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Survival after Parathyroidectomy in Patients with End-stage Renal Disease and Severe Hyperparathyroidism

Andrea Trombetti, MD,[1] Catherine Stoermann, MD,[2] John H. Robert, MD,[3] François R. Herrmann, MD,[1] Pietra Pennisi, MD,[1] Pierre-Yves Martin, MD,[2] René Rizzoli, MD[1]

[1]*Service of Bone Diseases (WHO Collaborating Center for Osteoporosis Prevention), Department of Rehabilitation and Geriatrics, University Hospital of Geneva, 1211 Geneva 14, Switzerland*
[2]*Service of Nephrology, Department of Internal Medicine, University Hospital of Geneva, 1211 Geneva 14, Switzerland*
[3]*Thoracic Surgery Unit, Department of Surgery, University Hospital of Geneva, 1211 Geneva 14, Switzerland*

Abstract

Background: Patients with end-stage renal disease (ESRD) and secondary hyperparathyroidism (SHPT) are at high risk of mortality. Whether an increased risk of death persists after a parathyroidectomy (PTX) is not clearly established.

Subjects and methods: The survival of 40 patients with ESRD and SHPT who underwent PTX was compared with that of 664 ESRD patients.

Results: From first dialysis, a lower mortality rate was found in the group of patients who underwent PTX than in the nonoperated ESRD group (hazard ratio: 0.23; 95% CI: 0.14–0.37). The patients who underwent PTX were younger, had a longer time on dialysis, and had a higher prevalence of kidney transplantation. The mean number of comorbidities was lower (Charlson score 4.2 ± 2.1 versus 6.4 ± 2.9, $p < 0.001$). Then, we randomly selected two matched controls for each PTX case (80 controls, 40 PTX) who had at least an equivalent mean duration of dialysis between the first dialysis and PTX of the PTX group. In a univariate model, there was a trend for PTX being associated with prolonged survival. The mortality was higher both among those at an advanced age and those with a high Charlson score. Adjustments for these covariates made the effect of PTX no more significant.

Conclusions: The risk of death of patients with severe SHPT leading to PTX differed from that of nonoperated subjects. The apparent differences in survival may be related to the number and severity of associated comorbidities. ESRD patients who undergo PTX may represent a subset of healthier subjects.

Secondary hyperparathyroidism (SHPT) is a common complication of chronic kidney disease (CKD) that can lead to clinically significant bone disease.[1,2] It is also associated with soft-tissue and vascular calcifications, cardiovascular disease, and calcifying uremic arteriopathy, all of which may contribute to increased risk of cardiovascular morbidity and mortality among CKD patients,[3–9] with a relative risk of death between 1.06 and 3.9.

Secondary hyperparathyroidism arises from disturbances in calcium, phosphorus, vitamin D, and parathyroid hormone metabolism, which develop at an early

Correspondence to: Andrea Trombetti, MD, e-mail: Andrea.Trombetti@hcuge.ch

stage of CKD[10] and become more prominent as kidney function declines. To overcome deleterious effects of SHPT, standard therapies recommended to correct mineral metabolism and bone disease include calcium supplementation, dietary phosphorus restriction, phosphate-binding agents, and/or vitamin D metabolites.[1,11] However, these agents frequently alter the serum levels of calcium and phosphorus, which result in worsening of serum values and significant extraskeletal morbidity and mortality. Calcimimetics, a new class of drugs offer the possibility to selectively reduce the levels of PTH, serum calcium, and phosphate at the same time. However, whether these effects can contribute to improved survival remains to be demonstrated.[1,12] Thus, PTX in patients on dialysis or in those who have had renal transplants is still frequently required for the treatment of severe SHPT, although recent studies have shown that the percentage of dialysis patients undergoing subtotal or total PTX is declining,[13,14] possibly as a result of more effective medical management.

