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How Long Should We Follow Patients After Apparently Curative Parathyroidectomy?

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Introduction

The incidence of primary hyperparathyroidism (1HPT) is steadily increasing and parathyroidectomy is the only curative treatment. Recent data from the Kaiser-Permanente system revealed a three-fold increase in 1HPT diagnosed during their study period from 1995-2010, across genders and races.¹ Previous studies have shown that parathyroidectomy for 1HPT is curative in greater than 95% of cases when performed by an experienced surgeon.²⁻⁴ In addition, prospective observation has confirmed that parathyroidectomy not only results in sustained improvements in short-term bone mineral density, but also produces a sustained benefit over time which is critically important to older patients at risk for osteoporosis and fractures.⁵

Despite the high cure rate following parathyroidectomy, recurrence of 1HPT remains a clinical challenge. A better understanding of recurrence risk has significant implications on operative strategy and duration of post-operative follow-up. Recurrence can be due to anatomic factors, such as ectopic or supernumerary glands or biologic factors such as genetics and environmental exposure, and rarely parathyroid cancer.⁶ Previous studies that have prospectively evaluated recurrence after parathyroidectomy occurred prior to several modern advances in surgical technique such as intraoperative parathyroid hormone (PTH) monitoring, the use of minimally invasive parathyroidectomy, and the development of more advanced imaging modalities for preoperative gland localization. Walgenbach et al prospectively followed a group of patients in Germany from 1987-1998 with 1HPT for a median of 2 years. They report a 98% cure rate after surgery, and a surprising 4.7% rate of permanent hypoparathyroidism.³ A prospective Swedish study of patients who had surgery for 1HPT from 1953-1982 reported an overall recurrence rate of 7% in patients including

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Conflicts of Interest

For the remaining authors, none are declared.

single or multi-gland disease, with instances of recurrence reported at more than 20 years after parathyroidectomy.⁷ However, the data on long-term rates of 1HPT recurrence in a more recent group of patients remains lacking.

The goal of this study was to evaluate the 10-year risk of recurrent 1HPT after parathyroidectomy in a contemporary cohort of patients. We additionally sought to identify factors that are associated with risk of recurrence.

Methods

We used the University of Wisconsin parathyroid surgery database to retrospectively identify all patients undergoing parathyroidectomy between November 1, 2000 and June 30, 2005. We excluded all patients with secondary or tertiary hyperparathyroidism, or a known family history of parathyroid disease. We also excluded patients with mediastinal adenomas requiring full or partial sternotomy, and those with parathyroid cancer. Patients undergoing re-operative parathyroid or neck surgery were also excluded. Persistent disease was defined as elevated serum calcium within 6 months of surgery. Surgical cure was therefore defined as having normal serum calcium values after 6 months after surgery. Patients with persistent disease, and those missing serum calcium levels after 6 months from surgery were also excluded from analysis. The remaining 196 patients were classified as having undergone a curative parathyroidectomy for their initial, sporadic 1HPT. (Figure 1)

We then examined predictors of 1HPT recurrence, which was defined as a serum calcium 10.2mg/dL, the upper limit of normal in our laboratory system, at any point beyond 6-months after parathyroidectomy. To be included in our study cohort, all patients had at least one serum calcium level drawn after 6 months from parathyroidectomy. Medical records were extensively scrutinized when available to rule out causes of hypercalcemia other than recurrent hyperparathyroidism, including calcium over-supplementation, thiazide use, paraneoplastic syndrome, or worsening renal function. Patient deaths during the follow-up period were confirmed either through the electronic medical record, or through cross-referencing with the Federal Social Security Death Index. Follow-up times were calculated from the date of surgery to the date of the patient's last available serum calcium level. Patients were censored at the time of death or last reported serum calcium.

Etiology of 1HPT was categorized as single adenoma, double adenoma, or hyperplasia based on the number of glands resected and was subsequently confirmed on final surgical pathology. Patients were categorized as either undergoing unilateral, minimally invasive parathyroidectomy (MIP) or bilateral neck exploration via a bilateral approach. As we retrospectively examined this cohort, this designation was based on the actual operation performed rather than intention to treat.

