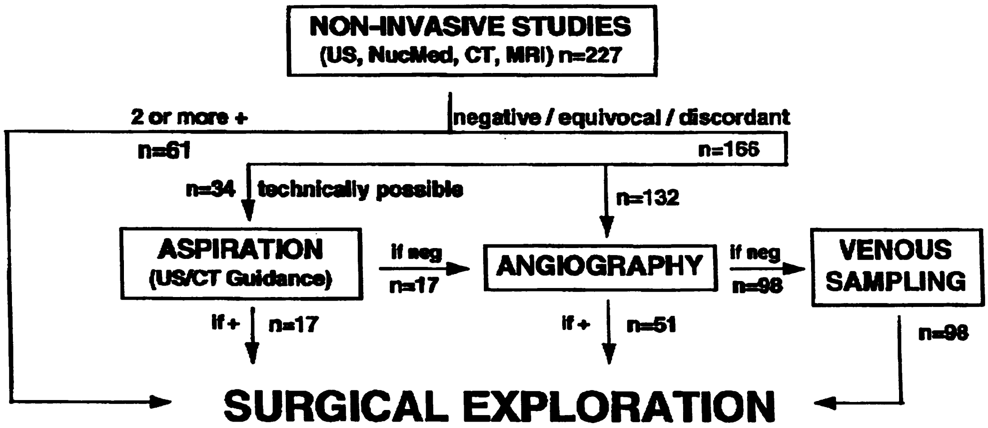

Figure 2. Flow diagram showing the preoperative radiologic work-up for patients with persistent or recurrent hyperparathyroidism. Two hundred twenty-seven radiologic work-ups were performed in 222 patients, and the number of patients undergoing each particular type of study is indicated on the diagram.

aortopulmonary window and the wall of the nasopharynx, respectively.

Intraoperative ultrasound was used in 153 of the 228 procedures (67%). In these 153 cases, there was a true-positive identification of the parathyroid adenoma in 109 patients (71%). The calculated accuracy was 78%, and sensitivity was 85%. A subset of 88 cases of the 109 true-positive cases was analyzed in detail to determine the benefit of the intraoperative ultrasound. In 46% of the operations in which they were positive, the intraoperative ultrasound results confirmed what was believed to be the parathyroid adenoma identified by palpation and visual inspection by the operating surgeon. In the other 54% of cases, intraoperative ultrasound was either essential for identifying the lesion or helpful. Therefore, it can be estimated that in approximately 25% of the 228 cases, intraoperative ultrasound was an extremely useful tool for the operating surgeon in identifying the abnormal parathyroid.

In the 222 initial reoperations at the NIH, a parathyroid adenoma was excised with resolution of hypercalcemia in 209 patients (94.1%). Six of the 13 patients who initially failed an excision underwent a second procedure, all with successful resolution of hypercalcemia (Table 6). One of these reoperations was performed a few days after the initial procedure, after the patient was found to have diffuse intramuscular seeding in the strap muscles and the sternocleidomastoid, and an *en bloc* muscle resection was performed in that patient. The other five patients were re-explored at least 6 months after the initial procedure, after a second evaluation with repeat localization studies. The repeat imaging work-up in three patients revealed abnormal gland locations in unusual sites such as the wall of the nasopharynx, the aortopulmonary window, and the mediastinum. Two patients failed initial re-exploration when intrathyroidal lesions were excised and identified incorrectly as parathyroid adenomas on frozen section. Subsequent re-exploration found lesions in the neck in both of these cases. The overall success rate in terms of resolution of hypercalcemia in the total population was 96.8% (215/222 patients; Table 6).

The single most common site for a missed adenoma in our series was the tracheal-esophageal groove because 59 of the 215 glands that were eventually resected were in

Table 5. OPERATIVE INCISIONS AND ADDITIONAL PROCEDURES USED TO RESECT MISSED ADENOMAS

Incision	No. (%)
Transverse cervical	169 (74.1)
Unilateral neck exploration	138 (60.5)
Bilateral neck exploration	31 (13.6)
Median sternotomy	45 (20)
High oblique neck incision	12 (5)
Posterolateral thoracotomy	1 (0.4)
Mandibular swing procedure	1 (0.4)
Additional procedures	
Thyroid lobectomy	27 (12)
Thyroidectomy, total/subtotal	2 (0.9)
Muscle resection	3 (1.3)
Clavicular head removal	1 (0.4)

