Parathyroid Surgery in the Elderly

Lilah F. Morris,[a] Juliette Zelada,[a] Bian Wu,[a] Theodore J. Hahn,[b] Michael W. Yeh[a]

[a]Endocrine Surgical Unit, Department of General Surgery, David Geffen School of Medicine at UCLA, Los Angeles, California, USA; [b]VA Greater Los Angeles Geriatric Research, Education and Clinical Center and Division of Geriatric Medicine, Los Angeles, California, USA

Key Words. Parathyroidectomy • Elderly • Primary hyperparathyroidism

Abstract

Introduction. The prevalence of primary hyperparathyroidism (PHPT) is expected to increase in developed nations as the aged population grows. This review discusses issues related to PHPT in the elderly population with a focus on differences in disease presentation, medical and surgical management, and outcomes.

Methods. Literature review of English-language studies of PHPT or parathyroidectomy (PTx) in the elderly was performed. Surgical literature reviewed included original clinical studies published after 1990. Priority was given to studies with >30 patients where institutional practice and outcomes have not changed significantly over time.

Results. Elderly patients primarily present with non-classic symptoms of PHPT that can sometimes be missed in favor of other diagnoses. They have equivalent surgical outcomes, including morbidity, mortality, and cure rates, compared with younger patients, although their length of hospital stay is significantly longer. Several recent studies demonstrate the safety and efficacy of outpatient, minimally invasive parathyroidectomy in an elderly population. Patients are referred for PTx less frequently with each advancing decade, although surgical referral patterns have increased over time in centers that offer minimally invasive parathyroidectomy. Elderly patients experience increased fracture-free survival after PTx. The majority of elderly patients report symptomatic relief postoperatively.

Conclusion. PTx can offer elderly patients with PHPT improved quality of life. PTx is safe and effective in elderly patients, and advanced age alone should not deter surgical referral. *The Oncologist* 2010;15:1273–1284

INTRODUCTION

Primary hyperparathyroidism (PHPT) predominantly affects the elderly, with a peak incidence between ages 55 and 70. U.S. longitudinal population-based studies have found that women 65–74 years old have an annual detection rate of 99 cases per 100,000, compared with 15.7 per 100,000 in the general population [1]. The U.S. population aged ≥65 years is projected to increase from 35 million in 2000 to 71

million in 2030, at which time the elderly will account for 20% of the U.S. population [2]. The number of new PHPT diagnoses in this country will likely increase in a parallel fashion. The advent of multichannel biochemical analyzers in the 1970s made chemistry panel testing commonplace. The resultant phenomenon of calcium "screening" changed the clinical presentation of PHPT such that most patients presently identified with PHPT have asymptomatic or minimally symptomatic disease [1].

The natural history of PHPT suggests that symptoms of hyperparathyroidism progress in nearly 40% of patients [3]. This becomes particularly important for management of the disease in elderly patients as the life expectancy in older individuals increases. Whereas U.S. life expectancy at birth is 77.8 years, current average life expectancy at age 65 is 18.7 years (20.0 years for women), and at age 75 it is 12.0 years [4]. In comparison, for Caucasians born in 1950, life expectancy for males was 66 years and for females it was 72 years [5]. Because of improved survivorship among the elderly, those living with PHPT today may be at higher risk for the development of complications in comparison to prior generations of elderly individuals.

It is well known that many diverse diseases present atypically in the elderly [6]. For example, elderly patients with acute myocardial infarction (MI) are more likely to present with neurological symptoms and weakness, rather than the classic symptom of crushing substernal chest pain [7]. Similarly, elderly patients with PHPT are less likely to present with kidney stones and more likely to present with vague neuropsychiatric complaints than are younger patients [8, 9]. Although some literature suggests that most elderly patients present with asymptomatic disease, there is concern that a substantial fraction of patients with PHPT are being misclassified as "asymptomatic," or just having "symptoms of old age," when they do, in fact, have specific symptoms referable to PHPT.

Studies utilizing disease-specific questionnaires reveal that 85%–90% of patients with PHPT have symptoms preoperatively that improve after surgery [10, 11]. These include a number of vague or subjective complaints such as weakness, irritability, easy fatigability, bone or joint pain, thirst, or itchy skin, which may be common in the general elderly population. Unlike objective symptoms such as nephrolithiasis or osteoporosis, nonclassic symptoms are difficult to quantify. Recently, Pasieka et al. defined and validated a survey tool that aims to better enumerate the impact of nonclassic symptoms [12, 13].

Parathyroidectomy (PTx) offers the only definitive therapy for PHPT, and multiple studies have demonstrated that it can be performed in the elderly as an outpatient procedure with low complication rates and outcomes that are equiva-

lent to those in younger patients [9, 14–16]. In a decision model analysis, Zanocco and Sturgeon demonstrated that surgical treatment of PHPT is cost effective for patients over 50 years of age with a predicted life expectancy of 5 years or more [17]. Despite these facts, elderly patients are much less likely to undergo PTx compared with their younger counterparts, a phenomenon that is independently attributable to age [8].

