

# Parathyroidectomy for Primary Hyperparathyroidism in Octogenarians and Nonagenarians

## A Plea for Early Surgical Referral

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**Background:** Surgical referral of elderly patients with PHPT is often deferred because of the perceived risks of general anesthesia, increased age, and comorbidities and also because many of the symptoms of PHPT are difficult to distinguish from the aging process.

**Hypothesis:** Parathyroidectomy for primary hyperparathyroidism (PHPT) in elderly patients is beneficial and safe.

**Design:** Retrospective study of patients with PHPT who were 80 years and older.

**Setting:** Tertiary academic referral medical center.

**Patients:** Fifty-four consecutive patients (43 women and 11 men) with a mean age of 83.6 years who underwent parathyroidectomy for PHPT.

**Main Outcome Measures:** Delay in surgical referral; improvement in symptoms and normalization of serum calcium and parathyroid hormone levels; and perioperative morbidity and mortality.

**Results:** Twelve (22%) of 54 patients had a mean delay of 5 years (range, 1.2-10.0 years) before surgical referral for a known diagnosis of PHPT. No patient had asymptomatic PHPT. There was no significant difference in the preoperative mean serum calcium level and symptoms of PHPT resulting from delay in surgical referral. Parathyroidectomy resulted in significant improvement of PHPT-associated symptoms of fatigue, weight loss, nocturia, bone pain, constipation, and major depression ( $P < .05$ ). All patients had normal serum calcium and parathyroid hormone levels postoperatively. The average length of hospitalization was 1.9 days. There were 3 complications (9%): 1 urinary tract infection, 1 bladder perforation, and 3 transient hypocalcemia. There was no perioperative mortality.

**Conclusions:** Parathyroidectomy in elderly patients is safe, curative, and beneficial. Surgical referral for parathyroidectomy should be considered in elderly patients with PHPT.

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**P** RIMARY hyperparathyroidism (PHPT) is common in the elderly population, with a prevalence of up to 7%.<sup>1</sup> Because life expectancy is increasing in the United States, the incidence and prevalence of PHPT will likely continue to increase in this growing geriatric population.<sup>2</sup> Even though parathyroidectomy is successful in more than 95% of patients with PHPT when performed by experienced surgeons, some patients with PHPT are observed or medically treated.<sup>3</sup> Furthermore, in elderly patients with PHPT, referral for parathyroidectomy may be delayed because of patient preference, the patient's increased age, unclear or limited life expectancy, perceived increase in perioperative morbidity and mortality, and difficulty in distinguishing neuropsychiatric symptoms caused by PHPT from those of the general aging process.<sup>4</sup> Although several stud-

ies in octogenarians undergoing other types of major surgical intervention have demonstrated that selected patients tolerate these procedures well, referral of elderly patients with PHPT for parathyroidectomy is often delayed even when clear metabolic complications of PHPT are present.<sup>5,6</sup>

Some contemporary studies have investigated the symptom profile of PHPT in younger as compared with older patients as well as outcomes of parathyroidectomy.<sup>7-9</sup> The reported morbidity and mortality rates associated with parathyroidectomy in elderly patients are up to 10% and 4%, respectively.<sup>10,11</sup> Some endocrinologists and surgeons may have a higher threshold for recommending parathyroidectomy in older patients with PHPT than in younger patients, whereas surgeons with high-volume practices may have a lower threshold for recommending parathyroidectomy in the elderly.<sup>12</sup> As the population of