Table 6. OPERATIVE OUTCOME IN PATIENTS UNDERGOING NECK REEXPLORATION FOR MISSED PARATHYROID ADENOMA AT THE NATIONAL INSTITUTES OF HEALTH (NIH)

No. of reoperations	222
Success at first NIH reoperation [no. (%)]	209 (94.1)
No. of second NIH reoperations	6
Success at second procedure [no. (%)]	6 (100)
Overall success rate [no. (%)]	215/222 (96.8)
Operative time [mean (range)] (min)	172 (25–550)

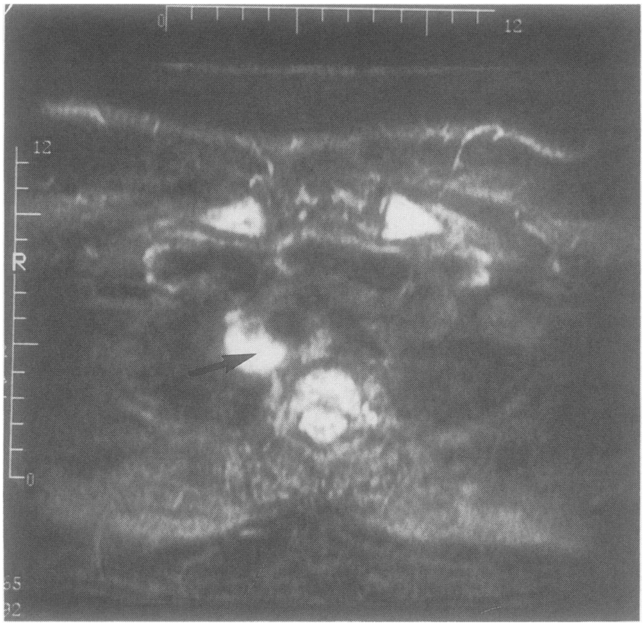

Figure 3. A stir magnetic resonance image showing a missed tracheal-esophageal groove parathyroid adenoma (arrow) in a patient who had undergone two previous operations, including a cervical procedure and a median sternotomy. The median sternotomy was performed at an outside institution after a technetium thallium scan suggested a mediastinal gland. A thymectomy was performed with no resection of parathyroid and no alteration in hypercalcemia. The region is at the tracheal-esophageal groove lesion imaged on this diagram was in the posterior-superior mediastinum at the level of the innominate vein as demonstrated on the magnetic resonance imaging scan.

this location. Tracheal-esophageal groove lesions may be identified as far inferiorly as the level of the innominate vein (Fig. 3). This region can almost always be explored with successful resection of the gland via a cervical approach with the neck extended even when glands lie below the thoracic inlet. The blood supply for these superior glands enters the upper pole of the lesions and can be used in some cases to help pull the abnormal gland up into the midneck. Because of the course of the recurrent laryngeal nerve within the tracheal-esophageal groove on the left side and its low crossing in the neck to the tracheal-esophageal groove on the right side, this common site of missed adenoma frequently is in direct opposition to the nerve (Fig. 4). The next most common site for finding missed adenomas are in the typical locations for parathyroids, combining both the normal upper and lower position (Fig. 5). A normal superior gland position is defined as the region posterolateral to the superior pole of the thyroid superior and posterior to the course of the recurrent laryngeal nerve. The normal inferior gland position is defined as in the region of the lower pole of the thyroid gland anterior to the recurrent laryngeal nerve and the inferior thyroid artery. Taken together, 24.3% of all lesions that were missed on initial procedure simply

Figure 4. A superior parathyroid gland in the low neck on the right side that is immediately related to the recurrent laryngeal nerve. The forceps identifies parathyroid (arrowhead) and the nerve (arrow) is obliquely crossing over the anterior surface of the gland.

were not identified in their normal positions during the original surgery. If the tracheal-esophageal groove can be considered an inferior extension of the normal superior gland position, then more than half of the missing adenomas were found in nonectopic locations. The remainder of the lesions can be considered to be in true ectopic sites for parathyroid (Fig. 5).

