Localization and Reoperation Results for Persistent and Recurrent Parathyroid Carcinoma

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Hypothesis: Reoperation is safe and benefits patients with persistent and recurrent parathyroid carcinoma.

Design: Retrospective study. The mean follow-up time was 8.1 years (median, 7 years; range, 1-23 years).

Setting: A university tertiary referral center.


Results: The mean serum calcium level was 13.7 mg/dL (3.43 mmol/L), and the parathyroid hormone (PTH) level was 1.6 to 20 times the upper limit of normal. Fourteen of 18 patients had persistent or recurrent parathyroid carcinoma and underwent 54 reoperations (28 at our institution). Mean time to recurrence was 4.8 years (range, 1-20 years). Symptoms of hyperparathyroidism were relieved in 86% of patients who had reoperation ($P_{.05}$).

Reoperation for parathyroid carcinoma (25 locoregional and 3 distant) significantly reduced and normalized the serum calcium and PTH levels in 75% and 62% of the cases, respectively ($P_{.001}$). The preoperative serum calcium level was a significant predictor of postreoperative normalization of the serum calcium level but not extent of initial resection, PTH level, time to recurrence, concordance of localization studies, or patient age and sex ($P_{<.01}$). Surgical complications consisted of 5 unilateral and 1 bilateral permanent recurrent laryngeal nerve palsies (2 intentionally resected en bloc), 1 transient hypoparathyroidism, 1 wound seroma, and 1 tracheoesophageal fistula. The sensitivity rates of sestamibi scan (n=14), magnetic resonance imaging (n=15), computed tomographic scan (n=6), ultrasound (n=13), and selective venous catheterization with PTH measurement (n=6) were 79%, 93%, 67%, 69%, and 83%, respectively.

Conclusions: Recurrence is common in patients with parathyroid carcinoma. Patients with this disease should have frequent, lifelong follow-up to ensure early detection of recurrence. Although reoperation for persistent or recurrent parathyroid carcinoma provides significant symptomatic relief and normalizes serum calcium and PTH levels in most patients, it is associated with some morbidity. Localizing studies of parathyroid carcinoma are helpful but do not detect all tumor foci.

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Primary hyperparathyroidism is a common endocrine disorder occurring in 1 in every 500 women and 1 in every 2000 men. This condition is commonly caused by parathyroid adenoma (87%) and parathyroid hyperplasia (12%). Parathyroid carcinoma occurs in 0.1% to 4% of patients with primary hyperparathyroidism. Although it is an uncommon cause of primary hyperparathyroidism, the distinction between parathyroid carcinoma and adenoma is sometimes difficult. Furthermore, no unequivocal histopathologic features of parathyroid carcinoma can be applied with confidence. Therefore, parathyroid carcinomas may be underdiagnosed or overdiagnosed depending on the criteria used.

Patients with parathyroid carcinoma usually have profound symptomatic hypercalcemia (serum calcium level $>14$ mg/dL [$>3.50$ mmol/L]) and local invasion at the time of diagnosis and treatment. Like most endocrine tumors, parathyroid carcinoma is slow-growing, and distant metastases occur late in the progression of the disease. To avoid local recurrence, initial en bloc resection of parathyroid carcinoma is recommended when the diagnosis is suspected at the time of parathyroidectomy. This surgical approach results in up to a 50% cure rate. However, “curative” initial resection cannot be reliably determined after a short follow-up time because subsequent locoregional recurrences or distant metastases may develop. Patients with parathyroid carcinoma commonly die of metabolic complications.
PATIENTS AND METHODS

The study cohort consisted of patients evaluated and treated for parathyroid carcinoma at the hospitals of the University of California, San Francisco, between 1966 and 1999. The following 3 criteria were used to identify cases of parathyroid carcinoma: (1) local invasion; (2) lymph node and distant metastases; and (3) histologic findings of parathyroid carcinoma. Eighteen patients with parathyroid carcinoma were identified, all of whom fulfilled at least 2 of these criteria.

