ORIGINAL ARTICLE

The Accuracy of Surgeon-Performed Preoperative Parathyroid Ultrasound Localization for Renal Hyperparathyroidism Patient

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ABSTRACT

INTRODUCTION: Parathyroid surgery for renal hyperparathyroidism (RHPT) is indicated when patients have a progressive disease despite optimal medical therapy. The success of total parathyroidectomy in RHPT lies in accurate localization and excision of all PTGs. Recently, surgeon-performed ultrasound (SPU) has been increasingly used for the preoperative localization of PTGs in the intent of focused approach and reduce morbidity. Thus, we conducted a prospective observational single-center study to determine the accuracy of SPU for PTG localization in RHPT and the factors affecting its accuracy. **MATERIALS AND METHODS:** This is a prospective, observational, single-center study conducted in University Kebangsaan Malaysia Medical Centre between March 2018 and March 2019. The patients' preoperative demography, clinical data, and relevant blood laboratory results, including calcium, phosphate, alkaline phosphatase, and intact parathyroid hormone, were recorded. Preoperative USG and surgery were performed by the same endocrine surgery consultant. **RESULTS**: SPU localization had an overall accuracy of 78.1%, sensitivity of 81.0%, and specificity of 30.0% with a positive predictive value of 94.8% and a negative predictive value of 10.5%. The SPU gland localization rate was significantly higher in patients without goiter (median=0.88, IQR=0.63–1.00) than in those with goiter (median=0.50, IQR=0.25–0.75) (p=0.028). **CONCLUSIONS:** SPU localization of the PTG in RHPT had an accuracy comparable with that in previous literature with the additional advantage of identifying concurrent unknown thyroid nodules. Considering the high prevalence of concomitant nodular thyroid disease in our RHPT population, we advocate the routine use of preoperative neck ultrasound for RHPT patients undergoing parathyroid surgery.

Keywords
renal hyperparathyroidism, surgeon-performed ultrasound, accuracy

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INTRODUCTION

Renal hyperparathyroidism (RHPT) is a common complication of end-stage renal disease (ESRD). Its prevalence in Asian populations is around 28%.[2] Long standing RHPT increases the risk of cardiovascular and bone disease.[1] Thus, parathyroid surgery is indicated in those long standing RHPT that failed medical therapy.[3] The annual incidence of RHPT patients requiring parathyroid surgery is estimated at around 1-2%.[2]

The success of total parathyroidectomy for treatment of RHPT lies in accurate localization and excision of all PTGs as the gland may appear small and be missed, leading to persistent or recurrent disease.[4,6] Surgeon-performed USG (SPU) may have the advantage of increased accuracy owing to the familiarity of the surgical anatomy of the neck region that lead to a faster and more focused surgery thus potentially reducing operative time and morbidity from the neck dissection.[7,8] This study aim to determine the accuracy of SPU PTG localization for RHPT patient and subsequently identify the factors affecting the accuracy of SPU localization.

MATERIALS AND METHODS

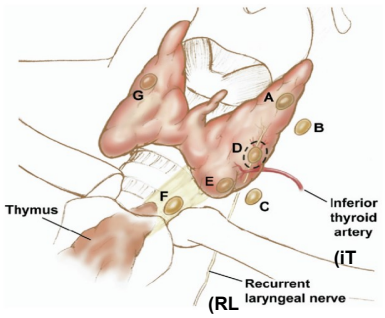
This was a prospective observational single-center study conducted in Hospital University Kebangsaan Malaysia between March 2018 and March 2019. Those with previous neck surgery was excluded. Demographic data, clinicopathological characteristics, and relevant blood laboratory results including calcium (Ca), phosphate (PO4), alkaline phosphatase (ALP) and intact parathyroid hormone (iPTH) obtained. Preoperative Ultrasound (USG) were performed a day before surgery. Both ultrasound and surgery of the same patients were performed by a same endocrine surgery consultant.

All patients underwent open all 4-gland exploration and excision of all identifiable PTGs. When indicated, a hemithyroidectomy, total thyroidectomy or thymectomy would be performed in the same setting. Intraoperative location of each excised PTG were recorded using the same schematic depiction (Diagram 1)[9]. Each specimen was then labelled appropriately and sent for histopathological confirmation.