Whether PTX modifies the mortality rate among patients with end-stage renal disease (ESRD) and severe HPT was studied recently in an observational matched cohort study using data from the United States Renal Database System (USRDS). It was shown that PTX patients displayed prolonged survival during chronic dialysis, with a 15% reduced risk of death. However, an important limitation of that study is that patient characteristics, in particular comorbidities and cardiovascular risk factors, were not taken into account in calculating the risk of death. Indeed, this may potentially explain the differences in mortality rates.[15] The present study was undertaken to determine whether patients operated on for SHPT would be at lower risk of premature death, and to examine whether differences persisted when all comorbidities were considered. We thus analyzed survival after PTX in a well-defined and closely followed cohort of patients in whom cardiovascular risk factors and comorbidities could be carefully recorded and analyzed.

SUBJECTS AND METHODS

Between 1977 and 2002, 741 patients were treated in our institution for end-stage renal disease. The following patients were excluded from the analysis: 19 with parathyroidectomy following a successful kidney transplant (tertiary hyperparathyroidism), 13 patients with 3 or more kidney transplants (9 with a history of parathyroidectomy and 4 never operated), and 5 whose date of first dialysis was not known.

A total of 40 patients (18 males, 22 females) with ESRD and severe hyperparathyroidism underwent PTX between 1977 and 2002 at the Geneva University Hospital, a large acute-care teaching hospital that manages 95% of cases for Geneva and its environs, representing a population of around 400,000. The survival rates of those 40 patients were compared to those of 664 ESRD patients treated at the same institution during the same period.

Renal failure was due to chronic glomerulonephritis ($n = 13$), polycystic kidney disease ($n = 9$), tubulointerstitial nephropathy ($n = 12$), vascular disease ($n = 4$), diabetes ($n = 1$), or undetermined causes ($n = 1$). Seventy-three percent ($n = 29$) were treated with hemodialysis, 10% ($n = 4$) with continuous ambulatory peritoneal dialysis, and 18% ($n = 7$) with the two treatments consecutively. This proportional distribution was quite similar to that of the control group. Mean age at surgery was 47.7 ± 14.7 years (mean ± SD, range: 20–74 years) and the mean time between the first dialysis and PTX was 5.3 years (95% CI: 0.2–17.5). Initial PTX involved removal of 1 to 3 parathyroid glands ($n = 12$, 32%); subtotal PTX ($n = 21$, 57%), or total PTX with autotransplantation ($n = 4$, 10%). Information was not available for 3 patients. Surgery was undertaken in 1 patient just before the onset of dialysis; in the other 39 (96%), during the period of dialysis. Age at first dialysis, gender, and year and date of surgery were noted for each patient. If the patient died during the study period, the year and date of death (but not the main cause of death) were recorded. For each patient, we retrospectively assessed the number of cardiovascular disease risk factors. Dyslipidemia, diabetes and impaired glucose tolerance, hypertension, tobacco use at any time during the follow-up, obesity, and family history of cardiovascular disease before the age of 65 years were taken into account. Comorbid conditions, present at the start of dialysis or that developed during the follow-up were obtained from the patient records. A modified Charlson's Comorbidity Index was computed for each patient.[16] Patients were considered to have a comorbid condition if a listed disorder (Table 1) was mentioned in his/her medical records, or if the patient had been treated for it. Four comorbidity groups were established: low comorbidity (scores ≤ 3), moderate comorbidity (scores 4 and 5), high comorbidity (scores 6 and 7), and very high comorbidity (scores ≥ 8).

Statistical analysis

Summary results are given as the mean ± standard deviation. When the data were not normally distributed, the summary descriptive statistics were the median and

Table 1.
Modified Charlson Comorbidity Index

Comorbidity score[1]	Condition
1	Coronary artery disease
	Congestive heart failure
	Peripheral vascular disease
	Cerebrovascular disease
	Dementia
	Chronic pulmonary disease
	Connective tissue disorder
	Peptic ulcer disease
	Mild liver disease
	Diabetes
2	Hemiplegia
	Moderate or severe renal disease
	Diabetes with end-organ damage[2]
	Any tumor, leukemia, lymphoma
3	Moderate or severe liver disease
6	Metastatic solid tumor
	AIDS

[1]In addition, for each decade > 40 years of age, a score of 1 was added to the comorbidity score.

