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ORIGINAL ARTICLE

Primary hyperparathyroidism: findings from the retrospective evaluation of cases over a 6-year period from a regional UK centre

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Abstract

Background Although there are international guidelines on diagnosis and management of primary hyperparathyroidism (PHPT), clinical practice varies in different centres. Periodic review of diagnostic work-up, surgical treatment by parathyroidectomy (PTX) and clinical surveillance in nonsurgical treatment group among patients with PHPT is expected to improve the quality of care. We report a retrospective study of cases with PHPT managed at a regional centre in the United Kingdom.

Methods Clinical data of cases with calcium ≥2.6 mmol/L and parathyroid hormone (PTH) ≥9.0 pmol/L was procured from biochemistry database from January 2011 to December 2016. Laboratory parameters, imaging studies for renal stones, osteoporosis and localisation of parathyroid adenomas, type of treatment received (PTX or nonsurgical), complications of treatment, other medical co-morbidities and mortality during follow-up was recorded in each case to examine the outcomes of care of patients with PHPT.

Results The study included 160 patients: 127 (79%) females and 33 (21%) males. Median age was 70 years in females and 74 in males. Thirty cases (19% of 159) had renal stones and 47 (37.3% of 126) had osteoporosis. Eighty-one cases (51%) received PTX. Logistic regression analysis showed that higher calcium levels (odds ratio (OR) = 73.991; $p < 0.001$), peak PTH (OR = 1.023; $p = 0.025$), peak alkaline phosphatase (OR = 0.985, $p < 0.001$), lower age (OR = 0.985, $p < 0.001$) and male gender (OR = 0.209, $p < 0.002$) as statistically significant predictors for patients receiving PTX. Higher age at diagnosis of PHPT was associated with increased risk of co-existent hypertension (OR = 10.904, $p = 0.001$) and fractures (OR = 1.067, $p = 0.004$). Higher peak calcium concentration was an independent predictor of acute kidney injury (OR = 9.631, $p = 0.011$). PTX cured 76 cases (94%) with only 7 (9%) postoperative complications. Twenty-four cases (15%) died from the entire cohort (only one from PTX group) during a median follow-up period of 3.6 years (interquartile range = 1.5).

Conclusions PTX treatment is associated with cure of disease in patients with PHPT with acceptable risk of complications. Improvements in diagnostic work-up and follow-up care should improve the morbidity from PHPT.

Keywords Primary hyperparathyroidism · Parathyroidectomy · Hypercalcaemia · Osteoporosis · Acute kidney injury

Introduction

Primary hyperparathyroidism (PHPT) is the third most common endocrine disorder after diabetes mellitus and thyroid disease. PHPT is characterised by abnormalities in calcium metabolism usually associated with hypercalcaemia and elevated or inappropriately normal levels of parathyroid hormone (PTH) [1]. PHPT is associated with premature mortality, and causes substantial morbidity by skeletal demineralisation and fractures, hypercalciuria and renal stone formation, cardiovascular involvement and cognitive dysfunction [1–3]. A small but important proportion of cases with PHPT may present with normal serum calcium and elevated PTH levels

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that can be associated with skeletal and renal manifestations of classical PHPT, and are termed as normocalcaemic PHPT [1, 4]. Early diagnosis and appropriate management of patients with PHPT is important to prevent excess morbidity and disease-related premature mortality.

Surgical removal of the abnormal parathyroid gland(s) by parathyroidectomy (PTX) usually cures PHPT. Surgery is recommended in patients with: persistently elevated serum calcium levels >0.25 mmol/L above upper limit of normal laboratory range; skeletal involvement in the form of osteoporosis or fragility fractures; renal involvement with creatinine clearance <60 mL/min or nephrolithiasis/nephrocalcinosis; hypercalciuria (urinary calcium excretion of >10 mmol per day) with increased risk of stone formation; and those aged <50 years [1–3, 5, 6]. However, management also depends on other co-morbidities and patients' willingness to undergo surgery. In these situations, symptomatic cases with hypercalcaemia are managed by calcium-lowering agents such as cinacalcet and those with osteoporosis by bisphosphonates [1–3].