Comparisons between groups were made using Chi-squared for proportions and student's t-tests for means. We evaluated time to recurrence using the methods of Kaplan and Meier with the log-rank test for comparison. We then used Cox regression in univariate analysis to identify independent predictors of recurrence risk. Applying a threshold of $p < 0.1$ on univariate analysis and additionally including operative approach, a clinically significant

factor, a multivariate model was constructed. Cox regression was then used to divide patients into age quartiles to specifically examine recurrence-free survival by age group. All statistical calculations were performed using SPSS (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.)

Results

Patient Demographics

A total of 196 patients met inclusion criteria with an overall median follow-up time of 9.2 years IQR (interquartile range) [5.4-10.9 years]. 193 (98.5%) patients presented with hypercalcemia, serum calcium 10.2 mg/dL. The majority of patients were female, with single adenoma found in 80.6% of patients. Most patients also underwent a pre-operative localization study, such as sestamibi scanning or neck ultrasound. (Table I) A total of 3 patients (1.5%) underwent concomitant thyroid surgery during parathyroidectomy. The median age of our cohort was 61 years IQR [51-70 years]. 46 (23.5%) patients died during this extended study period, most often from cardiovascular and neoplastic processes. Only 3 (6.5%) patients in the deceased cohort were categorized as having 1HPT recurrence, none of whom had a known malignancy at the time recurrence or at death.

Time to recurrence

The 10-year recurrence rate in our cohort was 14.8% (29/196), with median time to recurrence of 6.3 years IQR [3.4-10.8 years]. We found that 41.4% of recurrences were detected by 5 years, and 65.5% by 10 years. Additionally, 34.5% of all recurrences appeared 10 or more years after initial parathyroidectomy. Of the 29 patients who had recurrence, 16 (55%) patients underwent reoperation after successful localization at a median time of 8.71 years $\pm$ 1.06 years after initial parathyroidectomy. The cure rate after re-operation was 87.5% (14/16) with one patient lost to follow-up and one patient with persistent disease. 7 (24%) patients had incomplete medical records with respect to physician encounters, and 4 patients (14%) refused re-operative surgery. One patient was not localized, and the final patient with recurrence was diagnosed recently and is currently discussing treatment plans.

Factors Associated with Recurrence

There was no difference in recurrence rates for patients who had minimally invasive parathyroidectomy or bilateral exploration ($p=0.448$). Five year disease-free survival in patients undergoing unilateral MIP was 91.8% versus 97.9% in the bilateral group. However, the recurrence curves converge at 10 years with a disease-free survival for the MIP group of 87.9% versus 87.4% in the bilateral group. (Figure 2A)

Examining potential predictors of recurrence, we found that double adenomas (DA) were more likely to recur than single adenomas ($p=0.006$) but not hyperplasia ($p=0.525$). (Figure 2B) Additionally, younger age ($p=0.032$) and a drop in intraoperative parathyroid hormone (IoPTH) less than 70% were predictive of disease recurrence ($p=0.015$). Multivariate analysis further confirmed that older age (HR 0.97, 95% CI 0.94-0.99, $p=0.034$) and IoPTH drop greater than 70% (HR 0.45, 95% CI 0.20-0.98, $p=0.046$) to be protective against

recurrence. On the other hand, DA (HR 3.52, 95% CI 1.23-10.08, $p=0.019$) was an independent predictor of recurrence. (Table 2)

Lastly, to further examine the impact of age on recurrence, patients were divided into age quartiles and stratified according to disease etiology and IoPTH drop greater than 70%. Only single adenoma provided adequate sample size for this subgroup analysis. The curves for the oldest patient quartile, age ≥ 70 years, shows clear separation that trends towards improved recurrence-free outcomes compared to the remaining age quartiles. (Figure 3A and 3B) This further confirms the protective effect of older age on 1HPT recurrence. The improved trend in the oldest patients however was not statistically significant for either single adenoma ($p=0.311$) or IoPTH drop $> 70\%$ ($p=0.152$).