Pathology reports, operative notes, clinical medical records, laboratory data, and clinical follow-up notes were reviewed. Since 1975, patients undergoing reoperation have had direct laryngoscopy before neck exploration to evaluate the function of the vocal cords. Patients with severe symptomatic hypercalcemia or hypercalcemic crisis received preoperative medical therapy, including intravenous saline hydration, diuresis with furosemide, second-generation bisphosphonates, subcutaneous calcitriol, and gallium nitrate. Patients undergoing reoperation for parathyroid carcinoma commonly had at least 2 localizing studies before reoperation. If at least 2 concordant imaging studies did not occur, a selective venous catheterization for parathyroid hormone (PTH) was done.

Since 1987, we have used a questionnaire to ascertain the symptoms associated with primary hyperparathyroidism preoperatively and postoperatively. Before and after reoperation, symptoms of hyperparathyroidism as well as serum calcium and PTH levels were evaluated prospectively. The accuracy of the localizing studies was determined by comparing the results of the imaging study with the histologic findings of the resected tissue. The specificity of the localizing studies was not determined because all of the patients had parathyroid carcinoma (ie, no true negative results). We also evaluated the effect of several clinical factors on the outcome of reoperation for persistent and recurrent parathyroid carcinoma. Recurrent parathyroid carcinoma was defined as new evidence of locoregional or distant parathyroid carcinoma in patients with normal serum PTH and calcium levels for at least 6 months after initial surgical resection. The paired t test was used for comparison of continuous variables before and after operation. The χ² test and Wilcoxon signed rank test were used for comparison of categorical data.

Complications of recurrent or persistent primary hyperparathyroidism and not directly of tumor burden. Because external beam radiation and chemotherapies are generally ineffective for the treatment of persistent or recurrent parathyroid carcinoma, reoperation is often recommended to relieve symptoms and to eradicate residual disease.

In patients with persistent or recurrent parathyroid carcinoma, limited quantitative data exists on the long-term benefit and morbidity rate associated with reoperation. Successful reoperation for residual parathyroid carcinoma depends on accurately localizing all tumor foci. Therefore, we evaluated our experience treating patients with parathyroid carcinoma to quantitatively determine the benefit and morbidity rate of reoperation. We also determined the accuracy of various localizing studies by comparing the imaging study results with the findings of the resected pathologic specimen and clinical follow-up.

RESULTS

The mean age of the 18 patients (13 men and 5 women) at initial diagnosis was 46.1 years (range, 23-63 years). The mean total serum calcium level at diagnosis was 13.7 mg/dL (3.43 mmol/L; range, 9.9-18.4 mg/dL[2.48-4.60 mmol/L]). The serum PTH level was 1.6 to 20 times the upper limit of normal. Table 1 summarizes the metabolic and cardiovascular diseases associated with primary hyperparathyroidism in the 18 patients with parathyroid carcinoma. Three patients experienced a hypercalcemic crisis requiring medical treatment before surgery. Initially, 15 patients had local carcinoma, 2 patients had regional lymph node metastases, and 1 patient had lung metastases. Three patients developed distant metastases (1 bone and lung, and 2 lung) (Figure 1). The sites of locoregional recurrence were the neck (75%; 33% unilateral, 17% contralateral, and 25% bilateral) and the mediastinum (25%) (Figure 2).
Twelve patients had initial en bloc resection; 6 had local excision. Two patients were treated with postoperative external beam radiation, and 1 patient also received 5-fluorouracil. Four of the 18 patients had their initial surgery at our institution and were disease-free at follow-up (Figure 3). The remaining 14 patients were referred for recurrent or persistent parathyroid carcinoma (4 persistent and 10 recurrent) with a mean follow-up time of 8.1 years. Parathyroid carcinoma recurrences appeared 1 year to 20 years after initial surgical treatment. On average, patients with recurrent parathyroid carcinoma had 3 recurrences (range, 1-9). Initial surgical treatment at our institution was associated with a lower risk of persistent or recurrent parathyroid carcinoma (P<.01). These patients had a mean serum calcium level of 12.9 mg/dL (3.23 mmol/L; range, 11.4-14.2 mg/dL [2.85-3.55 mmol/L]). All gross tumors were resected, and 1 patient had an ipsilateral thyroid lobectomy (Figure 3). The overall cause-specific mortality rate was 22% at 10 years. Deaths caused by parathyroid carcinoma occurred in 3 patients with distant metastases and severe hypercalcemia that were resistant to surgical and