Although there are few international guidelines on the management of PHPT [2, 3, 5], the diagnostic work-up and management of the disease varies widely in hospitals of the United Kingdom as reported in multiple recent studies [7–11]. There are also wide discrepancies in the diagnosis and management of PHPT in different countries of Europe as reported previously by Langdahl and Ralston [12]. Moreover, there are still some uncertainties regarding the optimal strategy for PTX among patients with PHPT and the health outcomes following PTX, and we are currently evaluating this in a comprehensive Cochrane Review [13]. In order to plan an appropriate therapeutic strategy for each case, various factors need to be considered, such as patients' preference, fitness for surgery, residual/recurrent disease and accessibility to further surgery [14]. This may in turn compromise optimal care of patients with PHPT that increases complications of the disease and the related healthcare burden. Here, we report on 'real-world' data from a retrospective review of cases with PHPT managed in a regional hospital, from 2011 to 2016 that looked at various end-organ complications and the risk factors, and probable predictors of excess mortality.

Materials and methods

Biochemical data of patients who had estimation of calcium and PTH levels from January 2011 to December 2016 were procured from the laboratory information system in the Department of Biochemistry of the University Hospitals of Morecambe Bay NHS Trust. The three hospitals (total beds 490) under this NHS Hospital Trust cater for a population of ~370,000 people who live in the North Lancashire and South Cumbria regions of the United Kingdom. The Endocrine Department of the hospitals has six Endocrinologists, two Clinical Biochemists and two Endocrine Surgeons with expertise in parathyroid surgeries for the comprehensive work-up and management of PHPT. Cases of suspected PHPT are referred to the Endocrinologists by Primary Care Physicians or other specialists practicing within the region. After biochemical confirmation of the disease, Endocrinologists decide the appropriateness of parathyroid surgery and perform parathyroid imaging studies in surgical candidates through the Radiology Department of the hospitals. Those cases with indications for surgery are referred to the Endocrine Surgeons. The average number of cases of PHPT managed in the centre is 25–35 per year, and the average number of parathyroidectomies performed annually is 15–20. The surgical techniques used for PTX are: minimally invasive PTX (MIP), in cases with clear localisation of parathyroid adenomas, and/or bilateral neck exploration (BNE), where localisation is impossible pre-surgically/during attempted MIP/discordance between different localisation studies.

From the biochemical database, those cases with albumin-corrected calcium level ≥2.60 mmol/L and PTH level ≥9.0 pmol/L (both values upper limits of normal laboratory range) were selected. From these data, each case record was assessed and reviewed in detail to identify cases of PHPT. All cases with confirmed diagnosis of PHPT and at least one medical follow-up after diagnosis were included in the study. Cases with diagnoses of tertiary hyperparathyroidism and familial hypocalciuric hypercalcaemia (FHH) were excluded from the study. Cases of hypercalcaemia and hyperparathyroidism with chronic kidney disease (CKD) stage 4 and above (with an estimated glomerular filtration rate (eGFR) <30 mL/min) were considered to have tertiary hyperparathyroidism, and those with a urine calcium: creatinine clearance ratio of <0.01 in the absence of other causes for hypocalciuria (such as drugs) and with a serum vitamin D level >50 nmol/L were considered to have FHH meeting the exclusion criteria.

Initial and peak concentrations of calcium, PTH, alkaline phosphatase (ALP) and creatinine, and initial and minimum phosphate (PO_4) concentrations were documented for each case. Vitamin D levels and urine calcium:creatinine clearance ratio (where available) were also recorded. Cases that had kidney ultrasound or computed tomography scan for assessment of nephrocalcinosis or renal stones were reviewed, and findings recorded. Bone mineral density (BMD) was verified in each case where available, and the presence or absence of abnormal BMD (osteoporosis or osteopenia) documented. All those who underwent parathyroid imaging studies were reviewed for the presence or absence of parathyroid adenoma(s), and for concordance or discordance of localisation if more than one imaging modality was used.