Discussion

Through extended follow-up of this contemporary cohort, we report a 14.8% recurrence rate for sporadic 1HPT following apparently curative parathyroidectomy. In our series, over 1/3 of the recurrences occur 10 or more years after initial surgery, highlighting the importance of long-term follow-up for these patients. Our practice is to recommend annual serum calcium checks, however given the age and comorbidities of the patient, the frequency and duration of calcium surveillance may be shortened or extended. Though patients may seem asymptomatic at the time of detected recurrence, 1HPT is often associated with vague symptomatology and, more importantly, negative effects on bone health that can all be improved with parathyroidectomy.⁸

Retrospective studies that have looked at outcomes after parathyroidectomy for 1HPT have suffered from lack of long-term follow-up, with reported mean follow-up times ranging from zero to 7.4 years.^{9, 10} Reported recurrence rates in these studies range from 0%¹¹ to 5.2%.¹⁰ We report here a much higher incidence of recurrence when patients are followed for a longer period of time. This may be in part due to our definition of recurrence based on hypercalcemia alone. However, as 98% of our cohort presented with pre-operative hypercalcemia, this marker seems a reasonable surrogate for recurrence events even in the absence of available postoperative serum PTH levels. Therefore, the long-term recurrence rate for 1HPT after apparently curative parathyroidectomy is likely to be higher than previously reported.

Parathyroid surgery is safe, and associated with excellent outcomes without decreased long-term survival.^{12, 13} The increasing popularity of MIP, a unilateral neck exploration after appropriate pre-operative localization, has sparked much debate over the optimal surgical approach for sporadic hyperparathyroidism. While some have abandoned this approach and prefer to perform a bilateral exploration on all patients without reported increases in morbidity or operative time¹⁴, other groups continue to offer MIP to appropriately selected patients.^{15, 16} Long-term outcomes on 184 patients with sporadic 1HPT with pre-operative localization reported a 1.6% incidence of persistent hypercalcemia after surgery, with no recurrences at mean follow-up of approximately 5 years.¹⁷ A recent randomized clinical trial comparing unilateral versus bilateral cervical exploration for 1HPT with a primary endpoint of persistent disease concluded a similar failure rate of 2% with a mean follow-up time of 23

months.¹⁸ Five patients with 1HPT were excluded from our study due to persistent disease. Of these, 3 patients had preoperative localization of whom 2 underwent MIP with the last being converted from MIP to bilateral exploration.

Our group has also previously reported the equivalence of either MIP or a bilateral approach in selected patients in the short-term¹⁹, however all studies have failed to look at long-term recurrence rates. This study demonstrates that surgical approach is not independently predictive of long-term recurrence ($p=0.448$) in patients with 1HPT. Due to the low number of events and the diminishing number at-risk with longer duration of follow-up, we may be failing to detect if such a difference truly exists beyond 12 years where the curves diverge. However, extended follow-up to 10-years demonstrates equivalent recurrence-free survival regardless of operative approach, which suggests that bilateral exploration is not the absolute solution in adenoma recurrences.

DA is the least commonly identified form of 1HPT with reported rates ranging from 0-11.8%.²⁰ DA is particularly challenging to detect both preoperatively and intraoperatively.²¹ Preoperative localization often fails to distinguish between two-gland and multiglandular disease.²⁰ Early recommendations were to perform bilateral exploration on all of these patients with selective resection of abnormal glands.²⁰ Our recurrence-free survival analysis found all recurrences for double adenomas to occur within the first five years of follow-up, questioning the need for bilateral exploration in this subset of patients. However, a retrospective series of patients with 1HPT due to DA found a 50% drop in IOPTH did not reliably predict cure in 55% of cases despite a bilateral neck exploration in all patients.²² Therefore, it is not entirely surprising that we found DA to be highly predictive in multivariate analysis of having 1HPT recurrence during a 10-year follow-up period. Finding double adenomas during parathyroidectomy therefore should increase suspicion when evaluating for surgical cure and during subsequent follow-up for recurrence.

Our study has several limitations. First is the retrospective nature of our data collection, with almost 20% of our study population excluded due to lack of follow-up beyond 6 months during the decade long period of interest. It is unclear whether patients with incomplete follow-up would lead to over- or under estimation of recurrent hyperparathyroidism. Second, our definition of recurrence was based on hypercalcemia alone. While the records were carefully scrutinized to exclude other causes of hypercalcemia, examining serum calcium and parathyroid hormone concurrently is a more accurate picture of disease status. However, serum parathyroid hormone levels were rarely drawn, especially in patients with normal serum calcium levels. Therefore we may be under estimating the true recurrence rate without the available serum PTH values. The importance of long-term follow-up in patients with sporadic 1HPT should also take into consideration expected life-years. The median age at time of surgery for our cohort was 61 years IQR [51-70 years]. Advanced age is not a contraindication for parathyroid surgery²³⁻²⁵, but life expectancy is certainly an important factor when it comes to duration and frequency of continued surveillance. Notwithstanding these limitations, we have demonstrated the importance of having long-term follow-up after parathyroidectomy for sporadic 1HPT.