METHODS
A Medline search was conducted using the search terms "primary hyperparathyroidism," "parathyroidectomy," and "elderly." English-language original clinical studies were evaluated. Surgical reports published after 1990 were reviewed to accurately reflect modern standards in surgical technique and perioperative care. Although other references are made throughout this review, the studies represented in Table 1 are those that include both >30 patients and do not span periods during which institutional techniques and/or outcomes underwent substantial evolution.

CLINICAL PRESENTATION

Initial Evaluation of the Elderly Patient with Primary Hyperparathyroidism
The biochemical diagnosis of PHPT is based on elevated serum calcium in conjunction with inappropriately elevated parathyroid hormone level. Calcium elevation on serum panels typically triggers the workup in asymptomatic patients.

Thus, during the 1990 international consensus, the National Institutes of Health defined biochemical criteria intended to assist physicians in selecting "asymptomatic" patients for surgical referral [18, 19]. A limitation of these guidelines is the difficulty in defining asymptomatic disease.

Multiple studies demonstrate that elderly patients undergoing PTx present with different symptoms than their younger counterparts (Table 2). Bachar et al. found that patients >70 years were more likely to have hypertension (18.9% versus 1%, $p < 0.0001$), whereas those younger than 70 years were more likely to experience kidney stones (27% versus 14.3%, $p = 0.007$) and peptic ulcer disease (16.2% versus 7.4%, $p = 0.03$) [20]. Politz and Norman identified significantly more hypertension in patients >80 years, and significantly higher rates of sleep disturbances, poor concentration, and irritability in younger patients [14]. Chen et al. found that patients >70 years experienced more mental impairment (42% versus 12%, $p < 0.001$), fatigue (39% versus 18%, $p < 0.025$), and bone disease (33% versus 15%, $p < 0.005$), whereas patients <70 years presented

Table 1. Most common presenting symptoms and clinical disorders in elderly patients undergoing parathyroidectomy

Study	Fatigue	Mental impairment[a]	Bone pain/ disease	Muscle weakness	HTN	Kidney disease[b]	Asymptomatic
Bachar et al. [20]	11%		44%	11%	19%	14%	18%
Chen et al. [9]	39%	42%	33%			19%	6%
Chigot et al. [25]	35%	60%	15%				8%
Egan et al. [23]	12%	6%	44%				20%
Irvin and Carneiro [24]	15%	9%	50%	9%		15%	18%
Kebebew et al. [16]			26%		50%		0%
Politz and Norman [14]	62%	57%	44%		62%	15%	3%
Uden et al. [15]	35%		31%	28%	47%		7%

[a]Includes confusion and memory problems.
[b]Includes nephrolithiasis.
Abbreviation: HTN, hypertension.

Table 2. Signs, symptoms, and clinical manifestations (conditions) of PHPT in the elderly

Musculoskeletal disease signs and symptoms	Neuropsychiatric disease signs and symptoms	Clinical manifestations (conditions)
Osteoporosis	Fatigue/lethargy/drowsiness	Nephrolithiasis
Hip fractures	Irritability	Osteopenia
Bone pain	Mood swings	Weight loss
Joint pain	Depression	Hypertension
Vague muscle pains	Cognitive disturbances/dementia/mental impairment/ memory loss/confusion	Hematuria
	Constipation	Bruising
	Sleep pattern alterations	Pancreatitis
	Anxiety	Gout
	Apathy	Peptic ulcer disease
	Psychosis/paranoia/hallucinations	
	Coma	
	Neuroanesthesia	

with more nephrolithiasis (39% versus 19%, $p < 0.025$) [9]. Uden et al. found that renal stones were 2.6 times more common in younger patients <60 years ($p < 0.001$) and hypertension 1.7 times more common in those >60 years ($p < 0.05$) [15].

Given the variety of PHPT presenting symptoms, several studies of elderly patients with PHPT have used disease-specific symptom surveys to determine the impact of PTx on health-related quality of life. Validated tools, such as the Medical Outcomes Study Short-Form Health Survey and the Health Outcomes Institute Health Status Questionnaire forms, have been used to help quantify the burden of PHPT on health-related quality of life [21, 22]. Subsequently, the disease-specific PTx assessment of symptoms score was developed and validated to better quantify the im-

pact of nonclassic symptoms, including joint or bone pain, easy fatigability, abdominal pain, headaches, and feelings of forgetfulness, depression, irritability, or weakness [12]. A 10-year follow-up report demonstrated that quality of life was significantly better at 1 and 10 years post-PTx than preoperatively, compared with a group of post-thyroidectomy controls [13].