[2]Nondiabetic patients received a minimum score of 2 for moderate to severe renal disease, and diabetic patients received a minimum of 4 (2 for diabetic end-organ damage and 2 for end-stage renal disease)

interquartile range. Comparisons of continuous variables between two or more groups were performed with Student's *t*-test or analysis of variance (ANOVA). When appropriate, a non-parametric Kruskal-Wallis test was applied. Chi-square tests were used for comparing proportions. The survival of PTX patients and controls following the first dialysis was quantified using survival function estimates based on the Kaplan-Meier method.[17] Follow-up started on the date of first dialysis and continued until death or censoring. Censoring events were survival on 1 March 2003 or at the time of the first successful kidney transplant. A kidney transplant was judged successful if survival of the transplant was longer than 1 year. The resulting observed survival curves were compared using a log-rank test.[18] Because of the large age discrepancy between PTX patients and non-PTX patients and their relatively small number, it was not possible to match each PTX case concomitantly for age and duration of dialysis, or for comorbid conditions. As a result of a large variation in the duration of dialysis, we randomly selected two controls for each PTX case who had at least an equivalent mean duration of dialysis (± 2 years), between the first dialysis and PTX, in order to analyze the effect of PTX on survival.

A conditional logistic regression was used to estimate the influence of patient characteristics on the mortality rate. Independent variables evaluated were gender, age at first dialysis, number of cardiovascular risk factors, year when dialysis was started (± 10 years), modality of dialysis (hemodialysis, peritoneal dialysis, or both, at any time during the follow-up), modified Charlson score, and parathyroidectomy.

The significance level for two-sided *p* values was 0.05 in all tests. The data were analyzed using the STATA statistical software package (version 9.2; Stata Corporation, College Station, TX).

RESULTS

Patients characteristics

At the time of PTX, 40% of the patients had already experienced one or more cardiovascular events (coronary artery disease with angina pectoris or myocardial infarction: 7/40 (18%); cardiac insufficiency: 7/40 (18%); acute stroke: 3/40 (8%); or cardiac arrhythmia disorders: 2/40 (5%)). About half the patients (58%) had symptomatic SHPT, with diffuse bone or joint pains (17/40, 43%), general symptoms (fatigue, muscle weakness, anorexia, 3/40, 8%), neuropsychological disorders (1/40, 3%), and/or pruritus (2/40, 5%). Three patients (8%) had experienced a low trauma fracture and 10 (25%) were clearly identified by dual-energy x-ray absorptiometry as having osteoporosis. Osteitis fibrosa was diagnosed based on radiologic examination of 11 patients. The main cause of surgical referral was refractory hypercalcemia ($n = 29$; 73% patients) or hyperphosphatemia ($n = 23$; 58% of the patients). Data on serum PTH levels were available for 28 patients before surgery. The mean serum PTH level was 19 ± 15 times the upper limit of the normal range.

The patients who underwent parathyroid surgery for secondary hyperparathyroidism had different characteristics from those of the control group (Table 2). The primary causes of end-stage renal failure were different. The most significant differences were younger age at first dialysis, a longer period of dialysis, and a higher prevalence of kidney transplantation, even with unsuccessful outcome, but a lower mean number of comorbidities. Cardiovascular risk factors and dialysis modalities did not differ between the two groups.

Survival rate

Only one PTX patient died within one year of surgery. Using survival function estimates based on the Kaplan-

Table 2.
Patients' characteristics for the whole population

	Dialyzed patients without PTX (n = 664)				Dialyzed patients with PTX (n = 40)				P
	N (%)	Mean ± SD	min	max	N (%)	Mean ± SD	min	max	
Gender N (% of male)	391 (59)				18 (45)				0.060
Cause of renal failure									
Chronic glomerulonephritis	159 (24)				13 (33)				0.151
Polycystic kidney disease	62 (9)				9 (23)				**0.014**
Vascular	199 (30)				4 (10)				**0.001**
Tubulointerstitial	117 (18)				12 (30)				**0.045**
Diabetes	113 (17)				1 (3)				**0.001**
Other or unknown	74 (11)				1 (3)				0.059
Age at first dialysis		57.2 ± 17.1	11	90		42.6 ± 15.2	14	69	**0.001**
Modality of dialysis									0.708
Hemodialysis	509 (77)				29 (73)				
Peritoneal dialysis	52 (8)				4 (10)				
Both modalities	103 (16)				7 (18)				
Time on dialysis (years)		2.9 ± 3.3	0	28		10.2 ± 7.2	0	28	**0.001**
Renal graft (%)	252 (38)				22 (55)				**0.025**
Number of renal transplantations (RT)									**0.005**
Never	411 (62)				18 (45)				
One RT	221 (33)				15 (38)				
Two RT	32 (5)				7 (18)				
Functioning renal graft (%)	213 (32)				15 (38)				0.291
Mean number of cardiovascular risk factors		1.4 ± 0.9	0	3		1.4 ± 1.0	0	3	0.882
Mean modified Charlson score		6.4 ± 2.9	2	17		4.2 ± 2.1	2	17	**0.001**
Charlson score									
Low score (≤ 3)	123 (19)				18 (45)				
Moderate score (4 or 5)	143 (22)				13 (33)				
High score (6 or 7)	167 (25)				7 (18)				
Very high score (≥ 8)	231 (35)				2 (5)				**0.001**