Treatment modalities given to patients (PTX or biochemical follow-up only) and the reason for the choice of therapy were documented. When PTX was performed, the type of surgery (MIP or BNE), histologic confirmation of the adenoma removed, complications of surgery, operative cure and recurrence after initial cure were recorded. The follow-up duration of each case and hospitalisation for an acute complication related to PHPT (such as acute kidney injury (AKI); defined by a rise in creatinine level >26 µmol/L from baseline in 48 h, or 1.5 times above baseline in 7 days and/or drop in urine output to <0.5 mL/kg/h for ≥6 h) or severe hypercalcaemia (≥ 3.0 mmol/L) requiring treatment during follow-up were recorded. Additional co-morbidities such as various systemic diseases were also recorded to look for any relationship of these to the clinical outcomes of patients with PHPT including mortality during follow-up.

Statistical analysis

Due to violations of the assumptions of homogeneity of variances (all outcomes except age at diagnosis, basal ALP and PO_4, minimum PO_4 and vitamin D) and normality (all outcomes), to compare differences between outcomes, we used a Mann–Whitney *U* test along with the Hodges–Lehmann point estimate for the median difference —provided as location parameters—with accompanying 95% confidence intervals (CIs) (Hodges and Lehmann; Lehmann). The rank-biserial correlation (*r*)—the simple difference between the proportion of pairs where the PTX group was higher and pairs where the non-PTX group was higher—was provided as an effect size. In addition, χ^2 analyses were performed to determine differences in categorical variables between treatment type and PTX type.

To determine whether the treatment received, occurrence of fracture, AKI, and co-existent hypertension could be predicted by age, gender, and biochemical outcomes, we performed binomial logistic regression analyses. All assumptions of logistic regression were tested and met, namely, linearity between continuous predictors and their logit (no statistically significant interaction term between each predictor and its natural log), independence of errors (dispersion parameters <2) and multicollinearity (tolerance (<0.1) and variance inflation factor (<10) statistics, and eigenvalues, condition index and variance proportions (via the presence of predictors with high proportions on the same small eigenvalues)).

We performed a Cox regression analysis to determine which covariates could predict the event of death during the follow-up period. Covariates (i.e. age, gender, peak PTH, calcium, ALP, and creatinine, minimum PO_4, vitamin D level, fracture, AKI, hypertension, duration of follow-up and number of co-morbidities) considered in our prediction model were determined via clinical experience and Collett's model selection approach. The proportional hazards assumption was assessed by inspecting log–log plots for parallel lines. No violation of the proportional hazards was observed. For all analyses, a two-sided $p < 0.05$ was considered statistically significant.

Categorical variables were expressed as counts and percentages and continuous variables as median and interquartile range (IQR). All analyses were performed on JASP Version 0.8.6 apart from Cox regression analysis, which was completed with IBM™ Statistical Package for Social Sciences (SPSS) version 24.0.0.

Results

Our sample of 160 patients included 127 (79%) females and 33 (21%) males. The median (IQR) age of the patients was 70 (IQR 19) years (females = 70 (IQR 19) years; males = 74 (IQR 18) years). PTX was performed on 81 (51%) patients, whereas 73 (46%) were managed conservatively, and 6 (3%) cases were awaiting further management plan (incomplete work-up/awaiting surgery) during analysis of the data. We combined these six patients into the biochemical follow-up group (hereafter grouped as non-PTX group) for all analyses. There were more female patients in the PTX group compared with the non-PTX group ($n = 70$ vs. 57, 55% vs. 45%). Conversely, but based on a smaller sample of patients, there were more male patients in the non-PTX group compared with PTX ($n = 22$ vs. 11, 66% vs. 33%). Only 13 (8%) patients had no co-morbidities (non-PTX = 5, 6%; PTX = 8, 10%). Most patients had between one and three co-morbidities (total = 127, 79%; non-PTX = 63, 80%; PTX = 64, 79%).