In conclusion, our cohort of 196 patients who underwent apparently curative parathyroidectomy for sporadic 1HPT between 2000-2005 demonstrated an overall recurrence rate of 14.8%, with over a third of these recurrences diagnosed more than 10 years after initial surgery. While a definite long-term recurrence rate after parathyroidectomy is currently unknown, this highlights the importance and necessity of long-term follow-up for 1HPT patients.

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Figure 1. Patient selection

2HPT=secondary hyperparathyroidism, 3HPT=tertiary hyperparathyroidism, MEN=multiple endocrine neoplasia, HPT=hyperparathyroidism, 1HPT=primary hyperparathyroidism

*Recurrence defined as hypercalcemia at >6months after parathyroid surgery

A.

B.

Figure 2.

Kaplan-Meier Recurrence Free Survival Curves A. By parathyroid operation performed with reference line at 5 years and 10 years, number at risk for various time points shown below B.

By disease etiology

A.

B.

Figure 3.
Recurrence-Free Survival Stratified by Age A. With Single Adenoma B. With Intraoperative PTH drop > 70%

Table 1

Patient demographics and operative characteristics

Variable	Recurrence (n=29)	No Recurrence (n=167)	p-value
Age (years)	58 [47-62.5]	61 [52-72]	0.007
Gender (male/female)	4 (13.8%)/25 (86.2%)	33 (19.8%)/134 (80.2%)	0.448
BMI (kg/m ²)	31.3 ± 1.0	31.3 ± 0.7	0.955
Gland weight (g)	619.4 ± 97.9	902.3 ± 99.8	0.046
Etiology			
Adenoma (reference)	22 (75.9%)	136 (81.4%)	-
Double Adenoma	5 (17.2%)	13 (7.8%)	0.003
Hyperplasia	2 (6.9%)	18 (10.8%)	0.518
Symptomatic	22 (75.9%)	126 (75.4%)	0.962
Pre-op Calcium (mg/dL)	11.0 ± 0.1	11.2 ± 0.1	0.121
Pre-op PTH (pg/mL)	131.0 ± 19.7	128.3 ± 6.9	0.899
Minimally invasive	23 (79.3%)	125 (74.9%)	
Bilateral	6 (20.7%)	42 (25.1%)	0.606
> 70% Intraoperative PTH	12 (44.4%)	109 (66.1%)	0.011
Localization performed	27 (93.1%)	150 (89.8%)	0.581
Ectopic gland	10 (34.5%)	38 (22.8%)	0.175
Follow-up time (years)	7.0 ± 0.8	8.3 ± 0.3	0.130

Results presented as median [25th; 75th percentile], mean ± SEM (standard mean error), or *n* (%)

BMI=body mass index, PTH=parathyroid hormone,

Table 2

Cox-Regression model to predict recurrence

Variable	Univariate		Multivariate	
	Hazards Ratio (95% CI)	p-value	Hazards Ratio (95% CI)	p-value
Age (years)	0.97 (0.95-0.99)	0.032	0.97 (0.94-0.99)	0.034
Male gender	1.41 (0.49-4.10)	0.526	-	-
BMI (kg/m ²)	0.99 (0.95-1.05)	0.935	-	-
Gland weight (g)	1.00 (0.99-1.00)	0.229	-	-
Etiology		0.015		0.040
Adenoma (reference)	-	-	-	-
Double Adenoma	4.05 (1.49-11.04)	0.006	3.52 (1.23-10.08)	0.019
Hyperplasia	0.62 (0.15-2.67)	0.525	0.43 (0.05-4.02)	0.462
Pre-op Calcium 11.1 (mg/dL)	0.61 (0.29-1.30)	0.198	-	-
Pre-op PTH 101 (pg/mL)	1.02 (0.49-2.12)	0.959	-	-
Minimally invasive vs. bilateral approach	0.70 (0.28-1.76)	0.450	0.64 (0.20-2.02)	0.445
> 70% drop in Intraoperative PTH	0.39 (0.18-0.83)	0.015	0.45 (0.20-0.98)	0.046
Ectopic gland	1.60 (0.74-3.49)	0.233	-	-
Symptomatic presentation	1.40 (0.59-3.32)	0.449	-	-

CI=confidence interval, BMI=body mass index, PTH=parathyroid hormone,