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Current predictive models do not accurately differentiate between single and multi gland disease in primary hyperparathyroidism: a retrospective cohort study of two endocrine surgery units

O Edafe[1], EE Collins[1,2], CS Ubhi[2], SP Balasubramanian[1]

[1]Department of Oncology and Metabolism, University of Sheffield and Sheffield Teaching Hospitals Foundation Trust, Sheffield, UK
[2]Nottingham University Hospital NHS Trust, Nottingham, UK

ABSTRACT

BACKGROUND Minimally invasive parathyroidectomy (MIP) for primary hyperparathyroidism is dependent upon accurate prediction of single-gland disease on the basis of preoperative imaging and biochemistry. The aims of this study were to validate currently available predictive models of single-gland disease in two UK cohorts and to determine if these models can facilitate MIP.

METHODS This is a retrospectively cohort study of 624 patients who underwent parathyroidectomy for primary hyperparathyroidism in two centres between July 2008 and December 2013. Two recognised models: CaPTHUS (preoperative calcium, parathyroid hormone, ultrasound, sestamibi, concordance imaging) and Wisconsin Index (preoperative calcium, parathyroid hormone) were validated for their ability to predict single-gland disease.

RESULTS The rates of single- and multi-gland disease were 491 (79.6%) and 126 (20.2%), respectively. Cure rates in centres 1 and 2 were 93.2% and 93.8%, respectively ($P = 0.789$). The positive predictive value (PPV) of CaPTHUS score ≥ 3 in predicting single-gland disease was 84.6%, compared with 100% in the original report. CaPTHUS ≥ 4 and 5 had a PPV of 85.1 and 87.1, respectively. There were no differences in Wisconsin Index (WIN) between patients with single- and multi-gland ($P = 0.573$). A WIN greater than 1600 and weight of excised gland greater than 1 g had a positive predictive value of 86.7% for single-gland disease.

CONCLUSIONS The use of CaPTHUS and WIN indices without intraoperative adjuncts (such as IOPTH) had the potential to result in failure to cure in up to 15% (CaPTHUS) and 13% (WIN) of patients treated by MIP targeting a single enlarged gland.

KEYWORDS
Primary hyperparathyroidism – Adenoma – Hyperplasia

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CORRESPONDENCE TO
Ovie Edafe, E: ovieedafe@hotmail.co.uk

Introduction

Primary hyperparathyroidism (PHPT) is a common endocrine disorder. One UK study reported incidence rates ranging from 58–146 and 23–80 per 100,000 person-years for women and men respectively.[1] Most cases of PHPT are single-gland disease (around 85%), followed by multi-gland disease in up to 15% and, very rarely, parathyroid carcinoma (less than 1%).[2,3]

Minimal invasive parathyroidectomy (MIP) is gaining popularity in surgery for PHPT for presumed single-gland disease (disease co-localised in sestamibi scan and ultrasound). MIP in this context refers to all first-time operations for PHPT where less than a bilateral neck exploration is performed: targeted or focused parathyroidectomy and unilateral or limited neck exploration. Currently, MIP is offered to patients with disease localised on preoperative imaging. The successful employment of MIP is dependent on accurate preoperative localisation, although some centres also use intraoperative parathyroid hormone assay (IOPTH) to confirm adequate treatment during surgery.[4] IOPTH is not available in many centres and is also considered to significantly increase the costs of treatment, and is associated with false positive rates for detection of multi-gland disease and increased operating time.[5]

Kebebew et al. devised a scoring tool (CaPTHUS) based on five clinical parameters: preoperative calcium ≥ 3 mmol/l, intact parathyroid hormone (PTH) level ≥ 2 multiplied by the

upper limit of normal levels, ultrasound showing an enlarged parathyroid gland, sestamibi scan showing an enlarged parathyroid and concordant ultrasound and sestamibi scans.[6] The tool was created to aid preoperative identification of patients who may have single-gland disease, thereby enabling MIP. This tool was demonstrated to have a positive predictive value (PPV) of 100% for single-gland disease when three or more predictors are present. Kavanagh et al. found similar results with the CaPTHUS model.[5] Elfebein et al. also tested the model and included patients who did not have dual imaging (i.e. had only ultrasound or sestamibi).[4] They found that CAPTHUS ≥ 3 had a PPV of 91% for predicting single-gland disease. The PPV was still 91% when they included only those patients with dual imaging. The use of CaPTHUS model without IOPTH had a cure rate of 89% at 6 months compared with 98% when IOPTH was used).[4]

Mazeh et al. developed the Wisconsin Index (WIN) aimed to help decide between waiting for IOPTH and proceeding to bilateral neck exploration to optimise the need for PTH testing, particularly in cases where a minimally enlarged gland is found.[7] WIN was calculated by multiplying the preoperative serum calcium and PTH. Higher WIN levels and heavier parathyroid glands were associated with single-gland disease. The weight of the excised gland was measure intraoperatively to aid decision making. For example, the probability of single-gland disease for a WIN greater than 1600 varied from 3% to 81% for gland weights of 0.1–1 g, respectively.