![Figure 1. Recurrent parathyroid carcinoma secondary to metastases to the lung. A, Chest radiograph shows localized left lower lobe parathyroid carcinoma lung metastases. Left indicates posterior-anterior view; right, lateral view. Arrows indicate the 2 tumor foci. B, Sestamibi scan shows increased uptake in the same region (white arrow). C, Intraoperative findings at left thoracotomy.](http://archsurg.jamanetwork.com/pdfaccess.ashx?url=/data/journals/surg/9462/ on 10/01/2017)
medical treatment. Additionally, 1 patient died of renal failure.

The 14 patients with persistent or recurrent parathyroid carcinoma required 54 reoperations. Twenty-eight of these (25 locoregional and 3 distant) were at our institution (Figure 3). At cervical reexploration, 4 patients had parathyromatosis as well as parathyroid carcinoma. The overall complication rate was 17%. These complications consisted of 5 unilateral and 1 bilateral permanent vocal cord palsies, 1 transient hypoparathyroidism, 1 wound seroma, and 1 tracheoesophageal fistula. Two of the 6 vocal cord palsies occurred after intentional en bloc resection of the recurrent laryngeal nerve; the remaining 4 did not occur at our institution. The patient with transient hypoparathyroidism required oral calcium replacement. One year later, however, this patient developed recurrent parathyroid carcinoma requiring reoperation. The patient with wound seroma underwent needle aspiration, and the seroma resolved. The patient with tracheoesophageal fistula required reexploration and had primary repair of the fistula.

Reoperation for residual parathyroid carcinoma significantly reduced and normalized the serum calcium and PTH levels in 75% and 62% of the cases, respectively ($P<.001$) (Figure 4). All patients with persistent or recurrent parathyroid carcinoma had 1 or more symptoms of primary hyperparathyroidism (Table 2). These symptoms were relieved in 86% of patients who had reoperation for persistent or recurrent parathyroid carcinoma ($P<.05$). The preoperative serum calcium level was a significant predictor of normalization of the serum calcium after reoperation ($P<.01$); that is, in patients whose serum calcium level returned to normal, the mean was $13.5\pm2.0$ mg/dL ($3.38\pm0.5$ mmol/L) compared with those patients whose serum calcium level was not normalized ($16.3\pm1.9$ mg/dL [4.08±0.48 mmol/L]). The extent of initial resection, PTH level, time to recurrence, concordance of localization studies, and patient age and sex were not significant.

The sensitivity rates of sestamibi scan (n = 14), magnetic resonance imaging (MRI) (n = 15), computed tomographic (CT) scan (n = 6), ultrasound (n = 13), and selective venous catheterization for PTH (n = 6) were 79%,
93%, 67%, 69%, and 83%, respectively. The percentage of concordance between MRI and ultrasound (n=8), sestamibi scan and ultrasound (n=7), and sestamibi scan and MRI (n=10) was 62%, 71%, and 60%, respectively.

### Table 2. Symptoms of Hyperparathyroidism in Patients With Persistent and Recurrent Parathyroid Carcinoma Undergoing Reoperation

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Percentage of Patients With Symptom</th>
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<tbody>
<tr>
<td>Nocturia</td>
<td>55</td>
</tr>
<tr>
<td>Painful joints/bones or low back pain</td>
<td>44</td>
</tr>
<tr>
<td>Urinary frequency</td>
<td>44</td>
</tr>
<tr>
<td>Anorexia/nausea</td>
<td>44</td>
</tr>
<tr>
<td>Irritability</td>
<td>17</td>
</tr>
<tr>
<td>Lack of energy or fatigue/weakness</td>
<td>17</td>
</tr>
<tr>
<td>Increased thirst</td>
<td>17</td>
</tr>
<tr>
<td>Heartburn</td>
<td>11</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>11</td>
</tr>
<tr>
<td>Weight loss</td>
<td>11</td>
</tr>
<tr>
<td>Constipation</td>
<td>6</td>
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<tr>
<td>Depression or mood swings</td>
<td>0</td>
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<td>Forgetfulness</td>
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*Symptoms are based on prospective questionnaire responses in 7 patients with persistent and recurrent parathyroid carcinoma who had 18 reoperations.