In preoperative surveys, elderly patients undergoing PTx most commonly complain of fatigue, bone pain or history of bone disease, and mental impairment, including confusion, depression, or memory problems (Table 1). Politz and Norman reported that the average elderly patient referred for PTx most commonly had three PHPT-related symptoms, with 97% reporting at least one symptom [14]. Whereas three studies found that asymptomatic patients

comprised 18%–20% of their PHPT population [20, 23, 24], five others found asymptomatic patients to be ≤8% of the total [9, 14–16, 25]. One limitation of these data is selection bias: all patients studied underwent PTx, likely limiting the number of patients with truly asymptomatic disease. In addition, the severity of symptoms is likely to be higher in a patient population that ultimately was referred to and elected to undergo surgical intervention. Finally, survey tools can sometimes bias results by prompting patients toward a set of symptoms unrelated to their parathyroid disease.

Musculoskeletal Disease

As discussed, PHPT is a disease predominantly affecting postmenopausal women, approximately 3% of whom will develop the disease over their lifetimes [26]. Evidence suggests that, in this population, decreased bone mineral density (BMD) translates into increased fracture risk. In a retrospective, cohort study of 533 patients with PHPT followed for an average of 7.4 years, osteoporosis was associated with an increased risk of fracture compared with patients with normal BMD or osteopenia (hazard ratio [HR] 3.67; 95% confidence interval [CI]) 1.79, 7.51) [27]. Kebebew and colleagues found that 26% of surgical patients ≥80 years of age with PHPT had osteoporosis and 20% had a previous history of bone fractures [16]. Di Monaco et al. found that a significantly higher percentage of elderly women who had suffered hip fracture had biochemical evidence of PHPT, compared with sex-matched controls (4.7% versus 1.1%, $p < 0.01$) [28]. In addition, in a Danish observational study that followed 674 patients who underwent PTx for PHPT, each compared with age- and gender-matched controls, preoperative fracture risk was increased in patients with PHPT (RR 1.8, 95% CI 1.3, 2.3), but normalized postoperatively [29]. A long-term, prospective study by Rubin et al. that followed 116 patients with PHPT over 15 years found that, in patients who did not meet criteria for surgery or refused surgical intervention, significant reductions in femoral neck and distal radius BMD occurred over time [3]. Given this observed decline in BMD in areas commonly injured in falls, the implications of fracture risk are of particular relevance to the elderly population.

Hip fractures are concerning in an elderly population because of their associated morbidity and mortality. In the Fracture Intervention Trial, which followed nearly 6,500 elderly women, the age-adjusted RR of dying over a 1-year period following a hip fracture was markedly increased at RR 6.68 (3.08, 14.52, 95% CI) and following a vertebral fracture at RR 8.64 (4.45, 16.74, CI 95%). No increased mortality was found following a non-hip or non-vertebral fracture [30]. Braithwaite et al. used a Markov state transi-

tion model of the natural history of hip fracture to predict that, after hip fracture in an 80 year old, remaining life expectancy declines by 25%, and survivors spend 17% of their remaining life in a nursing facility. Lifetime cost of hip fracture in this elderly population was estimated at $81,300 [31].

Neuropsychiatric Disease

There is now strong evidence to support the association of PHPT with neurobehavioral symptoms, including fatigue, irritability, mood swings, depression, and other mental disorders, and alterations in sleep patterns [11, 32–35]. In a case-control study of postmenopausal women, Walker et al. found that patients with PHPT had significantly more symptoms of subclinical depression and worse scores for both immediate and delayed recall of contextually related material compared with controls without PHPT. Symptoms of depression were measured by the 21-item Beck Depression Inventory (a depression severity scale for adults). Although these patients had depressive symptoms, they did not meet the diagnostic criteria for major depressive disorder as defined by the Diagnostic and Statistical Manual of Mental Disorders. Memory for contextually related material was assessed using the Wechsler Memory Scale Logical Memory Test, Russell revision, which requires examinees to repeat two brief, orally presented stories immediately and after a 30-minute delay, evaluating units of ideas recalled [36]. Both symptoms of depression and immediate and delayed recall of contextually related material improved significantly after PTx such that there was no difference in symptoms between the control group and the postoperative group. Although lacking a control group, a small, retrospective French study of patients >75 years with PHPT found neuropsychiatric manifestations in 73% of patients [37].

Cardiovascular Disease

Several European studies have reported an increased mortality risk in patients with untreated PHPT related to cardiovascular conditions including MI, angina, hypertension, congestive heart failure, and arrhythmias [38, 39]. Hedback and Oden studied 4,461 patients operated on for PHPT in Sweden over an 8-year period, control matched with the whole population of Sweden for age, sex, and calendar year. There was a significantly increased baseline risk of death in PHPT patients compared with the general population: 1.3 risk ratio in men (95% CI 1.07–1.57) and 1.61 in women (95% CI 1.46–1.78). Death from cardiovascular disease was significantly increased in PHPT patients with risk ratio for men of 1.71 (95% CI 1.34–2.15) and for women 1.85 (95% CI 1.62–2.11). The increase in cardio-

vascular deaths was attributable to heart failure, MI, and stroke [40]. Whether the risk of death from cardiovascular disease declines after PTx still remains to be examined.