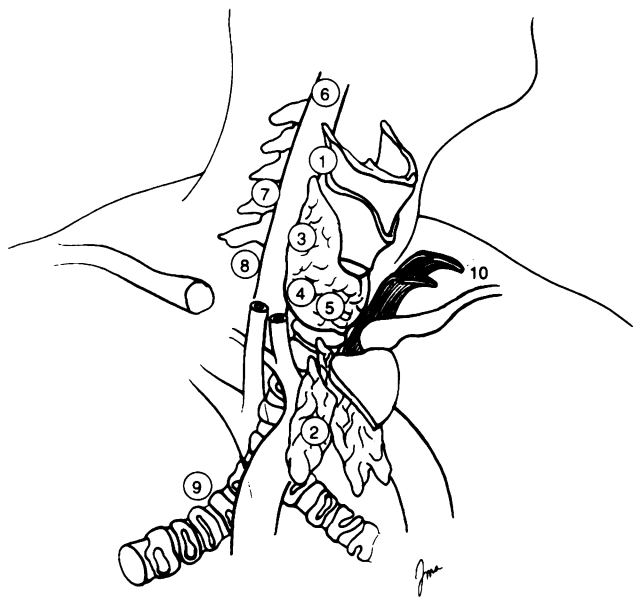

Figure 5. A sketch showing the distribution of the 215 abnormal parathyroid adenomas resected in this series. 1 = tracheo-esophageal groove (n = 59; 27%); 2 = anterior mediastinum/thymus (n = 38; 18%); 3 = normal upper (n = 28; 13%); 4 = normal lower (n = 26; 12%); 5 = intrathyroid (n = 22; 10%); 6 = undescended (n = 18; 8.4%); 7 = carotid sheath (n = 8; 3.7%); 8 = retroesophageal (n = 7; 3.3%); 9 = other mediastinal (n = 3; 1.4%); 10 = strap muscles (n = 3; 1.4%); 11 = other (n = 3; 1.4%).