The median follow-up duration for the total cohort was 3.6 (IQR 1.5) years. Sixteen patients were deemed unfit for PTX after complete diagnostic work-up for PTX following anaesthetic and surgical evaluation because of medical co-morbidities and were subsequently advised only medical follow-up periodically. Twelve patients declined surgery after complete evaluation for PTX. Four cases died while awaiting PTX.

Between-group difference in age at diagnosis and biochemical measures

Age at diagnosis and baseline biochemical parameters for each treatment group are shown in Table 1. There were statistical between-treatment group differences in age (younger in PTX group) and basal and peak PTH, peak ALP, and basal and peak creatinine concentrations. Based on the rank-biserial correlations, approximately 35% of pairs had higher basal and peak PTH in the PTX group vs. non-

Table 1 Baseline biochemical parameters in each type of treatment patients received

	Total	Treatment		PTX vs. conservative treatment			95% CI
		Conservative management	PTX	LHE	95% CI	Rank-biserial *r*	
Age	70 (19)	76 (19)	68 (16)	7.0*	3.0, 11.0	0.31	0.14, 0.47
Basal Ca	2.71 (0.16)	2.71 (0.16)	2.72 (0.18)	−0.03	−0.06, 0.01	−0.42	−0.29, 0.06
Peak Ca	2.84 (0.23)	2.84 (0.20)	2.84 (0.27)	−0.04	−0.09, 0.02	−0.12	−0.29, 0.06
Basal PTH	13.3 (9.6)	11.3 (5.4)	15.3 (11.9)	−3.8*	−5.9, −1.8	−0.35	−0.50, −0.18
Peak PTH	16.7 (12.2)	14.8 (9.5)	19.7 (15.9)	−4.8*	−7.5, −2.2	−0.34	−0.49, −0.17
Basal PO4	0.89 (0.25)	0.90 (0.27)	0.87 (0.24)	0.04	−0.02, 0.10	0.12	−0.06, 0.29
Min PO_4	0.71 (0.23)	0.71 (0.17)	0.68 (0.26)	0.02	−0.03, 0.08	0.07	−0.11, 0.24
Basal ALP	102 (40)	103 (38)	98 (44)	8.0	−2.0, 17.0	0.14	−0.04, 0.31
Peak ALP	131 (66)	143 (68)	115 (51)	27.0*	13.0, 42.0	0.34	0.17, 0.49
Basal Crn	72 (26)	76 (37)	68 (20)	8.0**	2.0, 15.0	0.25	0.08, 0.41
Peak Crn	86 (40)	93 (62)	84 (29)	10.0†	1.0, 21.0	0.19	0.01, 0.36
Vitamin D	37.9 (33.5)	42.7 (36.3)	32.9 (33.2)	6.5	−0.6, 13.5	0.17	−0.01, 0.35

Median (interquartile range) age at diagnosis and concentrations of Ca, PTH, PO_4, ALP, Crn, and vitamin D, and differences between treatment type and PTX type vs. conservative management

Ca calcium, *PTH* parathyroid hormone, *PO4* phosphate, *ALP* alkaline phosphatase, *Crn* creatinine, *PTX* parathyroidectomy, *LHE* Hodges–Lehmann estimate, *95% CI* 95% confidence intervals, *r* correlation

*$p < 0.001$; **$p = 0.006$; †$p = 0.037$

PTX, whereas 19%, 24%, 31% and 34% of pairs had lower peak ALP, age at diagnosis, and basal and peak creatinine in the PTX group compared with non-PTX (see Table 1).

Predictors of treatment type

A logistic regression analysis was performed to ascertain the associations between age, gender and biochemical parameters (peak_PTH, peak_calcium, peak_ALP, peak_creatinine, min PO_4 and vitamin D level) and the likelihood that participants underwent PTX. Minimum PO_4, peak creatinine and vitamin D concentrations were not statistically significant predictors ($p > 0.05$), and therefore not added to the model. The logistic regression model was statistically significant and identified that women were nearly 80% more likely to receive PTX than men (OR = 0.209, $p < 0.001$). Also, lower age ($p < 0.001$, OR = 0.985) and peak ALP concentrations ($p < 0.001$, OR = 0.985), and higher peak PTH ($p = 0.025$, OR = 1.023) and calcium ($p < 0.001$, OR = 73.991) were found to be independent predictors of receiving PTX as treatment for patients with PHPT (Table 2).