Although the European studies included patients of all ages, risk of death from cardiovascular disease in patients with PHPT is of particular importance in the elderly population. Older patients present with more cardiovascular comorbidities than their younger counterparts. In fact, in several studies of PTx in the elderly, 35%–72% of patients who presented for PTx had hypertension, 15%–32% had cardiac disease and 6%–11% had congestive heart failure [20, 23–25, 41]. Although the question has not yet been specifically addressed, pre-existing cardiovascular disease might make these patients more susceptible to the subsequent adverse cardiovascular effects of PHPT.

SURGICAL TREATMENT

Surgery remains the only definitive treatment for PHPT. However, elderly patients are significantly less likely to undergo PTx than young patients, even when they are generally healthy and eligible for surgery according to current consensus criteria [8]. Published reports examining PTx in the elderly are predominantly retrospective reviews of single-institution surgical databases. Despite the inherent limitations in these small studies, they demonstrate several consistent themes.

ANESTHESIA

Most endocrine surgery centers in the studies reviewed used general anesthesia with endotracheal intubation versus laryngeal mask airway for PTx. Focused (minimally invasive) PTx (MIP), made possible by accurate preoperative localization studies (e.g., sestamibi or ultrasound), intraoperative parathyroid hormone monitoring (IOPTH), or intraoperative radioguidance, can minimize operative time and lower anesthesia requirements.

Use of both local and regional anesthesia for elderly patients can facilitate shorter stays in recovery, earlier discharges, decreased need for postoperative narcotics, and decreased postoperative cognitive dysfunction [35, 42–45]. Although general anesthesia does not increase the incidence of postoperative delirium, some studies have demonstrated a beneficial trend toward improved postoperative cognitive function in elderly patients who received regional versus general anesthesia. However, large trials in the anesthesia literature examined patients with >3-day postoperative hospital stays, which is less applicable to patients undergoing mostly outpatient or short-stay procedures [46, 47].

Our preferred method of anesthesia for MIP in elderly patients involves a combination of sedation (propofol infusion with intermittent doses of fentanyl) with a regional block, unless contraindicated because of aspiration risk (e.g., gastroesophageal reflux disease and morbid obesity). A superficial cervical block is performed using 10 ml of 0.25% bupivacaine per side. The block is administered in the subplatysmal plane along the posterior border of the sternocleidomastoid muscle, unilaterally for patients with well-localized adenomas and bilaterally for those with poorly localized disease. At our institution, when given the choice, two thirds of patients select this option over general anesthesia.

Intrinsic to the overall care strategy for outpatient MIP are methods proven to reduce postoperative delirium in the elderly. A large study of general medicine patients from Yale-New Haven Hospital examined 852 patients aged 70 years or older, without baseline dementia but at moderate to high risk for development of dementia. Matched patients either received "usual care" or were placed on a specialized protocol with specific interventions designed to prevent delirium (Table 4). The rate of delirium in the intervention group was 9.9% versus 15% in the usual care group ($p = 0.02$). There was also a significant decrease in the number of days and episodes of delirium in the intervention group compared with the control, although median hospital length of stay was not different between groups [48]. Outpatient MIP targets a 3- to 4-hour postoperative observation period and patients are assisted with ambulation in the recovery area. Family members are encouraged to join the patients in the postoperative care unit within 15 minutes of the conclusion of surgery and can assist them with communication (e.g., by bringing eyeglasses or hearing aids). Patients are encouraged to drink liquids postoperatively, as soon as they are fully awake. The need for narcotics is minimized by the long-acting regional block (6–8 hour duration), which is supplemented with a single dose of 30 mg of ketorolac as needed in patients with normal renal function. Two thirds of patients do not require any narcotic pain medications after surgery, and no sedatives are given after emergence from anesthesia.

Surgical Technique

Although traditionally PTx was accomplished via a four-gland bilateral neck exploration (BNE), a more focused approach of excision of a single hyperfunctioning parathyroid adenoma via a <2-cm incision is associated with shorter operative time, decreased postoperative length of stay, decreased pain, more satisfactory cosmetic results, and biochemical cure in >95% of patients [49].

Although BNE and minimally invasive parathyroidectomy (MIP) have equivalent surgical success and complication rates in elderly patients [9, 16, 23–25], the