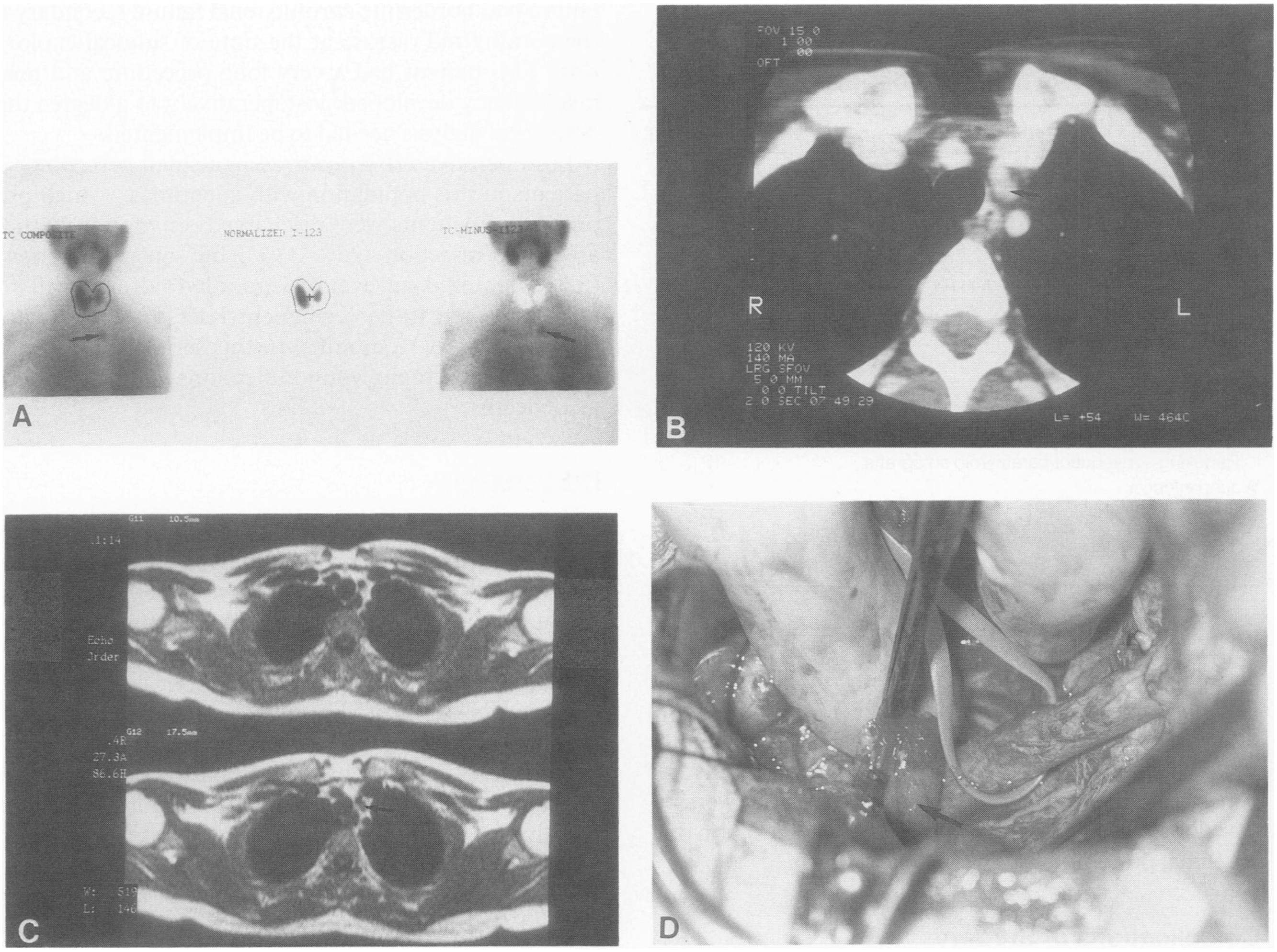

Figure 6. Preoperative imaging studies and an intraoperative photograph from a patient with a carotid sheath lesion posterior to the origin of the left common carotid artery. (A) An iodine sestamibi subtraction study that shows a lesion to the left of midline in the mediastinum, which may be interpreted as being in the thymic gland. (B) A computed tomography scan with contrast, which shows a cut in the upper thorax in which the three great vessels are captured as they arise from the aortic arch. An additional density is noted just posterior to the left common carotid artery (arrow). (C) A T1 weighted magnetic resonance image in the same area, which defines a lesion consistent with the parathyroid more clearly (arrow). (D) An intraoperative photograph taken from the left side of the neck. The common carotid artery is dissected down to the root of the neck and a parathyroid gland (arrow) is being extracted from the posterolateral left common carotid artery.

The most common ectopic site for an abnormal gland is within the thymus or mediastinum. Thirty-seven lesions (16.7%) were identified as lower glands that had descended with the thymus inferiorly down into the mediastinum. The second most common ectopic site after the mediastinal thymic gland is an intrathyroidal lesion identified in 22 patients (10%) of the total study population. Almost equal to the intrathyroidal location is the undescended parathyroid glands. These so-called parathymic lesions are located at the bifurcation of the carotid artery, high in the neck, and represent an inferior gland that is arrested in descent from the third branchial pouch.[27] Other more unusual ectopic locations include glands within the carotid sheath and in the retroesophageal space. Carotid sheath glands typically are found between the carotid artery and the internal jugular vein, but in certain situations can be found anterolateral to the jugular vein (Fig. 6). Retroesophageal glands are identified in the space just anterior to the cervical spine and directly posterior to the esophagus. The side of origin of retroesophageal adenomas can be identified only by tracing out the blood supply to the lesions. Glands found in this location typically are quite flat in shape as opposed to the typical ovoid lesions. In the current study, very rare ectopic sites included the aortopulmonary window in two

Table 7. COMPLICATIONS OF 228 NECK REEXPLORATIONS FOR MISSED PARATHYROID ADENOMA

Complication	No. (%)
Recurrent laryngeal nerve injury	
Permanent	3 (1.3)
Temporary	6 (2.6)
Marginal mandibular nerve injury	1 (0.4)
Hemorrhage requiring blood transfusion	3 (1.3)
Pneumonia	1 (0.4)
Myocardial infarction	1 (0.4)
Renal failure	1 (0.4)
Severe hypocalcemia	
Requiring vitamin D*	42 (25.3)
Requiring intravenous calcium	7 (3.1)
Requiring subsequent parathyroid autografts	12 (5.3)
Wound infection	0
Perioperative deaths	0

* From a database of 166

patients, the hypopharynx at the base of the tongue in one patient, the wall of the nasopharynx near the nasal septum in another patient, and within the vagus nerve high in the neck at the level of C1-C2 vertebrae. Three patients had parathyroid lesions within the strap muscles that were believed to be due to seeding from incomplete resection during initial procedures.