Many studies have contributed to the understanding of the natural history, diagnosis, and clinical treatment of parathyroid carcinoma.3-8,11,12 Large cohort studies often lack complete clinical data and suffer from nonuniform diagnostic criteria, and follow-up information regarding persistent or recurrent parathyroid carcinoma is not usually available.3,8,11 A study from a single institution with a smaller cohort circumvents such issues. This type of study allows the evaluation of treatment outcome in patients with persistent or recurrent parathyroid carcinoma, as well as a long enough follow-up time. Although our study is retrospective, a prospective study on the treatment of persistent or recurrent parathyroid carcinoma is impractical because the disease is rare. We believe that our study period and follow-up time are adequate to evaluate the treatment outcome for patients with persistent or recurrent parathyroid carcinoma.

The initial clinical manifestation of parathyroid carcinoma in our cohort was similar to that reported by other investigators.3-8,12 Although no definitive histologic diagnostic criteria exist for parathyroid carcinoma, it is imperative to have 1 of the following 3 criteria: (1) capsular or local invasion; (2) metastases to lymph nodes or distant organs; and (3) local recurrence following complete resection. Some investigators have reported that determining DNA ploidy of parathyroid carcinoma helps to distinguish it from adenoma.13-17 We believe that for all 18 patients, the diagnosis of parathyroid carcinoma was unequivocal. In addition to histologic findings consistent with carcinoma, 17 patients had locally invasive tumors (thyroid, recurrent laryngeal nerve, esophagus, strap muscles, and trachea), 2 patients also had lymph node metastases, and 4 patients had distant metastases.

The rate of recurrent or persistent parathyroid carcinoma was higher in our cohort (78%) compared with other reports (50%-60%).3,4,11 However, our follow-up time was longer. A referral bias might also account for this because 14 of the 18 patients were referred with persistent or recurrent parathyroid carcinoma after undergoing operations at other medical centers. The wide distribution of residual or recurrent parathyroid carcinoma emphasizes the need for an extensive localizing work-up and suggests that local recurrences are not necessarily caused only by tumor cell spillage during the initial or subsequent operation. Our approach has been to rule out metastatic disease and to use at least 2 noninvasive localizing studies that are concordant. Although the use of fine-needle aspiration biopsy to establish a tissue diagnosis has been advocated, we do not recommend this because it may lead to tumor cell spillage and seeding.18

It is intriguing that the preoperative serum calcium level was the only significant predictor of successful normalization of the serum calcium level after reoperation. This probably reflects the tumor burden or the extent of disease at the time of reoperation. Although PTH level was not a significant predictor of normalization of the serum calcium level after reoperation, various PTH measurement assays were used during the 4 decades of this study. We found that patients who had their initial operation (en bloc) at our institution were less likely to have persistent or recurrent parathyroid carcinoma, but a referral bias probably explains this difference. However, initial en bloc resection with ipsilateral thyroid lobectomy has been reported to be a significant favorable prognostic factor on multivariate analysis.8 Because 4 patients who did not have initial en bloc resection had recurrent parathyroid carcinoma with parathyromatosis, we recommend this procedure to avoid tumor cell spillage.2 Resection of the recurrent laryngeal nerve must be done in cases where it is invaded, but otherwise it should be preserved.