BMD assessment and results of renal imaging and parathyroid imaging modalities

Of the 126 cases who underwent baseline BMD assessment, 47 (37%) had osteoporosis and 17 (13%) had osteopenia (34 patients had no baseline BMD assessment) However, these data may be incomplete as this hospital did not perform BMD assessment for forearm during the study period. Morphometric vertebral fractures were also not assessed in the study subjects during this period. Of the 13 patients (10.3%) who had follow-up BMD data, 6 had improvement of BMD, whereas two cases had no improvement after PTX. One case had stable BMD, and one worsening BMD in the nonsurgical treatment arm.

Of the 159 cases who had renal imaging at baseline, 30 (19%) had renal stone disease. However, only 16 (53%) of these cases had PTX as treatment and the remainder were managed by biochemical follow-up only (for various reasons including patient preference). Eleven patients (6.9%) had CKD stage 3 (eGFR 30–60 mL/min), of whom only three cases developed AKI during follow-up. Fifty-one cases (32%) among the entire cohort had hospitalisation for correction of hypercalcaemia (34 cases (21.3%) had calcium level ≥3.0 mmol/L) and/or its complications, such as AKI (29 cases; 18.1%). However, only 27 (53%) of this group subsequently underwent PTX because of surgical contraindications and/or patient refusal, or death.

The results of various parathyroid imaging modalities for localisation of parathyroid adenomas are shown in Table 3, the concordance or discordance of various localisation studies are shown in Table 4 and type of PTX in relation to various imaging studies in Table 5.

Cases per treatment group and predictors of fracture, AKI, and co-existent hypertension

Twenty-three (14%) cases developed fractures before or after diagnosis of PHPT in the entire cohort. However, χ^2

Table 2 Predictors of PTX in the entire cohort with PHPT on logistic regression analysis

	B	SE	Wald	df	*p* value	OR	95% CI for *B*	
							Lower	Upper
Constant	−5.76	3.21	3.23	1	0.073	0.003	−12.054	0.527
Age	−0.07	0.02	13.62	1	<0.001	0.935	−0.102	−0.031
Male gender	−1.57	0.52	9.17	1	0.002	0.209	−2.578	−0.552
Peak PTH	0.02	0.01	5.00	1	0.025	1.023	0.003	0.042
Peak calcium	4.30	1.27	11.49	1	<0.001	73.991	1.815	6.793
Peak ALP	−0.02	0.00	12.34	1	<0.001	0.985	−0.024	−0.007

OR odds ratio, *95% CI* 95% confidence intervals, *PTH* parathyroid hormone, *ALP* alkaline phosphatase

Nagelkerke $R^2 = 0.429$; $\chi^2(5) = 58.31$, $p < 0.001$

Table 3 Results of various parathyroid imaging modalities in the individual treatment arms

	Total	Treatment		
		Conservative treatment	PTX	PTX operative cure
USS (n = 127)				
Negative	39 (31%)	23 (59%)	16 (41%)	15 (94%)
Positive	88 (69%)	24 (28%)	64 (73%)	61 (95%)
MIBI (n = 119)				
Negative	26 (22%)	17 (65%)	9 (35%)	8 (89%)
Positive	93 (78%)	21 (23%)	72 (77%)	68 (94%)
CT neck (n = 26)				
Negative	9 (35%)	5 (56%)	4 (44%)	4 (100%)
Positive	17 (65%)	5 (29%)	12 (71%)	10 (83%)

χ^2 analysis: USS by treatment type, $X^2 = 11.65$ (1), $p < 0.001$; MIBI by treatment type, $X^2 = 17.13$ (1), $p < 0.001$; CT neck, $X^2 = 1.70$ (1), $p = 0.192$

USS ultrasound scan, *MIBI* parathyroid sestamibi scan, *CT* computed tomography, *PTX* parathyroidectomy