Complications of Surgery

Four of the 222 patients had permanent nerve injuries (Table 7). Three of these injuries were to the recurrent laryngeal nerves, including a single patient who had a bilateral nerve injury and two patients with unilateral injuries. A fourth patient had transection of the marginal mandibular nerve during excision of very high intravagal parathyroid lesion at the level of C1-C2. Six patients had temporary recurrent laryngeal nerve paresis with documented recovery by indirect laryngoscopy. There have been no permanent recurrent laryngeal nerve injuries in the last 150 patients during the last 9 years. Three patients had bleeding related to surgery that required blood transfusion; two of these incidents were after mediastinal procedures that were believed to be due to internal mammary injuries. A third patient had a carotid artery disruption during dissection of the neck, which led to an urgent median sternotomy for control, but no permanent deficits. None of these three patients nor any other of the 228 procedures necessitated a reoperation for bleeding or postoperative hematoma. One patient each had pneumonia, a perioperative myocardial infarction, and postoperative renal failure. The patient with renal failure had borderline chronic renal failure secondary to the parathyroid disease at the time of surgical exploration. This patient had a very long procedure and renal insufficiency developed postoperatively to a degree that peritoneal dialysis needed to be implemented.

Postoperative HPT occurred in a small percentage of patients in this population with adenomas. A high proportion of patients were discharged on vitamin D therapy after resection (25%–33%), but only 12 patients (5.3%) required an eventual parathyroid autograft for what appeared to be permanent HPT after waiting an interval of 6 to 12 months. In this series of 228 procedures, there were no wound infections and no perioperative deaths.

DISCUSSION

A single parathyroid adenoma is the most common cause of primary HPT and should be imminently curable with almost no morbidity by appropriate surgical therapy. Multiglandular disease or parathyroid hyperplasia accounts for a slightly larger proportion of patients undergoing reoperation for persistent or recurrent HPT (20% in our series of almost 300 cases) compared with patients undergoing initial procedures (15%).[1] This minor increase is less than what might be expected from the early series evaluating reasons for failure after initial parathyroid procedures, which suggested that more than half of the cases were due to unappreciated multiglandular disease.[3–5] Therefore, the problem of a missed parathyroid adenoma is an important one because it represents patients who should be cured with essentially complication-free surgery because they have at least three normal parathyroids that prevent long-term HPT.

The 96.8% success rate in our series compares favorably to other reported reoperative parathyroid studies in the literature, which generally have correction of hypercalcemia between 80% and 96% of patients treated.[28–32] However, this series is selective for only patients with presumptive single gland disease and thus, is biased because it eliminates the patients with hyperplasia, who are more difficult to treat. Nevertheless, this series is equal or better than most studies of initial surgical procedures to treat primary HPT, which report success rates in the 90% to 95% range.[1,2,23]

The locations in which missed adenomas are identified and resected in this series in some ways provides a formula to surgeons undertaking initial parathyroid resections for patients with single parathyroid adenomas. Figure 5 shows the potential hiding spots and the percent incidence of gland in those locations in our series in which normal parathyroid glands are identified and biopsies are taken so that the clinical impression is that the patient has a single adenoma. Most series of reoperative parathyroid procedures report that the area of the posterior superior mediastinum or comparably called the tracheal-esophageal groove is the single most common spot for missed abnormal glands. Wang's series from MGH reported incidents of 33% for this site compared with our finding of 27%.[28] This region is in continuity with what would be considered as the normal position for superior parathyroid glands and in some ways represents an inferior descent of enlarged lesions in this space posterior to the inferior thyroid vessels and posterior to the course of the recurrent laryngeal nerve.[33] It is not uncommon for lesions to be identified that are very adherent to the undersurface of the nerve along this course (Fig. 4). Reluctance to dissect near the recurrent laryngeal nerve may be one of the major factors in the failure to appreciate abnormal superior parathyroid glands in this position.