To our knowledge, no retrospective or prospective studies have compared the results of observation and surgical intervention in patients found to have residual parathyroid carcinoma.19,20 Surgical reoperation for local and distant residual parathyroid carcinoma provided symptomatic relief and normalized the serum calcium and PTH levels in most patients. Unfortunately, these patients are only temporarily “cured.” Morbidity was associated with reoperation for locoregional parathyroid carcinoma (17% of all reoperations), but when complications at other hospitals and the intentional sacrifice of the recurrent laryngeal nerve were excluded, the complication rate at our institution was lower (6.2% of 28 reoperations). Although this risk of complication is too high, we believe that reoperation is more favorable than no intervention; severe hypercalcemia from recurrent parathyroid carcinoma currently has no effective long-term medical therapy and eventually leads to death, as observed in this and other studies.3-6,8 The relatively high overall complication rate emphasizes the difficult nature of these operations. Patients with recurrent or persistent parathyroid carci-
Parathyroid carcinoma should be referred to surgeons experienced in parathyroid and thyroid surgery.

In general, the use of localizing studies for persistent or recurrent hyperparathyroidism has been extensively evaluated in the literature, but rarely does this include persistent or recurrent parathyroid carcinoma. Although the presence of even occult-functioning residual parathyroid carcinoma can now be accurately diagnosed by measuring the intact serum PTH level, the localization of all tumor sites remains a clinical challenge. Because parathyroid carcinoma is usually a slow-growing neoplasm, locoregional or distant metastases may not be identified until follow-up time becomes longer or a large enough tumor is present. The accuracy of a particular imaging study depends on the size and site of parathyroid carcinoma, institutional experience with the imaging study, and confirmation of the findings after histologic examination of resected tissue. Magnetic resonance imaging and CT scans are especially useful for detecting mediastinal and thoracic parathyroid carcinoma recurrences. Surgical clip artifact may make the interpretation of cervical CT scans difficult, and T1-weighted MRI imaging with gadolinium may be more useful to detect residual locoregional parathyroid carcinoma (Figure 1). Ultrasound is fast, inexpensive, and useful for detecting cervical parathyroid carcinoma recurrence. Sestamibi scans allow for whole-body scanning and therefore may detect distal parathyroid carcinoma metastases. Although selective venous catheterization with PTH measurement is useful when noninvasive imaging studies do not identify a tumor site or are equivocal, it is invasive, not widely available, and localizes tumors only to a region. In the last 2 decades, we have used at least 2 noninvasive imaging studies complementarily. We generally proceed to selective venous catheterization if the imaging findings are negative or equivocal. This approach has resulted in no negative reexplorations. Because we found no statistically significant difference between the various localizing studies, we recommend using imaging studies that are readily available and are most accurate at a particular institution. If the imaging studies are nondiagnostic, we recommend proceeding to selective venous catheterization with PTH assay.

In summary, recurrent and persistent primary hyperparathyroidism is common in patients with parathyroid carcinoma. Thus, complete en bloc resection during the initial operation and frequent, lifelong follow-up are essential. Reoperation for persistent or recurrent parathyroid carcinoma results in quantitative symptomatic and biochemical benefits but is associated with some morbidity. Although patients who have residual parathyroid carcinoma usually cannot be cured with surgical resection, early detection of recurrence improves the results of surgical reopening.

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**REFERENCES**


**DISCUSSION**

David Byrd, MD, Seattle, Wash: Dr Kebebew and his colleagues at UCSF [University of California, San Francisco] have presented a series of patients with persistent and recurrent parathyroid carcinoma, a rare but frustrating and difficult clinical problem. This is a retrospective review of 18 patients over 33 years with a mean follow-up of 8 years, including 4 patients undergoing initial resection at UCSF and 14 patients who were referred with persistent or recurrent disease. The 2 aims of this study were to determine the benefit and morbidity of reopera-
tion, and the accuracy of imaging studies for the disease. All patients were symptomatic, and the majority of patients had symptom relief after reoperation. However, the morbidity of 54 operations in these 18 patients was substantial, with 6 patients ending up with recurrent nerve palsies (1 was bilateral). Also, 4 patients eventually died of uncontrolled disease. The description of imaging studies was less detailed and less clear, but the conclusion was that 2 concordant imaging studies predict a successful though rarely curative operation.

