Multiple-Gland Disease in Primary Hyperparathyroidism

A Function of Operative Approach?

Natalie C. Lee, MD; Jeffrey A. Norton, MD

Hypothesis: The approach to surgery for primary hyperparathyroidism (PHPT) is controversial. To determine whether routine bilateral neck exploration increases the detection of multiple-gland disease compared with a focused unilateral approach, we compared the incidence of single- vs multiple-gland disease in patients undergoing surgical treatment for PHPT as a function of unilateral or bilateral exploration.

Data Sources: From 1993 through 1997, 214 consecutive patients underwent initial bilateral neck exploration for PHPT by a single surgeon. Each patient underwent the surgical procedure without prior localizing studies. Four parathyroid glands were identified, and abnormal glands were excised. The results were compared with published studies of patients who underwent either bilateral neck exploration or focused unilateral neck exploration for PHPT.

Study Selection: All reported studies from 1995 through 2001 in a MEDLINE search using the terms “parathyroidectomy” or “primary hyperparathyroidism and surgery” and either “bilateral” or “conventional” or “minimally invasive,” “selective,” or “unilateral.”

Data Extraction: The studies were analyzed for numbers of patients and a final diagnosis of either a single adenoma or multiple-gland disease (double adenoma or hyperplasia). Proportions were compared statistically with a $\chi^2$ test.

Data Synthesis: In our series of 214 patients who underwent bilateral neck exploration, 79.4% had a single adenoma, and 20.6% had multiple-gland disease. Of 2166 patients in 14 studies who underwent bilateral neck exploration, 79.7% had a single adenoma, and 19.3% had multiple-gland disease. Of 2095 patients in 31 studies with a focused unilateral approach, 92.5% had a single adenoma, whereas only 5.3% had multiple-gland disease. The incidence of multiple-gland disease was significantly lower among patients treated with a focused unilateral approach compared with a bilateral approach as used in our series and the literature ($P<.001$).

Conclusion: The data suggest that a focused unilateral surgical approach for PHPT may underestimate the incidence of multiple-gland disease.

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Primary hyperparathyroidism (PHPT) is a common disease, affecting an estimated 27.7 per 100,000 people in the United States.1 Whereas malignancy accounts for the majority of hypercalcemia in hospitalized patients, PHPT is the most common cause in the outpatient setting;2 it is caused by a single adenoma in 85% of cases, hyperplasia in 15%, double adenoma in 1% to 2%, and carcinoma in 1%.3 Surgery is the only curative treatment for PHPT. Surgical exploration is recommended for all patients with biochemically documented PHPT and signs or symptoms of the disease.4 Even clinically asymptomatic patients often have subtle symptoms that improve after parathyroid surgery.5 However, the surgical approach to patients with PHPT is controversial.

Bilateral neck exploration with examination of all 4 glands has been the standard of care for years because an experienced surgeon can cure the disease in more than 95% of cases.6 In recent years, a selective approach has been advocated, with unilateral exploration based on preoperative localization studies such as ultrasound, computed tomography or sestamibi scan, and/or intraoperative methods, such as gamma probe detection or parathyroid hormone assay. However, because all these tests have a certain rate of false-negative results, this unilateral focused approach may potentially lead to failure to diagnose multiple-gland disease.

To determine whether routine bilateral neck exploration increases the detection and diagnosis of multiple-gland dis-
PATIENTS AND METHODS

From 1993 through 1997, 214 consecutive patients with PHPT based on elevated serum levels of calcium and intact parathyroid hormone and clinical symptoms or signs underwent an initial parathyroid operation by a single surgeon (J.A.N.). Each patient underwent bilateral neck exploration without prior localizing studies. Visualization of 4 parathyroid glands was attempted. Normal parathyroid glands were identified primarily by size criteria, in that normal glands are usually 3×4×5 mm and weigh between 30 and 50 mg. Abnormal glands were identified as considerably larger glands and when found were removed. A successful outcome was defined as the resolution of hypercalcemia at the 3-month follow-up. Adenoma was defined as having a single abnormal parathyroid gland, and multiple-gland disease was defined as having multiple abnormal glands. Hypoparathyroidism was defined as requiring oral calcium and calcitriol (vitamin D₃) treatment at the 3-month follow-up. Recurrent laryngeal nerve injury was defined as a hoarse voice and immobile vocal cord at the 3-month follow-up. Recurrent laryngeal nerve injury was defined as a hoarse voice and immobile vocal cord at the 3-month follow-up.

To compare our series of patients with the recently published literature on parathyroid operations, a MEDLINE search of articles published from 1995 through 2001 was performed using the terms "parathyroidectomy" or "primary hyperparathyroidism and surgery" and either "bilateral" or "conventional" or "minimally invasive," "selective," or "unilateral." Studies focusing only on patients with familial or multiple endocrine neoplasia syndromes were excluded because almost all these patients have parathyroid hyperplasia. Reported studies were grouped according to operative technique, either bilateral neck exploration or focused unilateral neck exploration. The studies were analyzed for number of patients and an anatomic diagnosis of single adenoma or multiple-gland disease (either double adenoma or hyperplasia). Information about complications including persistent hypercalcemia, hypoparathyroidism, and recurrent laryngeal nerve injury was obtained for each study. Proportions were compared statistically with a χ² test.