The 3-dimensional (3-D) measurement (cm) and weight of each specimen (gram) were measured before it was immersed in formalin solution. It was used to compute the volume of gland using the standard formula for an ellipsoid morphology. Statistical analysis performed using IBM SPSS version 21. The Mann-Whitney U test used to compare between continuous variables while Chi-square test was used for categorical variables. The accuracy, sensitivity, specificity, positive and negative predictive value of USG localization were obtained using the standard 2 x 2 table. When the outcome variables are more than two categories such as for the location type of each gland, the accuracy were measured based on strength of agreement by Kappa statistic.[10,11] All tests were two-tailed and a p-value <0.05 was considered statistically significant.

RESULTS

We had a total of 24 patients included in this study. They had a mean duration of ESRD of 10.4 years and median BMI of 23.6kg/m². 12 of the 24 (50%) subjects had concurrent thyroid nodular disease where 9 (75.0%) of them had solitary thyroid nodule and the other 3 (25.0%) with multinodular goiter.



Location	Gland	Description	
A	Superior	**A**dherent to posterior thyroid capsule	(NORMAL)
B	Superior	**B**ehind in tracheoesophageal groove/near carotid	(ECTOPIC)
C	Superior	close to **C**lavicle in prevertebral space	(ECTOPIC)
D	Any	**D**irectly at junction of RLN and iTA	(NORMAL)
E	Inferior	**E**asy to identify, near inferior thyroid pole	(NORMAL)
F	Inferior	**F**allen into thymus / thyrothymic ligament	(ECTOPIC)
G	Any	**G**auche, within thyroid gland	(ECTOPIC)

Figure 1: Schematic of location type A through G of parathyroid glands.[9,10]

With regards to the surgery performed, 18 (75.0%) patients underwent total parathyroidectomy alone, 5 patients had hemithyroidectomy and 1 had total thyroidectomy in the same setting. Histopathological examination of 2 (30.0%) of the thyroidectomy specimens revealed papillary thyroid microcarcinoma while the rest showed benign pathology (Table 1).

Table 1: Patient, disease, biochemical and operative characteristics

Patient characteristics	Findings
Gender, no. of patient (%)	
Male	15 (62.5%)
Female	9 (37.5%)
Age, years	
Mean ± SD	51.7 ± 9.7
BMI, kg/m2	
Median (IQR)	23.6 (19.9 – 29.5)
Duration of ESRD, years	
Mean ± SD	10.4 ± 2.8
Concurrent goiter, no. of patient (%)	
Normal thyroid	12 (50.0%)
Solitary nodule	9 (37.5%)
Papillary thyroid microcarcinoma	2
Benign pathology	7
Multinodular (all benign)	3 (12.5%)
Type of surgery performed, no. of patient(%)	
total parathyroidectoy alone	18 (75.0%)
combined with hemithyroidectomy	5 (20.8%)
combined with total thyroidectomy	1 (4.2%)
Preoperative serum biochemical level	
iPTH level (pmol/L), mean ± SD	226.8 ± 98.4
Corr Ca (mmol/L), mean ± SD	2.59 ± 0.25
PO4 (mmol/L), mean ± SD	2.04 ± 0.61
ALP (U/L), median (IQR)	362 (219 – 855)

BMI – body mass index, ESRD – end-stage renal disease, iPTH – intact parathyroid hormone
Corr Ca - Corrected Calcium, PO4 – Phosphate, ALP – Alkaline phosphatase

A total of 77 glands were detected by preoperative USG while 90 out of the 96 gland specimens excised were histopathological confirmed 'true' parathyroid glands. During surgery, we managed to localize and excise all 4 glands in 19 (79.2%) patients, while 4 (16.6%) patients had only 3 glands located and 1 patient had only 2 glands found.

With regards to the individual location type of gland either on USG or intraoperative, type E were the most common normal location occupied by PTGs, followed by location type D and A. In our series, surgeon-performed USG failed to detect any type G (intrathyroidal) ectopic gland. However, an intrathyroidal gland was discovered incidentally in two hemithyroidectomy specimens. The indication for concurrent hemithyroidectomy in these two patients were suspicious solitary thyroid nodule detected on USG. Both location type B and F were the more common ectopic location reported intraoperatively, each accounting for 40% of all ectopic locations.