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### Clinical, Biochemical, and Pathological Characteristics of Patients With PHPT

| Characteristic                                      | Value           |
|---|-----------------|
| Sex, No. F/M  | 43/11           |
| Age, y  |                 |
| Mean $\pm$ SD                                       | 83.6 $\pm$ 3.47 |
| Range   | 80-92           |
| Metabolic complications of PHPT, No. (%)            |                 |
| HTN   | 27 (50)         |
| Osteoporosis/osteopenia                             | 14 (26)         |
| Bone fracture history                               | 11 (20)         |
| Gout  | 7 (13)          |
| Peptic ulcer disease                                | 5 (9)           |
| Nephrolithiasis                                     | 4 (7)           |
| Hypercalcemic crisis                                | 1 (2)           |
| Pancreatitis  | 0               |
| Hereditary basis, No.                               |                 |
| Familial PHPT                                       | 1               |
| Sporadic PHPT                                       | 53              |
| History of radiation exposure, No. yes/no           | 3/51            |
| Calcium, mg/dL                                      |                 |
| Mean  | 11.6            |
| Range   | 10.3-15.6       |
| PTH level, $\times$ upper limit of normal           |                 |
| Mean  | 5.92            |
| Range   | 1.1-22.0        |
| Sensitivity of localizing studies, No. (%)          |                 |
| Ultrasound  | 18/32 (56)      |
| Sestamibi   | 23/28 (82)      |
| MR imaging  | 1/1 (100)       |
| CT  | 2/2 (100)       |
| Solitary adenoma*                                   | 42/54 (78)      |
| Double adenoma                                      | 0/4             |
| Hyperplasia   | 0/3             |
| ASA status, † No.                                   |                 |
| 1   | 0               |
| 2   | 25              |
| 3   | 21              |
| 4   | 4               |
| 5   | 0               |
| Anesthetic approach, No.                            |                 |
| General   | 53              |
| Local block   | 1               |
| Reoperative cases, No.                              |                 |
| Previous thyroidectomy                              | 8               |
| Previous parathyroidectomy                          | 3               |
| Concurrent procedures during parathyroidectomy, No. | 4‡              |
| Pathological findings, No.                          |                 |
| Solitary adenoma                                    | 40              |
| Double adenoma                                      | 8               |
| 4-Gland hyperplasia                                 | 6               |
| Complications, No.                                  |                 |
| Transient hypocalcemia                              | 3               |
| Urinary tract infection                             | 1               |
| Bladder perforation                                 | 1               |
| Mortality, No.                                      | 0               |

Abbreviations: ASA, American Society of Anesthesiologists; CT, computed tomography; HTN, hypertension; MR, magnetic resonance; PHPT, primary hyperparathyroidism; PTH, parathyroid hormone.

SI conversions: To convert calcium values to millimoles per liter, multiply by 0.25.

\*Sensitivity of localizing studies by pathological findings of parathyroid gland(s) included combined sestamibi, ultrasound, CT scan, and MR imaging.

†Two patients were classified as 3E because they underwent "emergency" parathyroidectomy for hypercalcemic crisis. Four patients did not have their ASA status documented in the medical records.

‡Total thyroidectomy for papillary thyroid cancer, bilateral orchiectomy for prostate cancer, Zenker diverticulum repair, and ventral hernia repair.

octogenarians and nonagenarians is expected to double during the next decade, even more geriatric patients will be considered for surgical evaluation for PHPT.<sup>2</sup> A better understanding of the results of parathyroidectomy in this group of patients will be necessary, especially considering the current climate of limited health care expenditure. Therefore, we studied our experience in patients with PHPT who were octogenarians and nonagenarians to evaluate surgical referral practices, efficacy of parathyroidectomy, and perioperative morbidity and mortality associated with parathyroidectomy.

### METHODS

Between June 1, 1986, and February 28, 2001, 1482 patients underwent parathyroidectomy for PHPT at the University of California, San Francisco, hospitals. The study cohort consisted of patients selected from an existing database who were 80 years of age or older; 54 patients fulfilled this criterion.