In our series and other published series of patients with PHPT undergoing bilateral neck exploration, there was a 20% incidence of multiple-gland disease. In marked contrast, only 5% of patients undergoing focused unilateral neck exploration were found to have multiple-gland disease. These findings suggest that the detection of multiple-gland disease in patients with PHPT may be a function of operative approach. Further, the diagnosis of multiglandular disease may be missed by a unilateral focused approach.

Noninvasive imaging techniques for preoperative localization include ultrasound, computed tomography, magnetic resonance imaging, and sestamibi scintigraphy. Sestamibi scintigraphy is the most accurate. Its sensitivity is between 80% and 90%. The other techniques may add to the efficacy of sestamibi scanning alone, but they also increase the cost. Prospective studies of preoperative localization have shown that using these imaging techniques does not significantly improve outcome or decrease the length of the operation. Further, these methods often fail to detect multiple abnormal glands. If a patient has hyperplasia or multiple abnormal parathyroid glands, preoperative imaging com-

### RESULTS

In our series of 214 consecutive patients with PHPT who underwent bilateral neck exploration, 79.4% had a single adenoma, and 20.6% had multiple-gland disease (Table). Of 2166 patients in 14 studies from the literature who underwent bilateral neck exploration, 79.7% had a single adenoma, and 19.3% had multiple-gland disease. The reported results were almost identical to our series. In contrast, of 2095 patients in 31 reported studies who underwent focused unilateral exploration, 92.5% had a single adenoma, and only 3.3% had multiple-gland disease. These results were significantly different from our series and the literature for bilateral exploration (P < .001).

Success rates were similar in all the series of unilateral and bilateral exploration (97%-98%). Further, there were no significant differences in complication rates. The rates of hypoparathyroidism (1%-2%) and recurrent laryngeal nerve injury (<1%) were the same among all series of bilateral exploration and unilateral exploration (Table).
monly does not visualize all the abnormalities. Finally, intraoperative parathyroid hormone assay may also fail to identify multiple-gland disease because levels may prematurely fall after removal of a single abnormal gland. The use of preoperative localization studies has gained acceptance and popularity because most patients have a single adenoma and a positive study can guide the surgical procedure, resulting in a more focused and less complex operation. Patients who have undergone the focused approach are commonly discharged from the hospital early, and the results are comparable to those from the bilateral procedure.

The major concern when using a focused unilateral surgical approach is a possible failure to diagnose multiglandular disease. The data presented here suggest that this may be the case because the incidence of multiglandular disease in series in which bilateral explorations were done is 20%, whereas the incidence with focused unilateral explorations is only 3%. This difference is significant and may be explained by 3 possibilities. First, the focused approach selects patients who have an adenoma based on localization studies, whereas patients with hyperplasia can then undergo the bilateral approach. This may be the case, but it has not been described in any of the articles describing the focused unilateral exploration.\(^2,3\) The second possibility is that complete bilateral neck exploration falsely identifies healthy parathyroid glands (normally functioning) as being abnormal. This would also explain why the results of the focused approach are different to those of the bilateral exploration. The third explanation, and the one that we favor, is that the focused approach fails to detect multigland disease. If this is the case, the development of recurrent PHPT may be much greater in patients with the unilateral approach. This has not been reported as yet,\(^2,3\) but it behooves surgeons who use the unilateral approach to carefully follow their patients for the development of recurrent hypercalcemia. This may take months or years to happen, and the follow-up of most studies is short. It will take more time and observation to discern if multigland disease has been missed.

Abnormal serum studies are used to diagnose PHPT, but the exact origin of the disease is determined at the time of the operation. Even the pathologist may not be able to discern adenoma from hyperplasia. The surgeon’s role in this process is critical. It is part of the art and science of endocrine surgery. Even in focused approaches, the surgeon should try to perform a biopsy of 1 normal gland in addition to the adenoma to unequivocally exclude hyperplasia. Further, the serum calcium level of the patient should be followed for long periods to determine if cases that appear to be successful really are. If long-term outcome studies suggest that the unilateral approach is as durably effective as the bilateral approach, then perhaps it may become the procedure of choice for patients with PHPT. However, if follow-up studies suggest that the rate of recurrence is high, as this study predicts, then bilateral neck exploration may again be the preferred procedure for PHPT.

REFERENCES


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**DISCUSSION**

Edward A. Dainko, MD, San Bernardino, Calif: For patients undergoing parathyroidectomy for hyperparathyroidism, the authors attempt to determine whether bilateral neck exploration increases the detection of multiple-gland disease by comparing their experience with 214 patients operated on over a 3-year period, 1993 through 1997, with those in published series of unilateral neck explorations and bilateral neck explorations. In the authors' series, each patient underwent bilateral neck exploration. No patient had preoperative localization studies.