Table 4 Comparison of concordance/discordance of various imaging studies in patients with primary hyperparathyroidism

	USS		
	Negative	Positive	Total
MIBI			
Negative	14 (56%)	11 (44%)	25 (21%)
Positive	17 (18%)	76 (82%)	93 (79%)
CT neck			
Negative	8 (89%)	1 (11%)	9 (36%)
Positive	4 (25%)	12 (75%)	16 (64%)
	MIBI		
	Negative	**Positive**	**Total**
CT neck			
Negative	7 (78%)	2 (22%)	9 (35%)
Positive	4 (24%)	13 (76%)	17 (65%)

χ^2 analysis: USS vs. MIBI, $X^2 = 14.47$ (1), $p < 0.001$; USS vs. CT neck, $X^2 = 9.42$ (1), $p = 0.002$; MIBI vs. CT neck, $X^2 = 7.10$ (1), $p = 0.008$

USS ultrasound scan, *MIBI* parathyroid sestamibi scan, *CT* computed tomography

analysis revealed no statistically significant between-group difference ($X^2 = 0.37$, $p = 0.54$) in prevalence of fractures in the PTX (13; 57%) and non-PTX (10; 43%) treatment groups. AKI was recorded in 29 cases (18.1%). No statistically significant incidence of AKI was recorded in the non-PTX group compared to those who underwent PTX (19 vs. 10 cases, 66% vs. 34%; $X^2 = 3.69$, $p = 0.055$). Prevalence of hypertension was comparable in both the non-surgical and surgical treatment groups (40 vs. 38 cases, 51% vs. 49%).

A logistic regression was performed to ascertain whether age at diagnosis, gender, and biochemical parameters (peak PTH, calcium, ALP, and creatinine, minimum PO_4, and vitamin D level) could predict the likelihood that participants sustained a fracture, or developed AKI or co-existent hypertension. In the model to predict fracture incidence, only age at diagnosis and female gender were statistically significant predictors ($p < 0.05$), and therefore included in the model. The analysis showed that higher age at diagnosis ($p = 0.004$, OR = 1.067) alone was an independent predictor for fracture incidence.

The logistic regression model to predict AKI included age, gender, and peak calcium, ALP and creatinine. In this model, peak calcium ($p = 0.011$, OR = 9.631) concentration was a statistically significant independent predictor of AKI. Only age at diagnosis was a statistically significant predictor for co-existent hypertension.

Nearly 80% of patients had between one and three co-morbidities. There were no statistically significant between-group differences ($p = 0.08$) in the number of co-morbidities in each treatment group (Fig. 1).

Predictors of risk of death during follow-up

A total of 24 deaths (15%) occurred during the 5-year period in the entire cohort (only one among the PTX group).

Table 5 Various imaging studies and type of surgery in the parathyroidectomy treatment group

	Total	PTX type	
		BNE	MIP
USS			
Negative	16 (20%)	8 (50%)	8 (50%)
Positive	63 (80%)	20 (32%)	43 (68%)
MIBI			
Negative	9 (11%)	4 (44%)	5 (56%)
Positive	71 (89%)	24 (34%)	47 (66%)
CT neck			
Negative	4 (25%)	3 (75%)	1 (25%)
Positive	12 (75%)	4 (33%)	8 (67%)

χ^2 analysis: No statistically significant differences between categories ($p > 0.05$)

USS ultrasound scan, *MIBI* parathyroid sestamibi scan, *CT* computed tomography, *PTX* parathyroidectomy, *BNE* bilateral neck exploration, *MIP* minimally invasive parathyroidectomy