Table 3. Summary of results for studies on parathyroidectomy in the elderly

Study	Study dates	Total patients	Elderly patients	Definition of elderly	Anesthesia	Type of operation	Pathology	% Cure	Complication	Mortality (%)	LOS (day)
Bachar [20]	Jan 1996 to Feb 2006	951	190	≥70	NS	NS	NS	94.8	11%	0	4 ± 3.6
Biertho [44]	Sep 1998 to Jan 2002	220	40	≥70	82.5% IV sedation + local,17.5% GET	UNE	SA 92.5%, DA 2.5%, carcinoma 5%	100		1 (2.5%)	0.1
Chen [9]	Aug 1990 to May 1996	184	36	≥70	GET	BNE	SA 89%, DA 11%, hyperplasia 0%	94.4	5.5%	0	2.1 ± 0.2
Chigot [25]	Jan 1978 to Dec 1992	542	78	≥75	GET	BNE	SA 95%, DA 4%, hyperplasia 1%	100	7.7%	3 (4%)	4
Egan [23]	Mar 2001 to Jun 2006		50	≥80	NS	NS	SA 90%, DA 4%, hyperplasia 6%	98	4%	0	0.5 ± 0.1
Irvin [24]	1993–2000	291	34	≥75	NS	85% UNE, 15% BNE	SA 97%	97	NS	1 (3%)	NS
Kebebew [16]	Jun 1996 to Feb 2001	1,482	54	≥80	98% GET, 2% local	78% BNE, 13% UNE, 9.3% MIP	SA 74%, DA 15%, hyperplasia 11%	NS	9.3%:	0	1.9 ± 1.8
Politz [14]	May 2003 to Jul 2006	2,600	150	≥80	IV sedation and local per protocol	MIRP	SA 91%, DA 7%, hyperplasia 2%	99.3	7.3%	0	0.08 ± 0.008
Shin [43]	Jan 2005 to Dec 2007	388	101	≥70	NS	90% MIP, 10% BNE	31.4% multiple gland resection	96.4	5.9%		0.63
Stechman [52]	Jan 2002 to Nov 2007	224	56	>75	NS	66% MIP	NS	96.8		0	1.6
Uden [15]	1980–1990	250	131	≥60	GET	BNE	SA 77%, DA 9%, hyperplasia 14%	98.8	4.6%	0	NS
Young [53]	1998–2007	687	247	≥65	NS	BNE versus MIRP	NS	NS	8.8%	3 (1%)	0.5 ± 0.1

Abbreviations: BNE, bilateral neck (four-gland) exploration; DA, double adenoma; GET, general endotracheal intubation; MGD, multigland disease; MIP, minimally invasive parathyroidectomy; MIRP, minimally invasive radioguided parathyroidectomy; NS, not stated; SA, single adenoma; UNE, unilateral neck exploration.

introduction of MIP led to a change in surgical referral patterns for the elderly. Both Pruhs et al. and Irvin and Carneiro found a significant increase in the proportion of elderly (≥70–75 years) patients referred for PTx since the introduction of MIP [50, 24].

In the minimally invasive era, BNE is now frequently performed via a small incision under local anesthesia with same-day discharge. In patients who do not have adequate preoperative localizing studies or where IOPTH fails to decline appropriately after excision of a localized parathyroid adenoma, examination of the ipsilateral gland can be performed via the same <2-cm MIP incision. Conversion to four-gland exploration typically requires only a slight extension of a more centrally located incision to examine both glands in the contralateral neck.

Pathology
MIP is based on excising a single, well-localized parathyroid adenoma and is applicable to up to 90% of patients with sporadic PHPT [51] Most studies reported no difference in parathyroid pathology between older and younger patients,

finding a single adenoma in 89%–97% of elderly patients and hyperplasia in 0%–6% (Table 3) [9, 14, 52]. The two studies that identified higher rates of double adenoma and hyperplasia in elderly patients employed BNE for the majority of the cases [15, 16]. Elderly patients should be offered MIP using the same algorithms as applied in younger patients because the underlying pathology/rate of multigland disease is no different.

Length of Stay and Postoperative Delirium
Worldwide, there is wide variation in average length of stay after PTx, between 2 hours for MIP and 4 days for BNE. Generally, patients who undergo PTx by either strategy are hospitalized for between 4 and 24 hours postoperatively with patients undergoing BNE more frequently admitted for an overnight observation. Multiple studies have found that elderly patients have significantly longer post-PTx hospitalizations compared with younger patients, although lengths of stay were not clearly defined by type of operation (BNE versus MIP) [52, 53]. Although two studies reported that same-day

discharge is half as likely in elderly versus younger patients at the same institutions [52, 53], other studies found no difference [9, 14, 43]. Recent shortened lengths of stay in all patients have been attributed to the introduction of minimally invasive techniques [50, 52].

There exists a considerable potential benefit to same-day discharge for elderly patients in that they can quickly return to their familiar home environment, minimizing the risk of confusion and delirium from sleep deprivation, as well as reducing the risk of falls, infections, and other hospital-related complications common in elderly patients [43]. In one report, 25% of elderly patients who stayed in the hospital for more than 1 night post-PTx experienced confusion [52]. Onset of postoperative delirium occurs, on average, after 2 hospital days, and rates of delirium are significantly increased in patients with older age, impaired functional status, pre-existing dementia, and pre-existing comorbidities [54]. Subjects who developed delirium had significantly worse outcomes, including increased length of stay and higher rates of discharge to long-term care facilities [54, 55]. As evidenced in the Yale-New Haven Hospital study on avoidance of delirium in elderly patients, protocols that work to immediately return patients to their home environment with resumption of normal activity are most effective in reducing the incidence of postoperative delirium (Table 4).