The predictive value of CaPTHUS remains unclear given the variable results.[4,6] In addition, the rates of single-gland disease varies between the studies (75.2–92%). The results therefore may not be generalisable to different populations.[4–7] However, the above studies are used to rationalise the practice of MIP without IOPTH in many centres.[8,9] The role of IOPTH in confirming cure in the setting of MIP remains unclear as studies have shown variable experiences.[10,11]

The accurate differentiation of single- and multi-gland disease in patients with PHPT will be useful in a number of situations for surgeons working in facilities with differing expertise and facilities. For example, prediction of multigland disease in patients prior to imaging may influence the decision to perform a bilateral exploration without imaging. In patients who have had imaging and where single-gland disease is predicted with a high degree of probability, IOPTH may be avoided following a targeted parathyroidectomy; this will result in significant reduction of theatre time and costs. In centres where IOPTH is not available, the decision for further exploration after excision of one gland may be facilitated by the prediction of the possibility of further enlarged glands.

The aims of this study were to validate the existing models in two UK cohorts and to determine if these can accurately predict single gland disease as the cause of PHPT.

Methods

This was a retrospective cohort study of patients who underwent surgery for PHPT at two endocrine surgical units in the UK between July 2008 and December 2013: Sheffield Teaching Hospitals (centre 1) and Nottingham University Hospitals (centre 2). Patient with known multiple endocrine neoplasia, parathyroid carcinoma and previous parathyroidectomy were excluded.

Data were collected from patient records (hard copy and electronic records) and included demographic information, preoperative biochemistry (serum calcium and PTH), preoperative imaging (sestamibi and ultrasound) results, excised gland weight, diagnosis, postoperative biochemistry, and outcome of surgery. OE collected data in centre 1 and EEC collected data in centre 2.

The operations were performed by four consultants in centre 1 and one consultant in centre 2. The practices on the use of preoperative imaging and intraoperative adjuncts (such as IOPTH, methylene blue and frozen section) varied over time and between surgeons in centre 1. In centre 1, targeted parathyroidectomy (where the intended aim was to recognize and excise the single enlarged parathyroid gland identified on preoperative imaging) was used when preoperative imaging was concordant for one enlarged gland at a specific location. In centre 2, unilateral neck exploration (both superior and inferior gland visualised) was performed in patients with concordant imaging, and bilateral exploration on others. IOPTH was used occasionally in some patients undergoing targeted parathyroidectomy in centre 1, but was not used in centre 2. For the purposes of this study, both targeted parathyroidectomy and unilateral neck exploration were grouped in one category.

A scan was labelled positive if it showed one enlarged parathyroid gland. If both ultrasound and sestamibi showed a single enlarged gland on the same side of the neck, imaging was considered to be concordant. Cure following surgery was recorded when the adjusted serum calcium was low or normal at follow-up. Patients who had clear evidence of hypercalcaemia within 6 months of surgery were thought to have persistent disease. Patients with calcium levels at or around the upper limit of normal were thought to have persistent disease if the PTH level was also elevated. Patients were assumed to have recurrent disease if hypercalcaemia was detected after 6 months following surgery. Patients were considered to have single-gland disease if they were cured after removal of only one gland or more than one gland of which only one was confirmed by histopathology to be abnormal. Patients who had more than one abnormal gland removed or who had persistent disease following removal of a single abnormal gland were considered to have multigland disease. Patients where this status could not be clearly ascertained were categorised as 'unclear'.

Data analysis

Patient demographics and clinical characteristics were compared between centre 1 and 2; and between single- and multi-gland disease using the chi-square test for categorical variables and the student t test for continuous variables. The WIN scores between patients with single- and multi-gland disease were compared using the student t test. Comparison of CaPTHUS score in the single- and multi-gland disease was performed using the chi-square test. The sensitivity,

specificity, accuracy, predictive values and positive likelihood ratio of current predictive models were calculated in this cohort. The statistical level of significance was set at 0.05.