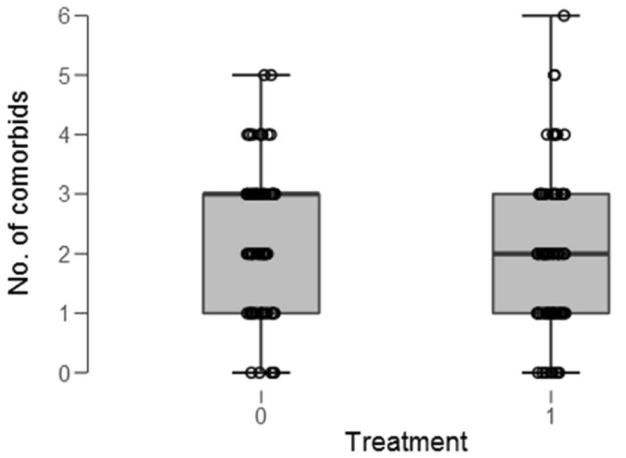

Fig. 1 Number of co-morbidities per patient who underwent either non-PTX (0) or PTX (1); $p = 0.08$

The final Cox regression model to predict death during follow-up consisted of treatment, age at diagnosis, fracture and peak ALP and creatinine (see Table 6). Unsurprisingly, given the lack of deaths within the PTX group, non-PTX was associated with a 93.6% increase in the risk of dying during follow-up. A 1-year increase in age was associated with a 5.5% (95% CI, 0.3–10.%) increase in risk, whereas a 1 mmol/L increase in peak creatinine was associated with a negligible increase in risk (hazard ratio (HR) 0.3%, 95% CI, 0.1–0.5).

Type of surgery, operative cure, histology and complications with PTX

Of the 81 patients who underwent PTX, 76 (94%) achieved operative cure. Twenty-eight cases (34.6%) underwent BNE and the remainder MIP. The decision for MIP or BNE was based on the preoperative imaging for parathyroid adenoma localisation (MIP if adenoma definitely localised) or absence of a clear adenoma visualised during attempted MIP by the endocrine surgeon (then PTX converted to BNE). Three cases among the BNE group and two in the MIP group had persistent disease even after surgery during follow-up. One case in the MIP group died from hospital-acquired pneumonia after surgery. Seventy-nine (97.5%) cases had proven parathyroid adenoma on histological examination of the excised specimen, whereas two cases did not reveal abnormal parathyroid tissue. The number of complications with BNE was higher than with MIP (5 vs. 2 cases, 71% vs. 29%). The seven (9%) incidences of post-operative complications included hypocalcaemia (four cases, all with BNE), dysphonia due to vocal cord dysfunction (two cases, one each with BNE and MIP) and hypothyroidism (one case with MIP).

Discussion

Our data are comparable with previously reported national data on management of PHPT in England and Wales with more than three times as many females treated with PTX as men [15]. The median age of patients in our PTX cohort is also comparable to this national data. However, the non-surgical treatment group was older in our cohort compared to cases from other reports from the United Kingdom and Europe [16, 17]. The gender ratio (female:male = 4:1) in the entire cohort also is also comparable to the global data [1].

We found statistically significant between-group differences in age at diagnosis and peak PTH, ALP and creatinine concentrations among those who underwent PTX and those managed non-surgically. However, peak calcium concentration along with age, gender, peak PTH and ALP were statistically significant predictors that an individual will undergo PTX.

The low prevalence of osteoporosis or osteopenia in our cohort, in comparison to other reported studies [18, 19], is most likely because of under-reporting from lack of availability of forearm BMD in our patients. If forearm BMD data were available during endocrine assessment of the cases, the prevalence of osteoporosis may have increased as reported by Castellano et al. [19] in their study and more patients may have undergone or been offered PTX. Morphometric vertebral fractures were reported to be highly prevalent among patients with PHPT as reported by De Geronimo et al. [20]. Therefore, the low prevalence of fractures observed in our cohort was likely from under-reporting as we did not have assessment of morphometric vertebral fractures in the data reported.