The 24% of parathyroid adenomas that were classified in normal superior and normal inferior positions speaks to the need for initial explorations to be performed by experienced parathyroid surgeons. The ability to identify an abnormal parathyroid gland in terms of shape, color, appearance, and palpation is an essential element to performing a successful parathyroid excision. Bruining classified glands found in the normal position during reoperations as attributable to inexperienced surgeons as an identifiable cause for failure for unsuccessful initial procedures.[34]

After eliminating normal superior and normal inferior positions and the tracheal-esophageal groove, which is an extension of the normal superior gland position, there are several ectopic sites that need to be evaluated routinely when searching for a missing adenoma. The single most common true ectopic site is within the thymus, either in the low neck or in the superior mediastinum, which occurred in 16.7% of our reoperative series. This value is lower than other reports of 22% thymic tumors at the initial operation and 38% for reoperation.[35] This difference may reflect a selection bias because studies of a missing gland in the mediastinum commonly are done elsewhere, as evidenced by the number of patients who had negative median sternotomies during reoperations at other institutions before referral to the NIH. The initial surgical approach during our early clinical experience for mediastinal thymic glands was a median sternotomy. However, the recent description of a mechanical retractor, which allows a safer and more complete transcervical retrosternal dissection, has led to an increase in the ability to deliver mediastinal glands well below the innominate vein through a cervical incision.[36] Other potential strategies such as thoracoscopic approaches also have been reported for this ectopic site.[37] The second most common ectopic site is parathyroid glands located entirely within the thyroid.[38] These lesions almost universally are not palpable because they have the same consistency as the surrounding thyroid tissue. In fact, palpable thyroid lesions are almost always of thyroid origin. A classic approach to the patient with initial primary HPT and a missed adenoma is to perform a blind unilateral thyroid lobectomy on the side with the missing gland, evidenced by the number of unsuccessful thyroid resections performed in our patient population. A more appropriate strategy would be to use intraoperative ultrasound, which almost always will demonstrate a hypoechoic lesion within the thyroid, if it exists. The incidence in this selected reoperative series of intrathyroid lesions is 10% compared with a report of 4% incidence in primary explorations.[38] The third most common ectopic site is the undescended parathyroid. Although originally reported to be medial to the carotid bifurcation, at least two patients in this series had lesions between the carotid and jugular, and one was unsuccessfully evaluated for a missed undescended gland elsewhere.[27,39] Evaluation of usual locations for parathyroids, the tracheal-esophageal groove, the thymus, the thyroid, and the area of undescended glands accounts for more than 90% of all missed lesions in our reoperative series.

Two additional ways to identify rare ectopic lesions would be dissection of the carotid sheath and dissection of the retroesophageal space. Glands within the carotid sheath may be anywhere from the bifurcation of the carotid down to the vessel origin within the mediastinum (Fig. 6). These lesions frequently are posterior or lateral to the carotid artery and, on occasion, have been found lateral to the jugular vein. Therefore, skeletonization of the carotid sheath structures, including palpation or ultrasound to look posterior to the vessels, is necessary to fully explore this area. Retroesophageal lesions tend to be flattened or "pancaked" against the posterior wall of the esophagus and the anterior surface of the cervical vertebrae. Because the color of parathyroid adenomas is quite similar to that of the muscularis of the esophagus, an appreciation of these lesions is quite difficult. Palpation of a nodular region that moves against the muscularis of the esophagus is the principle way to identify the lesions intraoperatively.

The very atypical locations as well as the more common ectopic sites highlight the need for preoperative imaging studies. We previously reported our undescended parathyroid experience and have indicated that when the presence of an undescended gland is appreciated preoperatively, the operative time and the potential morbidity of the procedure is very limited, and successful resections in these difficult patients can be accomplished frequently in less than 1 hour.[39] Similarly, the preoperative knowledge of a patient having a mediastinal gland allows a planned resection with the precise location of the target lesion.[26] Knowledge of where this gland is in relationship to the innominate vein allows for a surgical appreciation of the amount of thymus that needs to be delivered for a successful resection. Very unusual glands, such as glands at the base of the tongue and hypopharynx, lesions in the wall of the nasopharynx, and glands in the aortic pulmonary window, clearly would not be found by routine exploration of the neck or mediastinum. Combinations of noninvasive and invasive imaging techniques, in conjunction with intraoperative ultrasound, leads to successful identification of glands in these very unusual sites. Explanation for glands in this location, based on the knowledge of the embryology of parathyroid glands, is difficult. However, keeping an open mind and accepting that a parathyroid adenoma may be hidden anywhere from the pericardium up to the nasal septum should humble the endocrine surgeon approaching a patient with symptomatic primary HPT in the reoperative setting.