Preoperative Comorbidity

On average, older patients present with more comorbid conditions than their younger counterparts. In surgical series, 78%–88% of elderly patients aged 70 years and older referred for PTx have at least one comorbid condition, compared with 55% of younger patients [20, 25]. A recent study examining all patients with the biochemical diagnosis of PHPT within a large health maintenance organization showed that the proportion of patients with a Charlson Comorbidity Score of 1 or less was 95% in patients under age 50 years and 67% in patients aged 80 years or greater. In other words, despite age-related declines in overall health, the majority of older patients with PHPT are free from major comorbidities [8]. Shin et al. found that patients aged 70 years and older present with a greater severity of certain complications of parathyroid disease, including a higher median preoperative creatinine (2.0 versus 1.0, $p = 0.002$) and worse median BMD T score (-2.5 versus -1.8, $p < 0.001$), relative to younger patients [43]. Despite these surgical risks, elderly patients undergoing PTx have been reported to have outcomes that are similar to those of younger patients.

Table 4. Measures to prevent delirium in hospitalized patients older than 70 years

Avoidance of sleep deprivation and use of nonpharmacologic sleep protocol
Early mobilization protocol
Improvement in communication methods to avoid exacerbating visual or hearing impairment
Prevention of dehydration

Adapted from Inouye S, Bogardus S, Charpentier P, Leo-Summers L, Acampora D, Holford T, Cooney L. A multicomponent intervention to prevent delirium in hospitalized older patients. N Engl J Med 1999;340: 669–676.
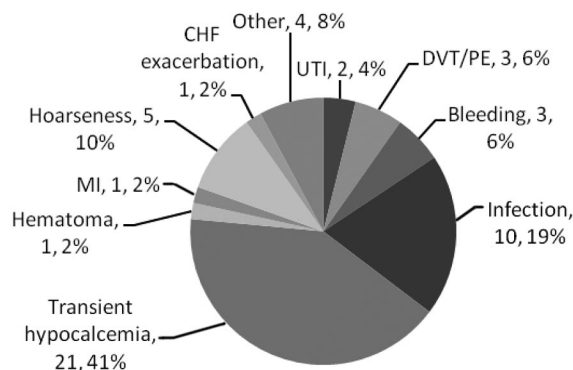
Other: temporary dysphagia, intravenous site cellulitis, cerebral hemorrhage, bladder perforation

Figure 1. Number and type of postoperative complications after parathyroidectomy in the elderly. This figure highlights the 55 complications that occurred in 1,079 patients in 9 studies, with an overall complication rate of 5.1%. Abbreviations: CHF, UTI, DVT, PE.

Major and Minor Complications

The perioperative morbidity (4%–10%) and mortality (0%–4%) for elderly patients is similar to that of the general population. Table 3 lists the percentage of complications in the elderly PHPT populations in each study reviewed, whereas Figure 1 lists the number of patients experiencing each complication across all studies that provided the number of specific complications [9, 14–16, 20, 23, 25]. Transient hypocalcemia is the most common complication of PTx, followed by infection and hoarseness from temporary recurrent laryngeal nerve injury. One report found that elderly patients are significantly more likely to experience cardiac complications than younger patients (2.8% versus 0.5%, $p = 0.022$), although this is rare even in elderly patients [53]. Mortality is uncommon after PTx, approaching 1% in some large studies of elderly patients undergoing PTx, and typically can be attributed to significant to comorbid conditions [25, 44, 24, 53].

Biochemical Resolution

Cure rates reported after PTx in the elderly are the same as those in younger populations, ranging from 94.4% to 100%. None of the reviewed studies reported any significant difference in cure rates, as measured by biochemical indices, between elderly and younger patient populations.

BENEFITS OF SURGICAL INTERVENTION

Although validated assessment tools are now available, many studies have used internally constructed surveys to assess symptom relief post-PTx. Various studies have reported that between 64% and 90% of elderly patients experienced some or marked improvement in symptoms 1 year post-PTx [9, 23, 25, 44, 52]. Approximately 2%–5% of patients felt that their symptoms were worse postoperatively, whereas up to 32% of patients reported no improvement in symptoms [9, 15, 24, 25]. Stechman et al. used the validated PTx assessment of symptoms to measure change in symptoms post-PTx. Patients in all age groups experienced a significant improvement in symptoms, with 87% of patients >75 years reporting an improvement in symptoms postoperatively [52].

Improved Bone Mineral Density

Following PTx, patients experience an increase in BMD and a decreased risk of fracture. In fact, these outcomes may in part explain why one longitudinal study found that the primary reason for referral for PTx has shifted progressively toward the presence of osteoporosis, climbing from 7% in 1985 to 20% in 2005 ($p = 0.03$) [56]. Undoubtedly, another key factor in this change in referral basis has been the increasing use of BMD to accurately detect significant bone loss in patients with PHPT.