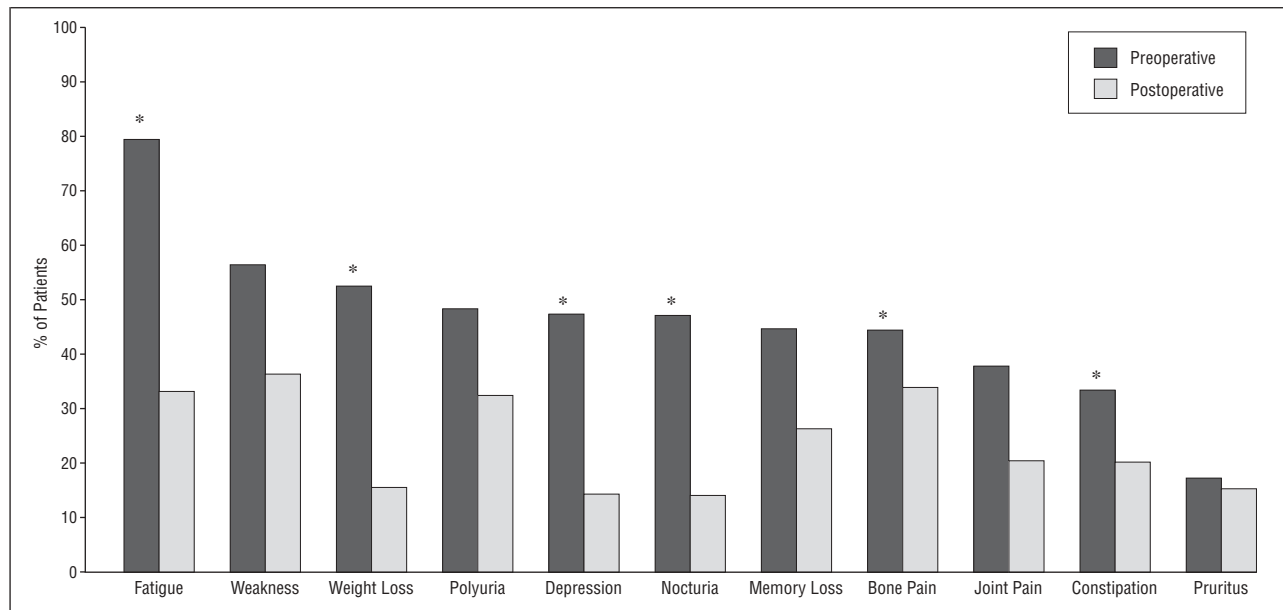
Pathology reports, operative notes, clinical medical records, laboratory data, and clinic follow-up notes were reviewed. Since 1987, we have used a standardized questionnaire to ascertain the presence or absence of symptoms associated with PHPT preoperatively and postoperatively.<sup>7</sup> As part of the patient's routine care, before and after parathyroidectomy, symptoms of PHPT and serum calcium and parathyroid hormone (PTH) levels were collected prospectively.

The accuracy of preoperative localizing studies was determined by comparing the results of the imaging studies with the operative findings, pathology report, and normalization of the postoperative serum calcium and PTH levels. The sensitivity of the localizing studies was calculated on the basis of the imaging study correctly identifying all abnormal parathyroid glands. The  $\chi^2$  test and *t* test were used for comparison of categorical data and continuous data, respectively. For comparison of data before and after parathyroidectomy, the paired *t* test was used for continuous variables and the McNemar test for nonparametric variables. Differences were defined as statistically significant if *P* < .05. Unless specifically stated, numerical values in the text and table represent mean  $\pm$  SD.

### RESULTS

There were 43 women and 11 men, with a mean age of 83.6 years (range, 80-92 years). The average serum calcium level was 11.6  $\pm$  1.3 mg/dL (2.9  $\pm$  0.3 mmol/L). All patients had 1 or more metabolic complications from PHPT and/or symptoms associated with PHPT (**Table** and **Figure**). Forty-two patients were referred for parathyroidectomy within 1 year of their diagnosis of PHPT and 12 patients were referred more than 1 year after their diagnosis. The mean interval from diagnosis to surgical referral in these 12 patients was 5.0 years (range, 1.2-10.0 years). There was no significant difference in patient age, sex, preoperative serum calcium and PTH levels, symptoms and metabolic complications of PHPT, perioperative complications, or hospitalization period in patients who were referred within 1 year and more than 1 year after their diagnosis of PHPT. In patients initially observed with known PHPT for more than 1 year, the reasons for eventual surgical referral were progressive osteoporosis or osteopenia (n=9), acute delirium (n=1), hypercalcemic crisis (n=1), and acute kidney stone formation (n=1).