The UCSF experience confirms the observation made by others that this is a chronic and eventually terminal disease in most patients. The history lesson described should lead us to focus on the initial aggressive surgical management of this disease and raises several questions for the authors. The 4 patients undergoing initial operation at UCSF have not recurred. What are their follow-up, and are they cured? What is the authors' definition of an en bloc resection? Because only 2 patients had positive nodes, should any nodal dissection be performed at initial operation? In patients without renal failure or familial disease, marked elevations in calcium and PTH [parathyroid hormone] levels before exploration should alert the surgeon to suspect or anticipate a possible diagnosis of carcinoma. Should all of these patients have preoperative localizing studies? Since 25% of the reoperative patients had bilateral disease, could one side of the neck be spared an exploration and possible recurrence by performing an initial unilateral exploration on the side with positive imaging studies, perhaps aided by intraoperative PTH testing? One criterion of malignancy was local invasion, including the thyroid gland, strap muscles, and other adjacent structures. Occasionally, long-standing adenomas can be adherent to the thyroid capsule. Are any of these "sticky" adenomas early carcinomas, and should they be treated differently? The authors also mention parathyromatosis. How does this finding differ clinically from carcinoma, and should it be treated similarly to carcinoma? For those patients with persistent or recurrent disease, especially if the recurrent nerves are still intact, we should encourage our patients to go to UCSF for their reoperation.

Ronald G. Latimer, MD, Santa Barbara, Calif: The finding of contralateral and bilateral carcinoma on reexploration is fascinating and suggests perhaps a pan-parathyroid tendency toward malignancy. Should a total parathyroidectomy be performed at the initial operation if carcinoma is truly suspected? Second, I would like to ask the authors, what is the follow-up on the 38% of patients for whom the PTH was not normalized?

Theodore X. O'Connell, MD, Los Angeles, Calif: One of the difficulties in judging the value of the different localization studies is that this study was done over almost 40 years, and obviously localization studies have changed over that time. Certainly MRI and sestamibi scan have really only come into predominance in the last 10 years. My question is, what would you do now with the present modalities that we have available as far as localization is concerned?

The second question also involves localization in that there was no mention of specificity because all of the patients were deemed to be positive, but were they positive in the areas that the localization tests said they would be positive in? Certainly in noncarcinoma parathyroid disease, we find that sestamibi is much more specific than ultrasound or MRI because they simply show a mass and really are not specific about what the mass is. Is this the same finding with parathyroid carcinoma?

William P. Schecter, MD, San Francisco, Calif: Can you elaborate on the cause of the tracheoesophageal fistula postoperatively? Was that related to malignancy, and what can we learn to avoid that complication?

John T. Vetto, MD, Portland, Ore: This has been an area of interest of mine, and the most recent paper I read on it was from the journal Surgical Oncology. They reported a group of mostly node-negative patients with an 80% rate of disease-related survival, and your group presented basically the same number today, which I think underscores your conclusion that aggressive operation is worthwhile. In that regard, I would like to ask the authors exactly what triggers they are recommending for reoperation: calcium or parathyroid hormone, and at what levels?

Second, in regard to imaging, is there any role for PET [positron emission tomography] scanning in this disease?

John A. Ryan, MD, Seattle: I was interested in the 6 cases that were referred to UCSF that had initial removal of only the parathyroid tumor. Were those cases considered to be cancer by the original surgeons, or were they thought to be benign parathyroid adenomas and were referred not as cancer cases but as persistent or recurrent hyperparathyroidism?

Jeffrey A. Norton, MD, San Francisco: I am interested in familial parathyroid cancer. I want to know if any of these patients have the familial form of parathyroid cancer. Second, if you have a family with parathyroid cancer and 1 of the offspring develops primary hyperparathyroidism, what operation do you recommend?

President John MacFarlane, Vancouver, British Columbia: Dr Clark, I would like to ask whether any of these patients had radiation therapy and whether it has any effect in this disease.

Dr Clark: I appreciate the opportunity to present this information. I am saddened not to have Dr Leonard Rosoff here to comment about our work because he, unfortunately, has recently died. Many of the senior members in this society are aware that Leonard frequently discussed our presentations in a most insightful and energetic manner. We will greatly miss him.