Ethical approval was obtained from research and development departments of both hospitals (STH18832). Individual patient consent was not required in view of the retrospective nature of the study design. Data confidentiality and patient privacy was maintained at all times.

Results

A total of 384 patients from centre 1 and 240 patients from centre 2 were included for analyses. Of these, 495 (79.3%) were female and 129 (20.7%) male. The mean (standard deviation, SD) age at surgery of the entire cohort was 60.9 (14.32) years. Table 1 shows similar demographic and clinical characteristics of patients in both centres. The cure rates were 93.2% in centre 1 and 93.8% in centre 2 ($P = 0.789$). There was no difference in cure rate ($P = 0.695$) between bilateral (93.8%) and unilateral neck exploration (93.0%).

Table 1 Demographics and clinical characteristics in patients undergoing surgery for primary hyperparathyroidism in two endocrine surgery units

Factor	Sheffield ($n = 384$)	Nottingham ($n = 240$)	P value[a]
Mean (SD) age at surgery (years)	60.5 (14.67)	61.7 (13.73)	0.327
Gender *n* (%):			0.162
Female	312 (81.2)	183 (76.2)	
Male	72 (18.8)	57 (23.8)	
Ultrasound performed *n* (%):			0.032
Yes[b]	353 (91.9)	231 (96.3)	
No	31 (8.1)	9 (3.8)	
Sestamibi performed *n* (%):			< 0.001
Yes[b]	335 (87.2)	232 (96.7)	
No	49 (12.8)	8 (3.3)	
Ultrasound and sestamibi performed *n* (%):			< 0.001
Yes[b]	324 (84.4)	231 (96.3)	
No	60 (15.6)	9 (3.8%)	
Ultrasound positive for one enlarged gland *n* (%):			0.054
Yes	220 (57.3)	130 (59.1)	
No	119 (31)	100 (45.5)	
Not done	31 (8.1)	9 (2.3)	
No report	14 (3.6)	1 (0.05)	
Sestamibi positive for one enlarged gland *n* (%):			0.018
Yes	243 (63.3)	154 (64.2)	
No	76 (19.8)	77 (32.0)	
Not done	49 (12.8)	8 (3.3)	
No report	16 (4.2)	1 (0.05)	
Surgical approach *n* (%):			0.229[c]
Bilateral	215 (56)	122 (50.8)	
Unilateral	169 (44)	117 (48.8)	
Mediastinal	0 (0)	1 (0.4)	
Pathology *n* (%):			0.593
Single-gland disease	303 (78.9)	188 (78.3)	
Multi-gland disease	78 (20.3)	48 (20)	
Unclear	3 (0.8)	4 (1.7)	
Outcome *n* (%):			0.798
Cure	358 (93.2)	225 (93.8)	
Persistent	26 (6.8)	15 (6.3)	

[a] chi-square test, except student t-test for age.
[b] Includes patients with no available report.
[c] bilateral vs. unilateral neck exploration.
SD, standard deviation.

Significantly higher numbers of neck ultrasound and sestamibi scans were performed in centre 2 compared with centre 1. The sestamibi positive rate was significantly higher in centre 1 compared with centre 2. Calcium levels were available for a median of 27 months (interquartile range 6–50 months) after surgery.

Table 2 shows comparisons of age, gender and clinical characteristics between patients with single- and multi-gland disease. Predictors for single-gland disease in univariable analyses include a positive neck ultrasound or sestamibi scan, concordance between neck ultrasound and sestamibi for one enlarged gland on same side of the neck and weight of parathyroid gland.

To validate the CaPTHUS score,[6] we only included patients who had both ultrasound and sestamibi. The PPV of CaPTHUS ≥ 3 was 84.6% for single-gland disease (Table 3). To validate 'modified CaPTHUS' as per Elfenbein et al.,[4] we included all patients, even if they had only one scan (Table 3). The PPV of modified CaPTHUS ≥ 3 was 84.4% for SGD. The PPV was 83.1% when only patients who were followed-up for 6 or more months were included.

There were no differences in WIN scores between patients with single- and multi-gland disease (median 2163 vs. 2142; $P = 0.573$). WIN categories of less than 800, 800–1600, over 1600 represented 1.4%, 26.8% and 70.0% of our population, respectively. A WIN greater than 1600 and weight of excised gland greater than 1 g had a PPV of 86.7% for single-gland disease (Table 3).