In all patients who underwent neck exploration for parathyroidectomy, the postoperative calcium and/or PTH



Symptom profile in octogenarian and nonagenarian patients (n=44) with primary hyperparathyroidism before and after parathyroidectomy. Asterisk denotes significant changes in symptom after parathyroidectomy,  $P < .05$ .

levels normalized. Significant improvement in symptoms of fatigue, weight loss, nocturia, bone pain, constipation, and depression occurred after parathyroidectomy (Figure) ( $P < .05$ ). Forty-two patients had a bilateral neck exploration, 7 patients had unilateral neck exploration (1 with persistent PHPT), and 5 patients had a focused approach (1 with persistent PHPT and 1 with recurrent PHPT). The sensitivity (all abnormal glands correctly identified) of technetium Tc 99m sestamibi and ultrasound scanning in this cohort was 82% and 56%, respectively. As expected, the sensitivity of the localizing studies was higher in patients with a single parathyroid adenoma than in patients with multiglandular disease (Table).

Three patients had transient hypocalcemia (serum calcium level,  $< 8.0$  mg/dL [ $< 2.0$  mmol/L]) requiring oral calcium replacement for less than 2 months. One patient with a history of bladder cancer had a bladder perforation from a Foley catheter placement requiring surgical repair, and 1 patient was treated for urinary tract infection on the basis of a positive urinalysis during his hospitalization. There was no perioperative mortality. The average length of hospitalization was  $1.9 \pm 1.8$  days.

#### COMMENT

As the geriatric population grows and the diagnostic workup for osteoporosis increases in this population, the number of individuals diagnosed as having PHPT will also likely increase.<sup>2,13</sup> Unfortunately, some elderly patients with symptomatic or metabolic complications of PHPT have a delay in surgical referral for parathyroidectomy. We found that 22% of octogenarians and nonagenarians had a delay of more than 1 year, which is comparable with results of a study of an unselected cohort from Australia<sup>5</sup> but higher than rates reported from Great Britain.<sup>6</sup> Delayed referral for parathyroidectomy was not associated with more advanced PHPT in the elderly patients, although 1 patient developed hypercalcemic crisis and 1 developed acute de-

lirium. This was a retrospective study, but it demonstrates that the quality of life in elderly patients with PHPT may be affected because virtually all patients had symptoms possibly related to PHPT and some patients developed progressive osteoporosis and acute kidney stones before their eventual referral for parathyroidectomy. Exactly how many such patients with PHPT have delayed or no surgical referral is unclear, but it may represent a larger segment of patients in the geriatric population and is difficult to determine from a single-institution study.

None of the elderly patients had truly “asymptomatic” PHPT, and all patients had improvement of 1 or more symptoms after parathyroidectomy (Figure). Forty-seven of the 54 patients had 1 or more of the National Institutes of Health consensus conference criteria for recommending parathyroidectomy.<sup>14</sup> The most common symptoms were fatigue, weakness, and mental impairment. These symptoms are common with aging and are difficult to distinguish in elderly patients with PHPT, especially in octogenarians and nonagenarians. Some investigators have suggested that a trial of bisphosphonate therapy, to reduce the serum calcium level, may be helpful in determining whether parathyroidectomy would be helpful for the neuropsychiatric symptoms associated with hypercalcemia caused by PHPT.<sup>15</sup> About a quarter of the patients with PHPT had osteoporosis and a history of bone fractures, common conditions in the geriatric population but even more common in patients with PHPT.<sup>16-18</sup> Several investigators have demonstrated that parathyroidectomy is also more effective than medical treatment for increasing bone density in elderly patients with osteoporosis and PHPT.<sup>16,17</sup> Parathyroidectomy remains the most effective treatment for symptoms associated with PHPT as well as for the metabolic complications of PHPT.<sup>14</sup>

