Single gland versus multigland disease in primary hyperparathyroidism at the Wits Donald Gordon Medical Centre in Johannesburg, South Africa.

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DECLARATION

I, Nicola Amy MacRobert (student number: 0701074X), declare that this research report is my own, unaided work. It is being submitted for the Degree of Master of Medicine in Surgery at the University of the Witwatersrand, Johannesburg, South Africa. It has not been submitted before for any other degree of examination at any other University.

9th Day of December 2020 in Johannesburg

ABSTRACT

***Background**:*

Primary hyperparathyroidism (PHPT) is caused by excessive parathyroid hormone production by autonomously functioning parathyroid gland(s). Most commonly this is by adenomatous change in a single parathyroid gland. This single pathological gland may then be removed in a focused or minimally invasive surgical approach rather than a traditional bilateral neck exploration. However, to do this, the abnormal gland needs to be localized preoperatively using imaging.

***Objectives**:*

To review patients with PHPT undergoing first parathyroidectomy at the Wits Donald Gordon Medical Centre, in Johannesburg South Africa, to determine the distribution of pathology between single and multigland disease, techniques used to localize disease preoperatively and outcome according to surgical approach.

***Methods**:*

A retrospective review was conducted on all eligible patients with biochemically confirmed PHPT undergoing first parathyroidectomy by a single surgeon for PHPT at the Wits Donald Gordon Medical Centre in Johannesburg, South Africa over a period from October 2008 to January 2018.

***Results**:*

Records of a total of 252 patients with PHPT who underwent first parathyroidectomy were reviewed. Single gland disease was the cause of PHPT in 83.3% (n = 210) of patients, multigland disease including double adenomas and hyperplastic change accounted for the remainder. A neck USS was done in 71.8% (n = 181) patients with a sensitivity of 77.1% (95% confidence interval of 68.5 to 84.4%) while 75.4% (n = 190) of patients had a Tc-99 Sestamibi SPECT scan with an comparable sensitivity of 72.9% in localizing SG disease (63.9 – 80.7%). Combined USS and Tc-99 Sestamibi SPECT scan had a sensitivity in SG disease of 79.7% (71.3 – 86.5%). However, only 44.8% (n = 113) of patients had a minimally invasive parathyroidectomy.

***Conclusion**:*

A bilateral neck exploration remains the gold standard surgical approach in the management of PHPT. However, given the predominance of single gland disease, accurate preoperative localization techniques, and successful surgical outcomes, minimally invasive parathyroidectomy is of equal importance in the parathyroid surgeon's armamentarium.

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TABLE OF CONTENTS

DECLARATION ii

ABSTRACT iii

ACKNOWLEDGEMENTS iv

LIST OF ABBREVIATIONS vi

LIST OF TABLES vii

LIST OF FIGURES vii

CHAPTER 1: INTRODUCTION 1

1.1 Background 1
1.2 Objectives 2

CHAPTER 2: METHODS 4

2.1 Patient selection 4
2.2 Ethical approval 4
2.3 Data acquisition 4
2.4 Statistical analysis 5

CHAPTER 3: RESULTS 6

3.1 Patient characteristics and preoperative biochemistry 6
3.2 Localization of disease with preoperative imaging 6
3.3 Surgical approach 9
3.4 Post-operative calcium levels 9
3.5 Post-operative PTH levels 10

CHAPTER 4: DISCUSSION 11

CHAPTER 5: CONCLUSION 13

REFERENCES 14

APPENDIX 1: Approved Protocol 16

APPENDIX 2: Data collection sheet 27

APPENDIX 3: Ethics Clearance Certificate 28

LIST OF ABBREVIATIONS

BNE: bilateral neck exploration

CEO: Chief Executive Officer

IQR: Interquartile range

MEN: Multiple Endocrine Neoplasia

MG: multigland

SG: single gland

SE: standard error

SPECT: Single Photon Emission Computed Tomography

Tc-99: Technetium 99

USS: ultrasound scan

WDGMC: Wits Donald Gordon Medical Centre

PTH: parathyroid hormone

PHPT: primary hyperparathyroidism

LIST OF TABLES

Table 1. Patient demographics, pre-operative clinical characteristics and histopathology in Single gland (SG) vs Multigland (MG) disease 7