I appreciate David Byrd's excellent discussion and questions. In answer to the questions, our follow-up in these patients treated at UCSF was from 2 to 27 years. As mentioned, 26 operations were done prior to referral to UCSF and 28 at UCSF. In response to the question as to whether some of these patients are cured, one does not initially know, but all patients with an increased PTH level after parathyroidectomy must be considered to have persistent hyperparathyroidism until proved otherwise. This situation is different from what occurs in patients who have primary hyperparathyroidism without parathyroid cancer when the PTH may be elevated postoperatively, in patients who are cured of their disease. The latter situation, that is, normocalcemia and a normal or increased PTH level, occurs in about 40% of patients using midregional or C-terminal PTH assays but in only about 5% of patients using an intact or 2-site PTH assay. The only factor that correlates with postoperative normocalcemia and increased PTH levels is the severity of the hypercalcemia preoperatively.

In patients with parathyroid cancer, however, increased PTH levels suggest persistent disease until proved otherwise. In patients with parathyroid cancer, the PTH often increases before the patient develops recurrent hypercalcemia.

The question was asked, what is an en bloc dissection for patients with parathyroid cancer? The operation includes resecting all tissues immediately adjacent to the parathyroid cancer, including the ipsilateral thyroid lobe, when the tumor is adherent to the thyroid gland. Parathyroid cancers are usually whitish and more scarlike and fibrotic rather than being dark whitish and more scarlike and fibrotic rather than being dark brown, with a smooth capsule as are large parathyroid adenomas.

The major decision the surgeon must make is whether to resect the recurrent laryngeal nerve. In patients where parathyroid cancer is suspected preoperatively or who have any change in voice, direct or indirect, it is essential to determine whether the vocal cords are functioning normally. When the ipsilateral vocal cord is not functioning, it should be resected. If it is functioning, it is debatable whether it should be resected, and this decision should be made by the surgeon de-
pending on the invasiveness of parathyroid cancer. Local lymph nodes are usually not involved, but any enlarged nodes near the parathyroid cancer should be removed.

As Dr Kebebew mentioned, preoperative localization studies are very useful in patients with recurrent and persistent hyperparathyroidism due to parathyroid cancer. Unfortunately, however, such studies often identify parathyroid cancer at one site, but other sites may also be involved. Remember, most of these patients die of hypercalcemic complications, not because of the tumor itself, so resection of metastatic disease can prolong survival and the quality of life of the patient by lowering the blood calcium level.

Should surgeons explore only one side of the neck and do intraoperative PTH testing? This would be an acceptable approach, but we do not recommend it. Dr Norton mentioned that patients with familial hyperparathyroidism are more likely to have parathyroid cancer and also multiple abnormal parathyroid glands. This is especially true in patients with familial hyperparathyroidism and jaw tumor syndrome. Intraoperative PTH assays are not as accurate in patients with parathyroid hyperplasia. We did not have any patients with familial hyperparathyroidism and jaw tumor syndrome in this series.

How does one diagnose parathyroid cancers? Differentiating between benign and malignant endocrine tumors can be difficult. This is especially true in patients who have recurrent and persistent hyperparathyroidism. Patients who have locally invasive or metastatic parathyroid tumors at initial operation obviously have parathyroid cancer. However, I have seen patients with persistent hypercalcemia who were told that they had parathyroid cancer when their persistent hypercalcemia was due to another abnormal, yet benign, parathyroid tumor. Other patients may develop recurrent or persistent hypercalcemia due to parathyromatosis that most often results from fracturing an apparently benign parathyroid tumor. Such tumors may then implant and cause recurrent disease. Parathyromatosis can also develop in patients who have never had a previous parathyroid operation. These patients are thought to have embryologic rests or little vestigial parathyroid glands that can result in primary or secondary hyperparathyroidism. Histologically, parathyromatosis looks exactly like hyperplastic parathyroid tissue and does not have any of the histological criteria used for diagnosing parathyroid cancer. We believe that some patients with parathyromatosis have a variant of parathyroid cancer because we have observed both conditions in the same patients. Patients with parathyromatosis, like patients with parathyroid cancer, are sometimes difficult to cure, so more than local seeding occurs.

