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Mortality associated with primary hyperparathyroidism ☆

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ABSTRACT

561 patients with primary hyperparathyroidism were followed between 1961 and 1994. Relative survival was compared to that of the Australian population studied during the same time interval. Mortality was significantly greater in the hyperparathyroid population ($P < 0.001$). Mortality was not greater in the patients with serum calcium levels >3.00 mmol/L compared to those with a serum calcium levels <3.00 mmol/L.

113 patients did not have parathyroid surgery. Their relative survival was not significantly different from those who had surgery but their mean serum calcium and parathyroid hormone (PTH) levels were significantly lower than those who had surgery.

A re-analysis of the 453 patients followed between 1972 and 2011 was carried out and a 20-year survival analysis made of those diagnosed between 1972 and 1981 and those diagnosed between 1982 and 1991. The latter group had significantly worse relative mortality than the former group ($P < 0.001$) but was significantly older at the time of diagnosis (56.94 ± 14.83 vs 52.01 ± 13.58, $P < 0.001$). The serum calcium and serum PTH levels were not significantly different between these two groups.

Introduction

Hyperparathyroidism has been associated with an increased mortality both in surgically treated patients and in patients who have not undergone surgery [1–4]. In other studies, mortality in surgically treated hyperparathyroidism was not increased [3,5,6]. There is uncertainty as to whether surgery for hyperparathyroidism confers benefit in terms of survival. The present study was therefore undertaken to examine survival in a cohort of patients with hyperparathyroidism studied over a 50-year period between 1961 and 2011, and to determine whether hyperparathyroidism was associated with increased mortality and whether surgery made any impact on survival.

Patients and methods

The first patient diagnosed and treated for primary hyperparathyroidism in our institution was in 1961. Between this time and at the end of 1994, all patients diagnosed with primary hyperparathyroidism were identified, medical records were obtained and examined, and a determination was made as to whether or not they were alive at the end of 1994. In Australia, each state has access to Australia-wide date of death data although each state maintains its own death register. The patient cohort list was submitted to each local state death registry, dates of death recorded for any of those who had died, and relevant states were contacted in order to obtain a copy of each death certificate.

The interval from the time of diagnosis to the time of death was calculated. Each patient was compared with a control population matched for age, sex, the year observation began, and the duration of the observation. The control population was the Australian population at large for whom Life Tables from 1961–1994 existed at the time. Life Tables are published by the Australian Government Actuary. Taking into account age, sex, start year of observation and duration of observation, survival data of individuals with primary hyperparathyroidism compared with expected survival in the general Australian population was obtained from the Life Tables.

A second analysis of relative survival over a 20-year time interval was calculated for the patients studied between 1972 and 2011 using a new methodology. The group was divided into two cohorts, those

☆ PBC-B, JNS, AMcE, EGW, BGR, GRF, DL, and SP made the diagnosis of primary hyperparathyroidism, made the decision regarding surgical or non-surgical treatment, and clinically reviewed patients until the final assessment date of the 31 December 2011.TSR and LD performed the parathyroid surgery.MLN reviewed all the clinical records and entered all the relevant data in the database.RS carried out the statistical analysis of the data. PBC-B is the principal author of the manuscript with input from all the contributors.The final manuscript was approved by all the authors.

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diagnosed between 1972 and 1981 and those diagnosed between 1982 and 1991, and a 20-year relative survival was calculated for each cohort.

Before 1972, the diagnosis of primary hyperparathyroidism was made if surgical removal of a parathyroid tumour restored eucalcaemia, or if a full investigation failed to find another cause for hypercalcaemia. After 1972, the diagnosis of primary hyperparathyroidism was made if the serum calcium and serum PTH was above the upper limit of the reference range. The PTH assay used was that of Kleerekoper et al. [7]. 561 patients were studied in the time interval 1961 to 1994 and 453 patients between 1972 and 2011. Because of the concept that persons with mild hypercalcaemia might not require surgery [3], 113 of our patients with mild hyperparathyroidism were not subjected to neck exploration. 448 patients had parathyroid surgery. The patients were predominantly of Anglo-Celtic ethnicity.

Statistics

In the first study of relative survival up to 1994, the statistical program developed by Guy Hedelin [8] was used. Cox's proportional hazard multivariate analysis was used to study the impact on survival of variables such as the presence or absence of known cardiovascular disease. In the later analysis up to 2011, the method outlined by Dickman et al. which uses a generalised linear model based on collapsed data using exact survival times and a Poisson assumption was employed [9].

Results

Table 1 shows the age, serum calcium and serum PTH in the surgically and non-surgically treated groups. There was no significant difference in age. As expected, the serum calcium and the serum PTH were significantly lower in the non-surgically treated group.