Discussion

MIP is gaining in popularity but it is reliant on accurate preoperative localisation and prediction of single-gland disease.[4,12] The role of IOPTH in patients undergoing MIP is recognised but is still not standard practice. A recent European consensus has suggested that IOPTH is of little value in patients with concordant imaging who are undergoing MIP, given the low rates (1–3.5%) of multi-gland disease in this group.[12] However, a large series (1158 patients) reported unsuspected multi-gland disease in 20% of patients with concordant sestamibi and ultrasound.[11] Many centres report high rates of cure with MIP alone.[13,14] Others suggest the use of IOPTH to increase cure rates and also to reduce conversion to bilateral exploration.[4,10]

IOPTH is not available in many centres and is only used selectively in others because of logistical and financial

Table 2 Predictors of single- (SGD) and multi-gland disease (MGD) in patients undergoing surgery for primary hyperparathyroidism

Factors[a]	SGD	MGD	*P* value[b]
Mean (SD) age at surgery (years)	60.4 (14.08)	63.0 (15.3)	0.072[c]
Gender *n* (%):			0.195[b]
Female	385 (78.4)	106 (84.1)	
Male	106 (21.6)	20 (15.9)	
Preoperative adjusted calcium (mmol/l)	2.967 (0.2354)	3.007 (0.3171)	0.118[c]
Preoperative parathyroid hormone (pg/ml)	253.73 (248.247)	238.51 (236.217)	0.538[c]
Preoperative adjusted calcium ≥ 3 mmol/l *n* (%):			0.319[b]
Yes	180 (36.7)	53 (42.1)	
No	310 (63.3)	73 (57.9)	
PTH ≥ twice upper limit *n* (%):			0.760[b]
Yes	337 (69.9)	85 (68)	
No	145 (30.1)	40 (32)	
Positive ultrasound *n* (%):			0.001[b]
Yes	290 (65.2)	56 (47.9)	
No	155 (34.8)	61 (52.1)	
Positive sestamibi scan *n* (%):			< 0.001[b]
Yes	331 (76.3)	62 (56.9)	
No	103 (23.7)	47 (43.1)	
Concordant imaging *n* (%):			< 0.001[b]
Yes	229 (54.4)	36 (33)	
No	192 (45.6)	73 (67)	
Weight of excised gland (mg) (median IQR)	800 (400–1500)	490 (300–900)	< 0.001[d]

[a] missing data excluded from analysis.
[b] chi-square.
[c] student t-test.
[d] Mann-Whitney U test.
IQR, interquartile range; PTH; SD, standard deviation.

Table 3 Predictive ability of the CaPTHUS scores of patients undergoing parathyroid surgery for PHPT

Score	Patients *n* (%)	Sn (%)	Sp (%)	PPV (%)	NPV (%)	Acc (%)	LR+
CaPTHUS:							
≥ 3	319 (61.7)	65.7	53.8	84.6	28.8	63.2	1.4
≥ 4	202 (39.1)	41.8	71.7	85.1	24.1	50	1.5
5	85 (16.4)	18	89.6	87.1	22	32.7	1.7
Modified CaPTHUS:							
≥ 3	346 (56.1)	59.5	57.1	84.4	26.6	59	1.4
≥ 4	203 (32.9)	35.2	76.2	85.2	23.2	43.6	1.5
5	85 (13.8)	15.1	91.3	87.1	21.6	30.6	1.7
WI > 1600, weight > 1 g	165 (28.7)	31.2	81	86.7	22.9	41.2	1.6

Acc, accuracy; LR+, positive likelihood ratio; NPV, negative predictive value; PPV, positive predictive value; Sn, Sensitivity; Sp, specificity; WI, Wisconsin Index.

constraints. In this context, the reliable prediction of single-gland disease and exclusion of multi-gland disease is of key clinical concern. This study aimed to evaluate previously reported predictive models for single- compared with multi-gland disease in PHPT. In keeping with previous studies,[5–7] the following factors correlate with single-gland disease: sestamibi or ultrasound positive for one enlarged parathyroid gland, concordant sestamibi and ultrasound imaging demonstrating one enlarged gland on same side of the neck, and heavier parathyroid gland. In contrast to Kebebew et al.,[6] we found that preoperative PTH and adjusted calcium levels were not predictive of single-gland disease. Kavanagh et al. also found no association between preoperative calcium levels and single-gland disease but they did find that higher PTH (≥ 2 time upper limit of normal) was associated with single-gland disease.[5]