Meier method, it was found that the mortality rate after the first dialysis was significantly lower in the PTX group (hazard ratio: 0.23; 95% CI: 0.14–0.37) (Fig. 1). Because of the differences between the two populations (Table 2), we tried specifically to evaluate the influence of PTX on survival. We randomly selected two controls for each PTX case, who had at least an equivalent mean duration of dialysis, between the first dialysis and PTX for the PTX group and the beginning of dialysis and any censoring event in the control group (± 2 years) to analyze the effect of PTX on survival (40 PTX patients and 80 controls) Some differences were still present after this matching: younger age at time of first dialysis, a lower number of comorbidities, and a higher number of renal transplantations (Table 3). The censoring at time of renal transplantation alleviated the confounding effect of transplantation on survival. Then, conditional logistic regression was used to estimate the influence of patient characteristics on the mortality rate. Independent variables evaluated were gender, age at first dialysis, number of cardiovascular risk factors, year of initiation of dialysis

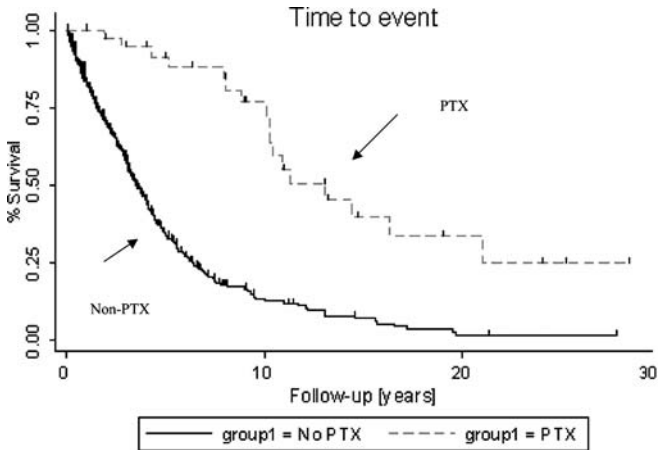

Figure 1. Survival after first dialysis. Kaplan-Meier survival estimates for 40 PTX patients and 664 nonoperated patients with ESRD. Follow-up started on the date of first dialysis, and continued until death or censoring. Censoring took place at survival on 1 March 2003 or first successful kidney transplantation. A kidney transplantation was judged successful if survival of the transplant was greater than one year.

Table 3.
Patient characteristics (matched case-control study)