124 patients died between 1961 and 1994. The relative survival rate over a 10-year period for the total hyperparathyroid group was significantly lower than the control population, 86.8% (95% CI 84.9–86.2, P < 0.001). There was no significant difference in the relative survival between surgically treated and non-surgically treated patients over a 10-year period (Fig. 1). The average number of years of life lost by the hyperparathyroid patients compared to the control population was 7.5 years. There was no significant difference in the death rate between those with an initial serum calcium of >3.00 mmol/L compared with those with an initial serum calcium of <3.00 mmol/L. In a multivariate analysis in the surgically treated group, Table 2, the serum calcium did not significantly influence survival (HR 1.43, 95% CI 0.79–2.59, P = 0.236). In the non-surgically treated group, Table 3, the serum calcium did not significantly influence survival (HR 1.57, 95% CI 0.30–8.30, P = 0.593). In a multivariate analysis, risk factors associated with death in the surgically treated group were diabetes mellitus (HR 4.09, 95% CI 1.42–6.74, P = 0.001), congestive cardiac failure (HR 5.46, 95% CI 1.31–22.87, P = 0.002), coronary heart disease (HR 2.16, 95% CI 1.08–4.31, P = 0.03) and hypertension (HR 1.54, 95% CI 1.01–2.34, P = 0.044), Table 2. Paradoxically, the presence of kidney stones before surgery was associated with reduced mortality (HR 0.364, 95% CI 0.22–0.68, P = 0.001). The association of kidney stones with improved survival was also observed in another study [6]. In the non-surgically treated group, death was significantly associated with a high serum PTH (HR 1.59, 95% CI 1.20–2.11, P = 0.001), coronary heart disease (HR 3.10, 95% CI 1.42–6.74, P = 0.004), and kidney stones (HR 2.48, 95% CI 1.07–5.76, P = 0.035), Table 3. This difference between the surgically treated and non-surgically treated group with respect to the impact of kidney stones is not clear. Compared with the non-surgically treated group, the hazard ratio of death for the surgically treated group adjusted for age, sex and time of diagnosis was 0.67 (95% CI 0.38–1.18, P = 0.167).

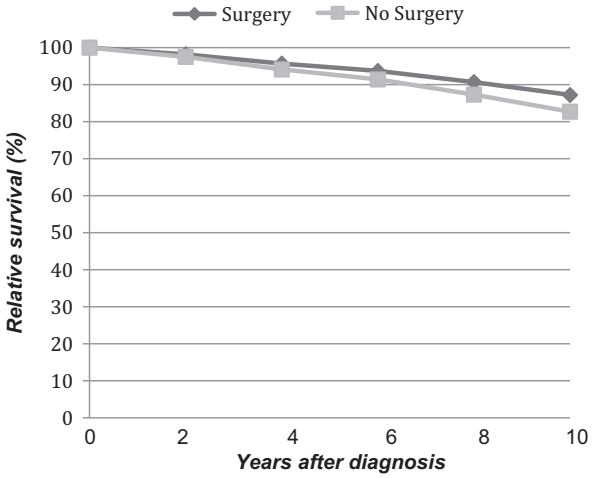

Fig. 1. Relative survival: Percent years after diagnosis, years 1961–1994. Relative survival for the surgically treated and non-surgically treated groups was not significantly different over 10 years of follow-up.

The study was continued until the end of 2011. Patients in the surgically treated group were compared with those in the non-surgically treated group matched with respect to age, sex, serum calcium and for the presence or absence of hypertension. This matching was performed before it was known whether any patient had died. 109 patients were matched; 44 in the non-surgically treated group and 65 in the surgically treated group. The serum calcium in this selected cohort was 2.88 mmol/L. In this cohort, 28 patients in the non-surgically treated group and 35 in the surgically treated group had died (HR 1.18, 95% CI 0.44–3.03, P = 0.732).

A reanalysis of the relative survival for the hyperparathyroid group from 1972 to 2011 showed that this group had a 20-year relative survival of 62.9% (95% CI 58.5–67.4, P < 0.001) compared to the general Australian population, Fig. 2. Relative survival appears to fall slowly

Table 1
Patient demographics: Baseline characteristics.

	Surgery n = 448	Non-surgery n = 113	p-value
Age	52.9 ± 14.7	55.5 ± 15.9	P = 0.117
Serum calcium (mmol/L)	3.04 ± 0.35	2.80 ± 0.18	P < 0.001
Serum PTH (ng/ml)	1.34 ± 1.12 (n = 344)	0.90 ± 0.74 (n = 98)	P < 0.001

Table 2
Overall relative survival for surgical group: Effect of possible risk factors for death.

Variable	P-value	Hazard Ratio	95% CI
Diabetes	0.001	4.085	1.836–9.089
Kidney stones	0.001	0.364	0.216–0.681
CCF	0.02	5.463	1.305–22.869
CAD	0.03	2.156	1.079–4.309
Hypertension	0.044	1.538	1.011–2.341
PTH	0.098	1.194	0.968–1.474
Paget's disease	0.137	1.653	0.853–3.204
CVA/PVD	0.141	1.974	0.797–4.889
Calcium	0.236	1.430	0.791–2.585
Fracture	0.283	1.585	0.684–3.673
Ulcer	0.431	1.306	0.672–2.536
Gender	0.493	1.185	0.729–1.927
Cigs/day	0.506	1.008	0.985–1.03
Smoking	0.511	1.203	0.694–2.086
Pancreatitis	0.600	1.365	0.427–4.367
Cholesterol	0.650	0.960	0.804–1.146
Cancer	0.896	1.048	0.520–2.112

Multivariate analysis of possible risk factors affecting relative survival in hyperparathyroid patients treated with surgery. Cox's proportional hazard analysis.
CCF: Congestive cardiac failure, CAD: Coronary artery disease, CVA: Cerebrovascular disease, PVD: Peripheral vascular disease.