Diagnostic parameters of preoperative USG localization were evaluated by comparing the 77 USG detected PTGs with the 90 histopathological confirmed 'true' PTGs with the assumption of 96 glands in total (assuming 24 patients should each have 4 glands theoretically). It was shown that in our series, surgeon-performed preoperative USG localization for RHPT carries an overall accuracy of 78.1%, sensitivity of 81.0%, specificity of 30.0%, positive predictive value of 94.8% and negative predictive value of 10.5% (Table 2).

Table 2: Comparison between the number of USG located gland and true gland excised

Superior glands

		True gland +	True gland -	
USG	+	33	2	35
	-	11	2	13
		44	4	48

Inferior glands

		True gland +	True gland -	
USG	+	40	2	42
	-	6	0	6
		46	2	48

Combined all glands

		True gland +	True gland -	
USG	+	73	4	77
	-	17	2	19
		90	6	96

Diagnostic parameters of USG localization[a]

Gland	Sn (%)	Sp (%)	PPV (%)	NPV (%)	Accuracy (%)
Superior gland	75.0	50.0	94.3	15.4	72.9
Inferior gland	86.9	0.0	95.2	0.0	83.0
Combined all gland	81.0	30.0	94.8	10.5	**78.1**

[a]Calculation based on 2 x 2 table
Sn-sensitivity, Sp-specificity, PPV-positive predictive value, NPV-negative predictive value

Table 3: Factors affecting USG detection rate of true gland

Factors		USG gland detection rate Median (IQR)	p-value[a]
Goiter			
	Present	0.50 (0.25 – 0.75)	0.028*
	Absent	0.88 (0.63 – 1.00)	
BMI			
	>30	0.38 (0.25 – 0.75)	0.137
	<30	0.75 (0.50 – 1.00)	

[a]**Mann-Whitney *U* test** ***p-value < 0.05 level**

DISCUSSION

The success of total parathyroidectomy in RHPT lies in accurate localization and excision of all PTGs. There are generally four PTGs in the human body, one superior and one inferior on either side of neck posterior to the thyroid gland.[5] The superior PTGs typically lie approximately 1 cm above the junction of the inferior thyroid artery and recurrent laryngeal nerve at the level of the cricoid cartilage while the inferior PTGs are most commonly situated on the posterolateral aspect of the inferior thyroid pole, below the junction of the inferior thyroid artery and the recurrent laryngeal nerve.[9] Thus, failed of removal all PTG will lead to persistent or recurrent disease in the future.[4]

Previous literatures had described an exhaustive list of ectopic PTG locations ranging from submandibular, retropharyngeal, retroesophageal, within the tracheoesophageal groove, carotid sheath, posterosuperior mediastinal, anterosuperior mediastinal, intrathyroidal, within thyrothymic ligament and intrathymic etc.[15,16] This made the localization documentation rather complex and inconsistent among observers.[9,17] Hence, in our study, we adopted the location classification system first proposed by Perrier et al. This classification scheme was originally designed to simplify and standardize parathyroid adenoma localization in primary HPT. It also gives precise description of the exact position of the gland in the neck with its relationship to surrounding structures.[9] In this classification system, type A, D and E are the normal locations while type B, C, F, G are for ectopic locations (Diagram 1).

The role of SPU is very well established in primary hyperparathyroidism for pre-operative localization as early as 2004[12,13] and recently advocated.[14] The sensitivity of SPU is 82% with specificity of 90% compared to radiologist performed USG sensitivity of 44% and specificity of 98%[12]. To date, inconsistent and wide range of sensitivity in the preoperative USG by radiologist in RHPT patients has been reported, ranging from 35.9% to 75%.[7, 18-21] Thus we inferred this evidence to ascertain the role of SPU in RHPT with a more consistent findings.