Several large, retrospective cohort studies of patients with PHPT have demonstrated improved fracture-free survival and decreased risk of fracture post-PTx, although one Danish study failed to show such a benefit. In a large, retrospective cohort study by VanderWalde et al. of over 1,500 patients with PHPT who either underwent PTx (28.8%) or observation (71.2%), the 10-year fracture-free survival after the diagnosis of PHPT was significant higher in the operative group (73% versus 59%, $p = 0.001$). Specifically, PTx patients experienced an 8% decrease ($p = 0.001$) in the 10-year fracture rate in the hip and a 3% decrease ($p = 0.02$) in upper extremity fractures as compared with patients with PHPT who did not undergo PTx [57]. A follow-up study to determine the influence of BMD on fracture risk post-PTx found that compared with observation, PTx decreased the risk of fracture in patients with normal, osteopenic, and osteoporotic BMD values, with the largest impact being in patients with osteoporosis [58]. A large,

Danish observational study that followed 1,200 PHPT patients, each compared with three age- and gender-matched controls, failed to demonstrate an effect of surgery on fracture risk [39]. However, in a similar nationwide Danish cohort study, patients with PHPT who underwent surgery had a lower fracture risk than those treated conservatively [58].

Three randomized, controlled trials have demonstrated benefit with respect to increased BMD post-PTx. A small, randomized controlled trial in mild, asymptomatic PHPT found that, in patients randomized to surgery ($n = 25$), BMD increased significantly postoperatively in the spine, femoral neck, total hip, and forearm. In contrast, in patients randomized to follow-up ($n = 28$), BMD increased slightly in the lumbar spine (0.5% per year, $p = 0.09$) and significantly in the forearm (0.2% per year, $p = 0.05$), while declining in the femoral neck (-0.4% per year, $p = 0.12$) [59]. A similar, small, randomized controlled trial of postmenopausal Swedish women with asymptomatic PHPT found decreased baseline BMD in the lumbar spine and femoral neck in PHPT patients compared with age-matched controls. A subset analysis of women ≥67 years old at the time of study entry who underwent PTx demonstrated an increase in total body BMD by 2.0% ($p = 0.01$) over the 5-year period, without any such difference seen in age-stratified controls. BMD in this group did not change in the lumbar spine or femoral neck postoperatively [60].

A European study of 191 patients who either underwent PTx or observation for mild asymptomatic PHPT demonstrated a significant increase in lumbar spine BMD at 2 years post-PTx ($p = 0.05$) compared with baseline and control values, with a trend toward a significant increase in BMD in the femoral neck ($p = 0.07$) [61].

Together, these data suggest that, in elderly patients, including those with asymptomatic PHPT recognized only via screening, PTx is beneficial in improving BMD and increasing fracture-free survival.

Improved Neuropsychiatric Symptoms

Many studies have demonstrated improvement in subjective neuropsychiatric symptoms post-PTx, although most have utilized institutional survey-based tools to assess pre- and postoperative symptoms. Kebebew et al. showed a significant improvement in fatigue, weight loss, depression, nocturia, bone pain, and constipation, specifically in patients >80 years [16]. Several other studies have similarly found improvements over a wide domain of neuropsychiatric symptoms, although most outcomes were measured without validated, formal neuropsychological tests [33, 62].

More recently, Perrier et al. performed a pilot randomized, controlled trial ($n = 18$) to objectively measure differ-

ences in neurobehavioral symptoms associated with mild, asymptomatic PHPT in patients with a mean age of 63 years. Objective tests, including functional magnetic resonance imaging, actigraphy for sleep assessment, and a validated neuropsychological battery were used to document the effect of improved sleep post-PTx. At 6 weeks postoperatively, hypersomnolence was increased in the observation group but decreased in the PTx group ($p = 0.03$). The trend continued at 6 months without statistical significance [35].

Another randomized, controlled trial involving patients with a mean age of 65 years examined quality of life in patients with mild, asymptomatic PHPT. Quality of life was assessed with two validated, standardized questionnaires, preoperatively and every 6 months for 2 years post-PTx. A statistically beneficial effect of PTx was demonstrated in areas of social and emotional role function. Patients who did not have surgery experienced a significant decline in the domains of social functioning, physical problems, emotional problems, energy, and health perception (5 of 9 domains). In contrast, patients undergoing PTx experienced a significant decline only in physical function score, whereas five other domains showed small, nonsignificant declines [59].

The literature on neuropsychiatric function in PHPT is interspersed with anecdotal reports of striking lifestyle improvements post- PTx in elderly patients. In a study by Chen, one patient reported being able to "throw away her cane and walk unassisted" after PTx for PHPT [9]. A number of case reports describe similar findings [63, 64]. Our institutional experience likewise confirms that elderly patients often make substantive gains in cognition and sensorimotor function when rendered eucalcemic. Some examples include an 83-year-old woman who returned to playing chess with her son, an aphasic 90-year-old woman who regained the ability to sing and participate in family activities, and a 67-year-old woman about to be institutionalized for Parkinsonism who returned to the family home with adequate performance of activities of daily living within a few weeks postoperatively. Objectively and subjectively, resolution of hypercalcemia can produce profound impacts on the quality of life in the geriatric population.