The protocol used in this large series is peculiar in regard to the number of preoperative imaging procedures obtained. The lack of budgetary constraints at our institution, combined with the inability to obtain potentially redundant tests in clinical practice, makes the protocol described here not feasible in virtually any other institution. Analysis of the success of each individual imaging studies would indicate that as a single test, the sestamibi subtraction scan has the advantage of relatively low cost, very good sensitivity, and high specificity. The second best noninvasive test in terms of cost and results is ultrasound of the neck because the results are equivalent to computed tomography or MRI, but the expense is much less. Success rate with preoperative ultrasonography evaluation depends to some extent on the skill and interest of the radiologist because there are several potential cervical lesions, such as lymph nodes and thyroid nodules, that may be false-positives in this patient population. Subtle appreciation of the imaging characteristics and location relative to the other structures are important components of the ultrasound evaluation. Taken together, sestamibi subtraction studies and ultrasound provide a combination that is complimentary and should provide information for up to three quarters of missed lesions.[40] Sestamibi scans image the mediastinum, which is missed by ultrasound studies. Ultrasound is a good tool to evaluate lesions that are either intrathyroidal or immediately adjacent to the thyroid capsule, which may be difficult to appreciate with sestamibi studies.

If these study results are negative, the patient should definitely undergo further imaging evaluation before proceeding to surgical exploration. The wide area in which abnormal parathyroids may be found may lead to very extensive operations in terms of time without success if surgery is not directed by some sort of localization procedure. Computed tomography scans and MRI scans are relatively redundant in terms of cross-sectional imaging studies. Computed tomography scans have the advantage of being less expensive whereas MRI scans, with current technology, may be superior in terms of imaging characteristics of parathyroid.[40] However, as highlighted in Figure 6 and Figure 3, occasionally cases occur in which cross-sectional imaging studies are very helpful when used in conjunction with sestamibi. Technological advances with single photon emission computer tomography images or nuclear medicine scans may allow this single test to give equivalent information. Selective angiography and venous sampling for PTH levels also are expensive and dependent on the skill of the interventional radiologist performing the procedure, but are necessary for the management of patients who have completely negative imaging study results.

One small subgroup of this patient population that deserves special comment are those with recurrent disease. Initial operations that fail to remove a single adenoma could be expected to lead to immediately persistent hypercalcemia. For 17 patients (8%) who had recurrent disease with a parathyroid adenoma resected with initial resolution of hypercalcemia, elevated calcium levels developed at a much later date. On preoperative imaging and subsequent exploration, most of these patients were found to have parathyroid glands that appeared to regrow at the site of a previous resection. Both gross pathologic evaluation in terms of removal of a lesion within dense scars as opposed to the typical excision around the gland capsule, as well as the finding of suture material from previous explorations adjacent to the parathyroid, support this interpretation.[41] A related category is patients who have parathyroid seeding or parathyromatosis from what is believed to be histologically benign parathyroid adenoma.[42,43] Three patients in our series had this finding, including one patient who had a second operation immediately after the initial one for a further excision of strap muscles and sternocleidomastoid muscles that were contaminated. In this series of 222 patients, 7 patients appeared to have recurrent disease in a single lesion that was on the contralateral side from an earlier excision of an abnormal lesion that resulted in a decrease in serum calcium levels. Recurrent hypercalcemia has not developed in any of these patients, with follow-up ranging between 2 and 10 years after the NIH procedures. Therefore, the possibility of a so-called double adenoma exists in these patients.[44] Again, the interval between the initial resection and the subsequent development of hypercalcemia in these patients were all greater than 6 months and in one case, up to 11 years. It certainly would be possible that a second genetic event could occur in another gland that would result in a second totally independent parathyroid adenoma developing, and that interpretation of metachronous double adenomas appears to be the case for this small group of patients.