	Dialyzed patients with no PTX (n = 80)				Dialyzed patients with PTX (n = 40)				P Value
	N (%)	Mean ± SD	min	max	N (%)	Mean ± SD	min	max	
Gender N (% of male)	41 (51)				18 (45)				0.326
Cause of renal failure									
Chronic glomerulonephritis	26 (33)				13 (33)				0.579
Polycystic kidney disease	9 (11)				9 (23)				0.090
Vascular	17 (21)				4 (10)				0.099
Tubulointerstitial	22 (28)				12 (30)				0.467
Diabetes	5 (6)				1 (3)				0.346
Other or unknown	7 (9)				1 (3)				0.186
Age at first dialysis		55.0 ± 14.6	26	88		42.6 ± 15.2	14	69	0.001
Modality of dialysis									0.310
Hemodialysis	65 (81)				29 (73)				
Peritoneal dialysis	3 (4)				4 (10)				
Both modalities	12(15)				7 (18)				
Time on dialysis (years)		8.4 ± 4.7	0	28		9.6 ± 6.9	1	28	0.275
Renal graft (%)	21 (26)				22 (55)				**0.002**
Number of renal transplants (RT)									**0.004**
Never	59 (74)				18 (45)				
One RT	17 (21)				15 (38)				
Two RT	4 (5)				7 (18)				
Functioning renal graft (%)	20 (25)				15 (38)				0.114
Mean number of cardiovascular risk factors		1.4 ± 1.0	0	3		1.2 ± 0.9	0	3	0.298
Mean modified Charlson score		6.0 ± 2.6	2	16		4.2 ± 1.6	2	13	**0.001**
Charlson score									**0.001**
Low score (≤ 3)	14 (18)				18 (45)				
Moderate score (4 or 5)	19 (24)				13 (33)				
High score (6 or 7)	27 (34)				7 (18)				
Very high score (≥ 8)	20 (25)				2 (5)				

(± 10 years), modality of dialysis (hemodialysis, peritoneal dialysis, or both, at any time during the follow-up), modified Charlson score, and parathyroidectomy.

In a univariate model, there was a trend for PTX being associated with prolonged survival (Fig. 2, Table 4). The mortality rate was higher with advanced age at first dialysis and high modified Charlson score. To evaluate to what extent these covariates could affect survival, independent variables were included in a multivariate model. Adjustments for these covariates made the effect of PTX not any more significant (Table 4). The age at first dialysis, the year of first dialysis after 1990, and a highly modified Charlson score were significant and independent predictors of death.

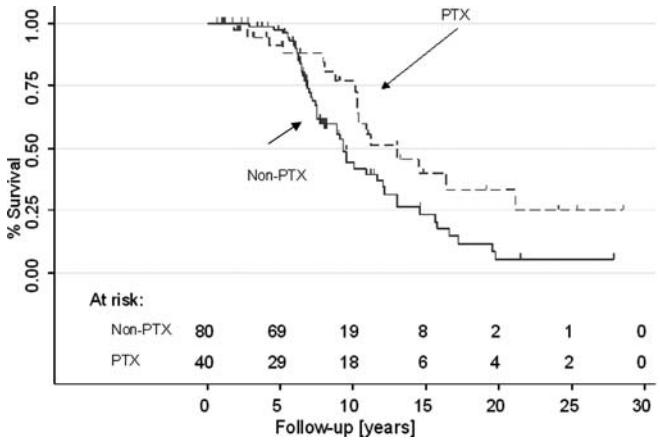

Figure 2. Survival after PTX. We randomly selected two controls for each PTX case who had an equivalent mean duration of dialysis, between the first dialysis and PTX for the PTX group and the beginning of dialysis and any censoring event for the control group (plus or minus 2 years) to analyse the effect of PTX on survival.

DISCUSSION

Patients with ESRD are at high risk of cardiovascular morbidity and mortality, particularly from ischemic heart disease and heart failure.[19] Secondary hyperparathyroidism is believed to contribute to an increased risk of cardiovascular mortality, but the direct link between PTH and disorders of cardiovascular structure and function in

Table 4.
Factors influencing mortality rate in patients with end-stage renal disease

	Unadjusted OR (95% CI)	p	R^2	Adjusted OR (95% CI)	p	R^2
PTX	0.54 (0.24–1.17)	0.117	0.017	1.50 (0.49–4.61)	0.478	
Mean N of cardiovascular risk factors	0.95 (0.64–1.41)	0.789	0.001	1.06 (0.60–1.88)	0.845	
Gender	1.15 (0.55–2.40)	0.704	0.001	.869 (0.30–2.53)	0.797	
Age at first dialysis	1.08 (1.05–1.12)	**0.001**	0.208	1.09 (1.03–1.15)	**0.003**	
Modality of dialysis		0.5244	0.009			
Hemodialysis						
Peritoneal dialysis	2.19 (0.41–11.51)	0.357		2.50 (0.24–26.31)	0.445	
Both modalities	1.48 (0.53–4.13)	0.453		1.79 (0.40–7.96)	0.447	
Charlson score		**0.001**	0.228			
Low score (≤ 3)						
Moderate score (4 or 5)	2.03 (0.67–6.18)	0.213		0.863 (0.20–3.74)	0.844	
High score (6 or 7)	5.03 (1.69–14.98)	**0.004**		1.37 (0.23– 8.11)	0.731	
Very high score (≥ 8)	62.66 (7.12–551.47)	**0.001**		44.50 (2.44–811.22)	**0.010**	
Years of first dialysis		0.480	0.001			
1970						
1980	1.42 (0.56–3.58)	0.457		0.80 (0.23–2.76)	0.730	
1990	0.827 (0.30–2.24)	0.709		0.06 (0.01–0.38)	**0.003**	
						0.39*