IMPROVEMENT IN CARDIOVASCULAR DISEASE

Cardiovascular benefits have been reported after PTx but have not been studied in the geriatric population specifically. Successful PTx has been reported to result in reversal of left ventricular hypertrophy and a halt in progressive calcification [33, 65]. Vestergaard et al. compared 674 Danish patients with PHPT undergoing PTx with 2,021 age- and

gender-matched controls. They identified an increased risk of acute MI starting a decade prior to surgery, declining to a normal level 1 year following surgery (preoperative RR 1.9, 95% CI 1.2–3.0; 1 year postoperative RR 0.9, 95% CI 0.5–1.5). Patients with cardiovascular disease experienced an increased mortality, with hypertension being the main factor in the excess mortality (RR 2.29, 95% CI 1.09–4.82) [39]. The findings have not been replicated outside of Scandinavia. In fact, a 28-year population-based study in Minnesota found a relative risk of death of 0.69 in patients with PHPT compared with controls (95% CI 0.57–0.83). However, elevated serum calcium level was an independent predictor for mortality in this study [66].

AGE-BASED BIAS AND DELAYS IN REFERRAL

Despite the considerable accumulated evidence indicating that PTx is a safe and effective treatment for PHPT, elderly patients frequently do not receive surgery. A recent, large, population-based study reported that whereas 41% of patients with PHPT who were <50 years of age received PTx, only 17% of patients aged 70–79 years and 5.1% of patients aged ≥80 years with PHPT were treated surgically [8]. Other studies support the conclusion that elderly patients are undertreated [9, 16]. Additionally, Kebebew et al. found that one fourth of patients >80 years with PHPT experienced delays in surgical referral of >1 year. Among these patients, two developed hypercalcemic crisis and acute delirium [16]. Others developed progressive osteoporosis and kidney stones in the interval between diagnosis and treatment [8, 9, 16].

Despite the evidence supporting equivalent operative outcomes in elderly patients, many primary providers still do not accept PTx as a safe option for their patients. This reluctance may be due to preconceptions about the outcomes of parathyroid surgery. At high-volume endocrine surgery centers, experienced parathyroid surgeons routinely perform PTx using the minimally invasive techniques described. Referring elderly patients to a high-volume parathyroid surgeon is crucial to achieving the highest cure rates, lowest complication rates, and shortest length of stay [67, 68]. With these achievable outcomes and recent evidence that outpatient PTx is cost effective for the management of PHPT in older patients with life expectancy >5 years, primary care providers should reconsider referral of elderly patients for PTx [17].

LIMITATIONS OF STUDIES

Many of the current randomized, controlled trials evaluating PTx versus observation in elderly patients involve relatively small patient numbers, and few have followed patients long term. Also, surgical studies all consist of ret-

rospective reviews of elderly patients undergoing PTx, derived from surgical databases. They provide no information on the natural history of PHPT in the elderly, and cannot be used to compare surgical versus medical treatment. Large, prospective trials of elderly patients with PHPT randomized to surgical versus medical treatment are needed to definitively evaluate the safety and efficacy of surgical management of PHPT in older patients.

CONCLUSION

The prevalence of PHPT will increase with the growth of the elderly population. Elderly patients often present with nonclassic symptoms of PHPT, including weakness, fatigue, bone pain, confusion, and memory problems, which impact their quality of life. They also have lower BMD values than their younger counterparts. Although many studies to date are retrospective in nature and evaluate patients from surgical databases, the studies reviewed here consistently demonstrate that PTx yields similar outcomes, in terms of morbidity, mortality, and cure, in both elderly and younger patients. MIP can be performed under local anes-

thesia and as an outpatient procedure, thereby minimizing the cardiopulmonary risk of general anesthesia and allowing elderly patients a rapid return to their home environment. Both subjective and objective assessments of elderly patients post-PTx clearly show improvements in quality of life and increased fracture-free survival. In spite of these results, even symptomatic elderly patients are often not being referred for PTx despite the potential serious consequences of untreated PHPT. We anticipate that the application of new validated tools for symptom assessment, combined with an increased awareness of the favorable risk/benefit profile offered by minimally invasive surgical techniques, should lead to more appropriate treatment of PHPT in an aging population.

AUTHOR CONTRIBUTIONS

Conception/design: Lilah F. Morris, Bian Wu, Theodore J. Hahn, Michael W. Yeh
Collection and/or assembly of data: Lilah F. Morris, Bian Wu, Michael W. Yeh
Data analysis and interpretation: Lilah F. Morris
Manuscript writing: Lilah F. Morris, Juliette Zelada, Theodore J. Hahn
Final approval of manuscript: Bian Wu, Theodore J. Hahn, Michael W. Yeh

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