Table 2. SG and MG disease according to imaging modalities..... 8

Table 3. Sensitivity and specificity of individual and combined imaging modalities..... 8

LIST OF FIGURES

Figure 1. Reduction in hypercalcaemia postoperatively 9

Figure 2. Reduction in PTH levels postoperatively 10

CHAPTER 1: INTRODUCTION

1.1 Background

Primary hyperparathyroidism (PHPT) is an endocrine disorder arising from dysregulated parathyroid hormone (PTH) production. Symptoms are caused by the resultant hypercalcaemia. Typically, PHPT affects middle-aged, post-menopausal females [1]. PHPT is diagnosed biochemically by hypercalcaemia in the setting of an inappropriately elevated PTH level. Autonomous PTH production arises from a single parathyroid gland, so called 'single gland' (SG) disease, in approximately 85% of patients with PHPT [2]. Adenomatous change is usually the underlying pathological change seen in SG disease. Hyperplasia, however, is mainly responsible for multigland (MG) disease, which occurs in approximately 15% of PHPT patients. Hyperplastic glands are smaller and less impressive than glands enlarged by adenomatous change. Multiple adenomas may also be found in MG disease. Carcinoma is rarely implicated in PHPT (<1%) [2].

PHPT can be cured and is primarily managed by expedient surgical removal of the pathological gland(s) [3]. Traditionally, the surgeon's gold standard involves a bilateral neck exploration in which all four parathyroid glands are explored and any abnormally enlarged gland resected – this approach has cure rates above 95% and does not fundamentally require preoperative imaging [4]. Post-operative cure is defined as normocalcaemia at six months post surgery. However, given that most patients with PHPT have SG disease this has led to an advocacy for a more focused and minimally invasive approach directed at removing the single pathological gland. Comparable successful cure rates of more than 95% have been reported to those achieved with a bilateral neck exploration [5]. In addition, this minimally invasive approach has the favorable outcomes of including a smaller, more cosmetically appealing scar, shorter operative time and hospital stay, and reduced postoperative complications, such as hypocalcaemia and recurrent laryngeal nerve damage [6, 7].

To remove a SG in a focused surgical manner, the surgeon has to be able to preoperatively localize it. Imaging modalities are used to localize the gland and not to confirm or exclude the diagnosis of PHPT [8]. Commonly used imaging modalities include a neck ultrasound scan (USS) and a Technetium (Tc)-99 Sestamibi Single Photon Emission Computed Tomography (SPECT) scan. A neck USS has the advantage of being widely available, cheap and easy to use. However, the success in localizing the gland is believed to be operator dependent [9]. According to a meta-analysis published in 2012, the pooled sensitivity of a neck USS was reported to be 76.1% (95%

CI 70.4 – 81.4%) with a pooled positive predictive value in SG detection of 93.2% (90.7 – 95.3%). The pooled sensitivity and positive predictive value of a Tc-99 Sestamibi SPECT scan were reported as 78.9% (64 – 90.6%) and 90.7% (83.5 – 96.0%), respectively, for SG disease [10]. However, the latter modality is not widely available, less cost-effective than USS and requires more skill to interpret [11]. Combining the two imaging modalities has been shown to increase preoperative localization accuracy to a sensitivity between 79 -95% and such a combined imaging approach is recommended [12]. Both neck USS and Tc-99 Sestamibi SPECT scans, unfortunately, perform poorly in detecting MG disease [13, 14]. Indeed, negative, equivocal or discordant imaging results should raise the suspicion of MG disease and necessitate a bilateral neck exploration [15]. Missed MG disease is a preventable cause of persistent or recurrent hypercalcaemia and, therefore, of 'surgical failure' postoperatively [16, 17]. Such an outcome may lead to ongoing target organ damage from hypercalcaemia, in which case a re-exploration is indicated. Re-exploration is technically more challenging and is associated with increased surgical morbidity [18].