They found that 79.4% of their patients had single adenomas, with 20.6% having multiple-gland disease. In the literature that they reviewed, which is a slight increase over their abstract, 2166 patients in the studies that they reviewed underwent bilateral neck explorations, and the results in the literature were exactly the same as the authors'. This tends to support their hypothesis. In 2095 patients in 31 studies undergoing unilateral exploration, however, 92.5% were found to have single adenomas, with 5.3% having multiple-gland disease. This should suggest that unilateral neck explorations will miss some patients with multiple-gland disease. This makes their case for bilateral neck exploration in PHPT.

Most surgeons agree with the premise that bilateral neck exploration with visualization of all 4 glands when operating for PHPT is the standard. Not everyone, however, would perform biopsies of normal glands. The new and improved preoperative localization techniques, along with availability of intraoperative intact parathyroid monitoring, however, have led some surgeons recently to advocate exploration on the basis of these findings. Even employing preoperative high-resolution ultrasound and sestamibi scintigraphy, the presence of multiple-gland disease, however, could not be ruled out entirely.

There are at least 2 recent studies that have suggested this. Reasons for postoperative persistence of hyperparathyroidism are usually the missed parathyroid adenomas, most often in their usual anatomic locations. Incomplete removal of multiple adenomas or hyperplastic glands accounts for many of the other failures. Rarely, variants of localization of the usual glands is another cause. Reoperative parathyroid surgery results have been improved with the use of these noninvasive localization studies, such as the sestamibi scan, the ultrasound, computed tomography, magnetic resonance imaging, and the intraoperative parathyroid hormone monitoring.

We have already had some discussion concerning this paper and the previous paper, so I would like to ask the authors a few questions. You did talk about the size of the adenomas found in the multiple-gland disease were. What was your incidence of recurrent nerve injury and hyperparathyroidism in both the literature and in the authors' papers to suggest that the unilateral approach is not necessarily going to resolve the laryngeal nerve injury. Was your incidence of recurrent or persistent hyperparathyroidism? I expect that it should be low. Were any patients included who were operated on for the multiple endocrine neoplasia syndrome?
Quan-Yang Duh, MD, San Francisco, Calif: Although I agree with your hypothesis that some of these multiple-gland diseases are missed, my belief is that the results actually come from patient-selection bias by preoperative localization studies. The problem is that most studies do not take into account the principle of intent to treat. What happened is this: The limited exploration approach is usually done only after a positive localization study. Because sestamibi and other localization studies are less accurate for multiglandular disease, positive localization studies select out a group of patients less likely to have multiple-gland disease. To put it another way, a scan-directed operation is performed in a scan-selected group of patients. This selection can lower the apparent percentage of multiglandular disease. I will give you an example. If you take 100 patients and 80 of them have single-gland disease and 20 of them have multiple-gland disease, as in our series, the sestamibi is 80% sensitive for the single-gland disease, so you have 64 positive patients (true-positive). Of the other 20 patients who have multiglandular disease, one third will show nothing, one third will show multiple-gland disease, and one third (let us say 7 patients) will have a positive scan that shows only 1 gland. So now you have 7 plus 64 patients for a total of 71 patients (out of the initial 100 patients) who will have a positive scan showing only 1 gland. So the percentage of multiglandular disease becomes 7 divided by 71, which is slightly less than 10%, instead of 20% in the original 100 patients. In fact, this is not very different than what Dr Norton showed in the literature.

Ronald G. Latimer, MD, Santa Barbara, Calif: From the southern part of the United States, Dr Irvin and Dr Norman tell us that we need to not talk about morphologically enlarged glands but physiologic-functioning glands and that intraoperative parathyroid hormone and the nuclear sestamibi localization with the 20% rule measure the glands that are actually functioning and producing the disease. So we are discussing multiple-gland enlargement in this situation vs multigland disease. The last observation is that we have heard about modern parathyroid surgery and modern gallbladder surgery. There may be hope for some of us who are retired being recalled to do an open gallbladder and occasionally a bilateral neck exploration.

Dr Norton: In response to Dr Dainko, the typical weight of the parathyroid glands in the patients with hyperplasia is 300 mg. The patients with multiple-gland disease were older than those with adenoma. We tried to perform biopsies of 4 parathyroid glands in every patient at the time of surgery. However, if you look at our ability to find and perform biopsies of 4 glands, it was only 86%. So although we tried, we didn’t successfully perform biopsies of all the glands. We did have an interest in multiple endocrine neoplasia type I. The incidence of it may be greater in our patient group than the literature.

In response to Dr Duh, I agree wholeheartedly that this may be a patient-selection phenomenon. Your point is well taken. However, I ask you the question, where are the patients with hyperplasia going? There is currently no evidence that patients with negative imaging are being referred to a special surgeon for bilateral neck exploration.

In response to Dr Latimer, I agree with you that there is a need for surgeons who can still do bilateral neck exploration.