There was a very acceptable complication rate for 228 parathyroid re-explorations. The overall incidence of permanent recurrent laryngeal injury is 1.3%, with no recurrent laryngeal nerve injuries in the past 150 patients undergoing re-exploration for missed adenomas at the NIH. These results support the notion that experience in performing this procedure, even in specialized centers, leads to improved outcomes. The most common complication is postoperative hypocalcemia. This is more a complication of the initial failed operation than the secondary successful operation to remove the adenoma. All of these reoperative approaches were very directed toward excising only the abnormal gland without attempts to identify and biopsy normal parathyroid lesions. Therefore, patients who suffered profound postoperative hypocalcemia requiring intravenous calcium and oral vitamin D provide evidence that the other normal parathyroid glands were either excised or devascularized by the initial procedure or procedures. The majority of the patients who required vitamin D because of profound hypoparathyroidism recover, with only a small group (5%) eventually requiring a parathyroid autograft in this clinical situation.

The other complication that may be expected from this type of procedure is hemorrhage. Reoperative procedures are dividing tissue planes that are not anatomic but rather are adhesive scars and lead to a dissection through tissue planes that are more likely complete. For this reason, it is our common practice to drain virtually all reoperative parathyroid procedures. Using this strategy, there has been no incidence of postoperative hematoma requiring evacuation in this series of 228 procedures. The three incidents of bleeding included two cases of mediastinal explorations done through median sternotomy, which presumptively are related to internal mammary injuries. The third patient had a carotid artery disruption during the exposure of the lateral neck. This problem occurs because the common carotid artery low in the neck is related immediately to the posterior strap muscles that are divided at their origin. There may be a rather dense adherence at this tissue plane, and great care needs to be taken to develop this dissection plane during this procedure.

This large single institutional series defines the distribution of missed parathyroid adenomas over a relatively short and recent time interval. Patient selection is an important component of deciding which individuals, after a failed initial procedure, should undergo re-exploration. Because the clinical condition almost universally represents a benign endocrine disorder, only patients who have symptoms that can be related clearly to the primary HPT should be considered for surgical intervention. Consistent with those lines of reasoning, imaging studies should only be obtained in patients who are considered to be surgical candidates and should not be obtained as a deciding factor in who should be referred for surgical re-exploration. The current available imaging strategies and the operative approaches described lead to very successful outcomes with minimal morbidity for these patients.

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Discussion

DR. ORLO H. CLARK (San Francisco, California): I would like to congratulate Dr. Jaskowiak, Dr. Fraker, Dr. Norton, Dr. Doppman, and their colleagues for updating us about their experiences in patients with persistent or recurrent hyperparathyroidism. A 94% success rate in patients having persistent or recurrent hyperparathyroidism is certainly admirable. I have several questions.

One is, you state that you selected your 222 patients based on a presumed single adenoma. I think you need to explain why you selected your series this way rather than perhaps eliminating patients with familial disease. Obviously selecting patients with presumed single adenomas eliminates failures due to multiple abnormal parathyroid glands and does not represent one's overall experience.

My second general question concerns the relatively poor results of your noninvasive localization studies. This is especially surprising because Dr. John Doppman is recognized internationally as one of the most experienced radiologists in this field. You quoted a success rate of approximately 50% for most of your noninvasive studies. In our own series with excellent radiologists at UCSF and UCSF/Mount Zion Medical Center, we have approximately a 70% to 80% success rate using noninvasive localizing studies in patients with persistent or recurrent hyperparathyroidism. Magnetic resonance imaging (MRI) is perhaps the best single test but like ultrasound, is both user and equipment dependent. Ultrasound is very useful for parathyroid tumors in the neck, especially within or immediately adjacent to the thyroid, but obviously will not detect parathyroid tumors within the mediastinum, unless you use it intraoperatively. My question is, why did only 27% of your patients have positive noninvasive localizing studies? When we used all three studies (MRI, sestamibi and ultrasonography) preoperatively in patients with persistent and recurrent hyperparathyroidism, we identify the parathyroid tumor or tumors in 90% of our patients so that only approximately 10% of our patients require selective venous catheterization for parathyroid hormone. This invasive study gives superb results, especially when combined with equivocal or conflicting noninvasive localizing studies.

Another question is, do you believe in double parathyroid adenomas? This is a most important question especially when treating patients requiring reoperation because it certainly influences one's plan for a focused or complete re-exploration.

Although I compliment you on your excellent overall results, I am a little concerned about your high rate of patients requiring vitamin D and subsequent transplantation of cryopreserved