Although geriatric patients are usually viewed as having a higher risk of perioperative morbidity and mortality because of their age and presence of comorbid conditions, several investigators have documented in more

invasive surgical procedures, such as cardiac valve repair, coronary artery bypass graft, carotid endarterectomy, and pancreaticoduodenectomy, that elderly patients can have a good outcome.<sup>19-21</sup> Obviously, symptoms and metabolic complications of PHPT, projected life expectancy, and the expected impact on quality of life and operative risk need to be carefully assessed in geriatric patients with PHPT. Several investigators have reported relatively low perioperative morbidity and mortality in elderly patients (older than 65 or 70 years), while some have reported higher rates.<sup>7,8,10,11</sup> Even among experienced endocrine surgeons, a higher threshold for recommending parathyroidectomy in elderly patients with PHPT has been reported.<sup>12</sup> Although the reason for this is unclear, it probably reflects the difficulty in distinguishing symptoms of PHPT and the perceived higher risk of parathyroidectomy in elderly patients. In our cohort, half of the patients were in American Society of Anesthesiologists class 2 or less, with no deaths and no cardiopulmonary events associated with parathyroidectomy. This indicates that parathyroidectomy in the geriatric population is safe and effective with appropriate patient selection and perioperative management.

Some surgeons are using “minimally invasive” or “focused” approaches to parathyroidectomy and have suggested that this approach is well suited for geriatric patients with PHPT to reduce complications.<sup>13,22</sup> We observed no difference in perioperative complications between focused, unilateral, and bilateral neck exploration approaches. More important, 26% of patients in our cohort had multiglandular disease. Therefore, in these cases a focused approach might have resulted in a lower surgical cure rate. These results emphasize that, unless elderly patients with PHPT are selected on the basis of a positive preoperative localizing study (such as a sestamibi or an ultrasound scan) and have an appropriate decrease in their intraoperative PTH level, a lower cure rate will be obtained with a focused approach as a tradeoff for the perceived benefit of avoiding a higher-risk procedure. Furthermore, the surgical approach used for parathyroidectomy does not replace appropriate patient selection and perioperative management in reducing morbidity and mortality from parathyroidectomy.

In addition to being safe and effective for treating geriatric patients with PHPT, parathyroidectomy can have significant benefits in reducing premature death from cardiovascular diseases and may also reduce the risk of other malignancies developing from untreated PHPT.<sup>23-25</sup> Correcting the hypercalcemia also makes it easier to treat these patients when they are hospitalized for other medical reasons. Careful surveillance of patients with “mild” or “asymptomatic” PHPT results in about 25% of these patients developing additional surgical indications for parathyroidectomy and some metabolic complications of PHPT. These metabolic complications that develop during surveillance for PHPT may be more severe and less well tolerated in the geriatric population. We believe that parathyroidectomy remains the most effective treatment for patients with PHPT and it is important for geriatric patients with PHPT to receive early surgical referral for parathyroidectomy before they develop metabolic complications from PHPT.

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## DISCUSSION

**Philip D. Schneider, MD, Sacramento, Calif:** Dr Kebebew has presented a unique and intriguing subgroup of patients referred for parathyroid surgery. The 54 patients accumulated over a 15-year period represent an elderly population with metabolic and symptomatic complications of hyperparathyroidism. This is not a discussion of asymptomatic patients with incidentally discovered hypercalcemia. The paper is disturbing from several standpoints stemming not from the surgery itself or the selection of patients but from the delays in referral, presumptive delays in diagnosis, and the reluctance on the part of physicians to refer their patients for surgery. In essence, this implies an ageist approach to the management of these patients by misguided physicians.

As the population ages, assumptions about longevity have to be carefully rethought in light of life-table statistics that suggest that these elderly patients are destined to live even longer and potentially more vigorous lives. Hyperparathyroidism is a disease that occurs in 1 in 700 adults, and, as the population ages, more elderly patients will acquire this common disease. That parathyroid neck exploration can be safely employed with little morbidity is endorsed by this group's excellent results.