Table 6 Predictors of excess mortality

	B	SE	Wald	df	*p* value	HR	95% CI for HR	
							Lower	Upper
PTX treatment	−2.753	1.038	6.960	1	0.008	0.064	0.008	0.493
Age at diagnosis	0.054	0.026	4.380	1	0.036	1.055	1.003	1.109
Fracture	0.800	0.437	2.749	1	0.097	2.226	0.864	5.735
Peak ALP	0.004	0.003	1.063	1	0.302	1.004	0.996	1.012
Peak creatinine	0.003	0.001	6.599	1	0.100	1.003	1.001	1.005

Although the prevalence of kidney stone disease was considerably lower in our patients compared with that reported by Cipriani et al. [18] and Starup-Linde et al. [21], we observed higher prevalence of the disease than that reported by others [22, 23]. The discrepancy in prevalence of nephrolithiasis in our cases compared with previous reports may be a consequence of a number of factors such as renal function, calcium excretion rates and dietary factors. Future research may clarify this issue.

Nearly a fifth (18.1%) of our cases needed hospitalisation for correction of AKI related to hypercalcaemia. This is comparable to the incidence of AKI (17.3%) related to calcium levels >10 mg/dL (>2.5 mmol/L) reported by Thongprayoon et al. [24] in their large series of hospitalised patients. The peak calcium levels of 2.84 (0.20) mmol/L observed in our cohort is comparable to the degree of hypercalcaemia in cases reported by Paravastu et al. [11] (2.81–2.86 mmol/L) from United Kingdom and Medas et al. [25] (2.84 (0.32) mmol/L) from Italy. The severity of hypercalcaemia predicted AKI in the multivariate model in our cases. However, even after hospitalisation for correction of hypercalcaemia and/or AKI, only 53% of cases received PTX for various reasons including unfitness for surgery or patient refusal of PTX. The higher incidence of AKI in the non-PTX group (19 vs. 10 in the PTX group) may also be explained by these reasons. Statistically higher risk of fractures among older individuals in our cohort corresponds with previous reports [18, 26].

Although the operative cure rate of 94% in our cohort after PTX was slightly lower than that reported from various previous reports (≥96%) [10, 11, 27, 28], the complication rate of 9% was lower than from other centres (>10%) [28, 29]. As one would expect, the complication rate was higher for BNE compared to MIP as reported by others [10, 11, 28, 30]. Only one death occurred in the PTX cohort, and this was unrelated to surgery (hospital-acquired pneumonia).

We observed 15% mortality in the entire cohort during the 6-year period; 23 of the 24 deaths occurred in the non-PTX group. The reported mortality among patients with PHPT varies widely from 1 to 12% [31]. Many patients had multiple and major disease co-morbidities (and therefore contraindication for PTX) that may explain the excess mortality in our cohort. Fractures, associated comorbid illnesses, higher age and high PTH were found to be associated with excess mortality risk, while PTX, male gender and presence of AKI appeared to confer protective effect in the multivariate analysis. The late median age at diagnosis coupled with high levels of co-morbidities and high mortality in the non-PTX group suggest that earlier diagnosis and treatment by PTX may reduce complications and possibly decrease the excess mortality. This should prompt advocating screening for hyperparathyroidism at a younger age.

We acknowledge several limitations to our study. Being a retrospective cohort study with relatively small number of cases, many of the observations may not be generalisable with regards to a common disorder such as PHPT, especially from a single centre. Baseline and follow-up of BMD assessment data were inadequate in the cohort. Therefore, we could not properly assess the benefit of PTX on BMD and future fracture risk. Similarly, vertebral fractures were likely under-reported in our series because of lack of assessment for morphometric vertebral fractures. The relatively higher number of hospitalisations for treatment of hypercalcaemia and AKI might be related to referral bias and the local practices in managing such cases. As we used raised PTH and calcium levels to identify cases with PHPT, we might have missed several cases of normocalcemic hyperparathyroidism in our study. Although we could record the co-morbidities from case notes, the severity and exact influence of each on mortality could not be assessed, and they may have skewed the results.

Even with consideration of the above limitations, our study may give an insight to the overall care of patients with PHPT across the UK regional centres, and prompt healthcare professionals to improve the quality of care provided to their patients with this common endocrinopathy.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The study was a retrospective analysis of data of patients managed in the hospital, and therefore informed consent from cases could not be obtained. The study was approved by the audit and research department of the institution (Registration No: 408/2017).

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