During subgroup analysis, USG localization for inferior glands reported a higher sensitivity. It was explained that the superior PTGs are usually situated at the level of the thyrolaryngeal groove, a place which is difficult for USG wave penetration due to overlying airway shadowing effect.[20] Plus, superior glands usually lie behind thyroid lobes and closed to the thick thyroid tissue that limits the USG wave penetration.[20]

Our result revealed that the number of topic (normally located) gland has a significant positive correlation with the USG gland detection rate. This explained that ectopic PTG are difficult to find due to acoustic shadowing from overlying air or bone.[5] Its rate is as high as 12 - 16% of cases as demonstrated by previous case series.[20, 21] In this study, we found that type F seems to be the most easily identified ectopic location with a true positive localization rate.[22] However, SPU failed to detect any type G (intrathyroidal) gland in our study correlate with other previous study.[20, 22]

During surgery, we managed to localize and excise all 4 glands in 79.2% patients. This was possibly due to incomplete intraoperative localization rather than a true less than 4 glands, which is extremely rare.[5] Nevertheless, we were able to achieve an intraoperative identification rate for true PTGs as high as 93.8% solely based on the macroscopic characteristics of PTGs, thus help reduce the usage of frozen section.[20]

In our study, analysis was carried out to identify factors which might affect the USG gland localization rate using Spearman's correlation and Mann-Whitney U test. The significant factors which showed positive correlation with USG gland detection rate were the absence of goiter and the number of normally located glands. On subgroup

Table 4: Subgroup analysis comparing accuracy of USG location type in patient with and without goiter

Superior gland location type

Patient with goiter

		Intraoperative					
		Not located	**A**	**B**	**D**	**G**	**Total**
USG	Not located	2	2	1	4	1	10
	A	0	2	0	0	0	2
	B	0	2	1	1	0	4
	D	1	4	0	3	0	8
Total		**3**	**10**	**2**	**8**	**1**	**24**

Kappa = 0.154 (slight agreement)
p-value = 0.103

Patient with goiter

		Intraoperative				
		Not located	**A**	**B**	**D**	**Total**
USG	Not located	0	1	1	1	3
	A	1	7	0	1	9
	B	0	0	0	1	1
	D	0	0	1	10	11
Total		**1**	**8**	**2**	**13**	**24**

Kappa = 0.528 (moderate agreement)
p-value = 0.000*

Inferior gland location type

Patient with goiter

		Intraoperative					
		Not located	**A**	**D**	**E**	**G**	**Total**
USG	Not located	0	0	0	5	0	5
	D	0	1	0	2	0	3
	E	2	0	2	11	1	16
Total		**2**	**1**	**2**	**18**	**1**	**24**

Kappa = -0.147 (less than chance)
p-value = 0.259

Patient with goiter

		Intraoperative			
		D	**E**	**F**	**Total**
USG	Not located	0	1	0	1
	D	0	0	1	1
	E	1	18	1	20
	F	0	0	2	2
Total		**1**	**19**	**4**	**24**

Kappa = 0.487 (moderate agreement)
p-value = 0.001*

analysis, the group without goiter also showed significantly better agreement between USG and intraoperative location. Thus, patient with nodular goitre may affect the parathyroid pre-operative localization.

In our institute, we routinely offered concurrent thyroid surgery rather than watchful waiting for patients with thyroid lesion. As such, we can avoid a redo neck surgery in the future which is more difficult and carries higher potential morbidities. We found that 8.3% of thyroid malignancy in our RHPT population. Japanese population had a 15 - 36% prevalence of papillary thyroid carcinoma at parathyroidectomy as compared to a lower 2.4 – 3.2% in the western population.[24] As a matter of fact, a recent large cohort revealed a 10.1-fold risk of thyroid cancer in ESRD patients with RHPT than those without RHPT.[25]

Previous authors demonstrated a lesser BMI is a significant predictor for higher gland detection rate by USG. One postulation might be the reduced penetration of USG waves in thicker subcutaneous fat in the neck region and shorter neck in obese patients making scanning technically challenging.[23] However, in our study BMI was not statistically significant.

Multiple studies in the literature have reported that detection of hyperplastic glands in RHPT increased with the greater size of the glands.[7,20,23] However, we found this correlation is not statistically significant. Interestingly, there were significant positive correlation of average gland volume and weight with serum phosphate level and serum corrected calcium level. Consistent to previous literature[26], we also found that USG tend to underestimate the volume of gland by about 13.3% less than the actual volume measured post-excision. A possible postulation may be the compression effect by surrounding tissues on the relatively softer PTG when it is in vivo leading to a smaller size measured by USG in contrast to the size measured post excision.

CONCLUSION

Surgeon-performed USG for the assessment of cervical endocrine disease is becoming more established in the recent years. Considering the high prevalence of concomitant nodular thyroid disease in our RHPT population, we advocate the routine use of preoperative USG neck for RHPT patients going for parathyroid surgery.

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