To clarify points in the presentation, I would like to ask the following questions of Dr Kebebew's group:

1. How many patients had a delay in diagnosis of their hypercalcemia, rather than a delayed referral? Personal experience suggests that the obtaining of serum calcium is no longer routine, and may be infrequent. Hypercalcemia as a cause of systemic illness is often overlooked.

2. During the period of this study, how many patients were referred for surgery that they subsequently declined? Is there information on their outcomes?

3. The 26% incidence of multigland disease is high even by referral center standards. I would be interested to learn how many of these patients had some element of chronic renal failure and, therefore, the potential for secondary, rather than primary, hyperparathyroidism. We are seeing more elderly patients on dialysis or nearing dialysis, and have seen several quite ill patients with secondary and tertiary hyperparathyroidism. If chronic renal failure is not an underlying cause of the hyperparathyroidism in these patients, how then do the authors account for this incidence of multigland disease?

**Lawrence A. Danto, MD, Truckee, Calif:** Have the authors encountered any resistance from third-party carriers in allowing access to parathyroid exploration in elderly patients?

**Dr Clark:** Hyperparathyroidism is a common disease, and the more one screens for it, the more patients will be identified, especially in the elderly population.

Dr Schneider asked about delay in diagnosis vs delay in referral. This is difficult to answer, as we do not know the denominator for the delay in diagnosis or delay in referral. It is also difficult to know whether there is more delay in the elderly than in younger patients. There appears to be considerable variation regarding indications for referral by various endocrinologists and primary care physicians. Most patients are referred within a few months of diagnosis, but some patients have documented hypercalcemia and hyperparathyroidism for 15 to 20 years before referral, usually when they develop possible complications of their hyperparathyroidism such as kidney stones and osteoporosis. In the elderly population, 87% of our population fulfilled the NIH [National Institutes of Health] consensus criteria for parathyroid surgery. One must remember that these criteria are based more on complications such as kidney stones, osteoporosis, etc, than symptoms such as fatigue, depression, musculoskeletal aches and pains, etc.

Dr Schneider asked how many patients have not been recommended for parathyroidectomy among these elderly individuals. We believe that virtually all patients with primary hyperparathyroidism are candidates for parathyroidectomy unless there is a contraindication to surgery. To my knowledge, all published articles document that patients benefit both symptomatically and metabolically from successful parathyroidectomy. I did, however, refuse one 98-year-old man for operation. He only had one symptom possibly related to hyperparathyroidism, and that was constipation. When I asked how long he had had constipation, he said 96 years. Many of our colleagues in internal medicine and endocrinology continue to debate the appropriate indications for operation in patients with hyperparathyroidism. Although most patients with mild primary hyperparathyroidism do well, about 25% to 35% develop progressive disease and complications. To date, no one has been able to determine who will develop complications on progressive disease and who will not. Also, the treatment of other medical problems becomes more difficult when patients are hospitalized with coexistent hyperparathyroidism. Patients with PHPT also appear to die prematurely from cardiovascular disease and cancer.

The third question was, did our patients have coexistent chronic renal failure because 26% had multigland disease? I have 2 responses: First, as patients get older, more have multiple abnormal parathyroid glands, as Dr Norman Thompson and our group have previously independently reported. This is also true in rats. The number of patients who have PHPT and multiple abnormal parathyroid glands, however, will probably decrease in the future. The reason for this finding is, even though multiple abnormal parathyroid glands are present, fewer abnormal parathyroid glands will be identified in patients having focal or unilateral rather than bilateral parathyroid explorations. For example, Dr G. Irwin found that only 4% of his patients had more than one abnormal parathyroid gland. When a bilateral approach is used in similar patients, 15% have more than one histologically proven abnormal parathyroid gland, as Dr Jeffrey Norton and our group have previously reported. In the short follow-up period, patients treated with a focal approach with removal of one gland appear to be cured. Time will tell, however, whether some of these patients will develop recurrent hyperparathyroidism.

Dr Danto, to my knowledge, we have not had resistance from third-party payers for patients scheduled for parathyroidectomy. Some of our referring physicians have to write specific letters to insurance companies so that their patients can be referred for treatment.