*Whole model.

ESRD is not fully understood. The deleterious effects of high PTH levels in ESRD might be related to an increase in cell calcium content. Previous studies have suggested that high levels of PTH are associated with impaired ventricular diastolic and systolic function.[20–24] Secondary hyperparathyroidism is also associated with left ventricular hypertrophy.[25–29] In combination with the higher prevalence of hypertension, this could contribute to the greater prevalence of congestive heart failure in SHPT patients. Several studies have suggested that hyperlipemia in renal failure is related to elevated PTH levels.[30–32] Decreased PTH-related insulin sensitivity may also augment atherosclerotic changes.[33] Myocardial disease, along with atherosclerosis of the coronary arteries,[34] may increase the risk of myocardial infarction and arrhythmias, which could contribute to sudden death, and thus to higher mortality rates among ESRD patients.

Whether PTX reduces the risk of premature death of patients with ESRD and severe SHPT is not clearly accepted because data on the influence of PTX in ESRD on survival are very scarce. A beneficial effect was suggested in a recently published report.[15] Long-term post-PTX survival improved, with a relative hazard ratio for mortality of 0.85 (95% CI: 0.78–0.92) after one year. A higher short-term mortality rate was also indicated in the first 30 days after surgery.

It has been demonstrated that PTX leads to a statistically and clinically significant decrease in blood pressure levels.[35–37] However, these data were not confirmed by others groups.[38,39] Another recent study has demonstrated that left ventricular function in patients with advanced SHPT and dilated cardiomyopathy markedly improved following PTX.[40] Goldsmith et al. noted reduced progression of calcification in haemodialysis patients who underwent PTX.[41]

Our own study suggested that the survival rate of patients who develop severe SHPT leading to PTX may differ from that of nonoperated subjects. Indeed, in a first step, we analyzed survival after the first dialysis of all the patients in the study. Mortality was significantly lower in the PTX group, but the patient characteristics were markedly different. We then selected a control group that was more comparable to the PTX patients. The only differences that persisted after matching were age at first dialysis and the modified Charlson morbidity score. Parathyroidectomy patients were younger at first dialysis and had fewer comorbidities. The small number of patients and adjustments for these covariates made the effect of PTX nonsignificant.

It is unlikely that the population had a selection bias, as all cases of SHPT in Geneva are managed at our institution. Thus, patients selected for surgery are more likely to have had advanced disease with symptoms than those selected for conservative management, most of whom had asymptomatic disease with a lower risk prevalence of comorbidity. Nevertheless, some patients may have been in too poor a condition to tolerate surgery, and this would mean that the risk of death for some of those who were managed conservatively might have been higher than for those undergoing surgery.

The low number of patients and deaths could have limited our ability to detect an effect on survival. This was compensated by the fact that a homogeneous population was studied, with consistent and homogeneous data collection. Finally, the study was performed during the period (1977 to 2002) before new, less-hypercalcemic active vitamin D analogs (such as paricalcitol) and sevelamer became available. It is therefore improbable that survival was altered by modification of treatment strategies. These results could also suggest that PTX should be performed earlier, before these comorbidities develop. But, as serum PTH levels were not analyzed, this assumption remains hypothetical.

In conclusion, we found that the risk of death of patients who developed severe SHPT leading to PTX was different from that of nonoperated subjects. But this apparent difference may be related to the number and severity of associated comorbidities. Thus, ESRD patients who undergo PTX may represent a subset of possibly healthier subjects than those not undergoing PTX.

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