Dr Latimer asked whether patients should be treated by total parathyroidectomy. I assume that he meant total parathyroidectomy with autotransplantation of a portion of a normal parathyroid gland into the forearm. I would not recommend this approach. However, in patients with parathyroid cancer at the first operation, one might remove the parathyroid cancer and normal parathyroid gland on the side of the cancer and consider autotransplanting a portion of the normal gland. It should be mentioned that parathyroid cancers usually (50 or 60%) recur at the site of the original cancer but can occur in the contralateral neck, as our study documents.

Dr O’Connell inquired about the best localization study. Ultrasound is excellent for tumors in the neck but requires an experienced radiologist. Sestamibi is quite good for parathyroid tumors situated in ectopic sites and, as our series demonstrates, can identify distant metastases. Unfortunately, sestamibi scans can fail to identify some large parathyroid tumors. Therefore, it is probably best to use more than 1 localization study in patients with recurrent or persistent hyperparathyroidism.

As you know, the parathyroid glands are usually situated on the posterolateral capsule of the thyroid gland. Dr Schecter asked about the 1 patient in our series who developed a tracheoesophageal fistula after a reoperation for parathyroid cancer. In patients with parathyroid cancer, the tumor sometimes invades the muscular wall off the esophagus. In resecting these tumors, one must resect the muscular wall of the esophagus. This situation probably resulted in the tracheoesophageal fistula. In such situations, especially when invasive tumor is resected from both the trachea and esophagus, I recommend placing the sternothyroid muscle between the trachea and esophagus, which are denuded. I might mention that this is not necessary to reapproximate the muscle wall of the esophagus as long as the inner layer is intact. Placing the sternothyroid muscle between the trachea and esophagus, however, makes it more difficult to interpret subsequent MRI scans.

Dr Vetto asked about the criteria we use for reoperation. When the site or sites of recurrent parathyroid cancer are known in patients with recurrent or persistent hyperparathyroidism, all such patients should be considered for reoperation. Last month I operated on a patient with a blood calcium level of 19 mg/dL and parathyroid cancer identified by MRI scanning beneath his sternum. I removed a 7-cm substernal parathyroid cancer via a median sternotomy. Unfortunately, his hypercalcemia only decreased to 14 mg/dL, so he must have other metastatic deposits.

A question was raised about the value of PET scans. Some institutions, such as Memorial Sloan-Kettering in New York City, have had excellent success in patients with thyroid cancer using PET scans. In general, I have not found PET scans to be useful in patients with recurrent or persistent hyperparathyroidism. I have only used them when other localization studies were equivocal or negative so that the elusive tumor was obviously difficult to identify. Positron emission tomography scans are also quite expensive.

Dr Ryan asked whether parathyroid cancer was suspected at the initial operation. I do not know the answer to this excellent question. Surgeons are reluctant to resect a functioning recurrent laryngeal nerve, so a parathyroid tumor might have been fractured to preserve the recurrent laryngeal nerve. When this happens and the patient has parathyroid cancer, recurrent disease is likely.

Dr Norton asked whether patients with familial disease and parathyroid cancer should be managed differently. This is an excellent question. Although I am not a strong advocate of parathyroid autotransplantation, one should consider autotransplantation of the most normal-appearing parathyroid gland to the nondominant forearm in patients with familial disease and parathyroid cancer, as recurrent disease would be easier to manage. I would probably individualize the treatment of such patients because I think that there are aggressive and nonaggressive parathyroid cancers. Some are low-grade tumors, as we have shown, and these patients can be cured, whereas others are aggressive, and we can unfortunately only offer palliative treatment.

Dr MacFarlane asked about the value of radiation therapy. Most reports, but not all, suggest that radiation is not helpful. Surgeons are reluctant to recommend radiation treatment because reoperation after radiation is often not possible. However, if everything else fails, radiation may be beneficial, especially for bony metastases.