In our population, CaPTHUS score ≥ 3 had a positive predictive value of 84.6% in predicting single-gland disease compared with 100% reported by others.[5,6] A 2016 European study validated CaPTHUS in 241 patients.[15] Their incidence of single-gland disease (92%) was considerable higher than the original report by Kebebew et al. (75%),[6] but was similar to the report by Kavanagh et. al (92%).[5] They found that a CaPTHUS score of 3 or more had a positive PPV of 96% and concluded that intraoperative adjuncts are still needed to prevent failure in patients undergoing unilateral exploration. It was interesting to note that CaPTHUS score ≥ 4 or 5 only slightly increased the PPV for single-gland disease. This suggests that the CaPTHUS model alone will not be useful in directing targeted parathyroidectomy in our population. A CaPTHUS score of 3 or more to direct targeted parathyroidectomy without the use of intraoperative adjuncts would result in failure in approximately 15% of patients in our population.

In our population, there were no differences in WIN (serum PTH multiplied by serum calcium) scores between patients with single- and multi-gland disease. We found that a WIN greater than 1600 and weight of excised gland greater than 1 g had a PPV of 86.7% for single-gland disease, which is higher than the value of 81% reported by the Wisconsin group.[7] The authors plotted a nomogram of the probability of finding an additional enlarged gland for a given weight and WIN score. However, no cutoff point was given to aid decision making intraoperatively.

Other methods have been used to differentiate between single- and multi-gland disease. Hagag et al. examined the use of oral calcium loading preoperatively to differentiate between parathyroid gland adenoma ($n = 22$) and hyperplasia ($n = 10$).[16] They found that a PTH decline of less than 30% after administration of one gram of calcium had a PPV of 100% in predicting an adenoma; total accuracy of the test was 65%. However, the small numbers of patients, the relatively high proportion of patients with multi-gland disease (31%) and the need for an additional preoperative testing prevent more widespread use. Udelsman et al. developed software using mathematical models to predict cure during parathyroidectomy.[17] The model used preoperative, intraoperative and postoperative PTH and calcium values to predict cure or presence of additional hyper-functioning gland. The mathematical model predicted cure in 78/81 patients with single-gland disease. These studies have yet to be validated.

This study has validated CaPTHUS and WIN in 624 patients. Our finding suggests that these models, alone cannot be used to exclude the presence of multi-gland disease in patients who may be suitable for MIP. Many centres justify the use of MIP without IOPTH based on this model.[5,6,12] Thus, this study supports consideration of IOPTH in MIP. In centres where IOPTH is not available, surgeons and patients should be aware of the increased risk of failure with MIP alone.

The study has the limitations inherent in a retrospective cohort study. There was variation in treatment protocols within and between centres. However, this does not affect the primary aim of this study; particularly as cure rates and incidence of multi-gland disease were similar in both centres. This cohort may not be representative of routine practice in the average centre, as they include patients with negative imaging referred to these centres from other hospitals. The definitions of single- and multi-gland disease were

based on histopathology reports and clinical outcome post-operatively; the weight of the excised gland was taken into account only when available. It is possible that there may have been an overestimate in the diagnosis of multi-gland disease, as incidentally enlarged but non-functioning parathyroid glands may have been removed during a neck exploration and the patient may have been incorrectly labelled as having multi-gland disease. We do not think that this is a significant problem, however, as despite different practices relating to the use of adjuncts and the MIP procedure in the two centres, the proportions of multi-gland disease were similar. Other studies have also reported similar proportions of multi-gland disease patients.[4,7] The highest PTH and calcium levels were used in cases where more than one result was available preoperatively and so may have resulted in a higher WIN in our cohort. Another limitation of the study was the differences in the proportion of positive imaging between the two centres, highlighting variability in technique and reporting, although this did not have an impact on the overall accuracy of the tests between the two centres. Not all patients had calcium levels measured at 6 months following surgery. Persistent disease may therefore have been underestimated. However, no significant changes were seen in predictive values for single-gland disease when only patients who had calcium levels at 6 months were included in the analysis.

In summary, CaPTHUS and WIN do not accurately predict single-gland disease in PHPT in our population. If used alone, up to 15% (CaPTHUS) and 13% (WIN) of our populations may not be cured by a MIP targeting only one enlarged gland. Although this study does not provide data on intraoperative PTH assay, the inability to accurately predict single-gland disease on the basis of preoperative imaging and biochemistry warrants consideration of IOPTH or other intraoperative adjuncts in patients.

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