In addition to imaging, other proposed markers of potential use to differentiate SG and MG disease preoperatively include the degree of clinical symptomatology and elevation of hypercalcaemia, both of which are of a worse degree in adenomatous rather than hyperplastic disease [19]. However, studies have shown inconsistent results using these variables and the widespread clinical use of such strategies has not gained popularity [13, 20]. Vitamin D, commonly deficient in the African populations [21], is a known contributing factor to severity of disease and accuracy of preoperative localization. Ideally, vitamin D levels should be measured in patients with suspected PHPT [22].

This study reviewed a cohort of patients with PHPT who underwent parathyroidectomy at the WITS Donald Gordan Medical Centre (WDGMC) in Gauteng, South Africa, to primarily determine the predominance of SG disease and whether SG disease can be predicted preoperatively by means of biochemistry and imaging modalities.

1.2 Objectives

The aim of this retrospective study was to determine whether SG and/or MG parathyroid disease was accurately predicted preoperatively in patients with PHPT undergoing parathyroidectomy at

the WITS Donald Gordon Medical Centre (WDGMC) between October 2008 and April 2017. The objectives were to:

1. Determine the incidence of SG versus MG disease.
2. Compare the preoperative biochemical profile in SG versus MG PHPT specifically considering serum calcium, PTH and vitamin D levels.
3. Determine the radiological description of disease according to neck USS and Tc-99 Sestamibi SPECT scan.
4. Describe the operative approach (unilateral/focused/minimally invasive versus bilateral neck exploration), as well as associated intraoperative and histopathological findings.
5. Determine the cure rate according to six monthly serum calcium levels between each operative approach based on preoperative assessment of SG versus MG disease.

CHAPTER 2: METHODS

2.1 Patient selection

Data from patients 18 years and older undergoing parathyroidectomy for PHPT at the WDGMC by a single surgeon over the study period of October 2008 to April 2017 were collected retrospectively. Patients undergoing reoperation and those undergoing parathyroidectomy for renal-related or Multiple Endocrine Neoplasia (MEN) parathyroid disease were excluded.

2.2 Ethical approval

Ethical approval was obtained from the University of the Witwatersrand's Human Research Ethics Committee (clearance certificate number M180918) and permission to conduct the study was granted from the Chief Executive Officer (CEO) of the WDGMC.

2.3 Data acquisition

All data were recorded in a REDCap database. Data was anonymized to ensure patient confidentiality and included basic demographic characteristics and relevant biochemistry results of preoperative serum corrected calcium, PTH and vitamin D levels; also, postoperative serum corrected calcium results were recorded. Preoperative biochemistry done more than 180 days pre-surgery was excluded. Six-month follow up blood results outside of seven months post-surgery were also excluded. Hypercalcaemia was defined as a calcium level above 2.60 mmol/L and normocalcaemia as a calcium level ≤2.60 mmol/L. Normocalcaemia was defined as 2.00 – 2.60mmol/L.

Preoperative imaging results from neck USS and Tc-99 Sestamibi SPECT were reviewed. SG or MG disease was determined from the number of glands identified by each of these imaging modalities individually and combined. For the use of both imaging modalities together, patients were classified as having MG disease if one or both imaging modalities identified MG disease, otherwise patients were classified as having SG disease.

Classifications based on imaging modalities were then compared to the "true" or gold standard classification based on surgical and histological assessment. Therefore, a true positive imaging result of SG disease was based on the surgical and histological assessment showing only a single gland as pathologically abnormal. Specifically, histological outcome was defined as follows: if one abnormal gland was identified, regardless of whether this was an adenoma, carcinoma or hyperplasia, this was diagnosed as SG disease. If more than one abnormal gland was identified, a diagnosis of MG disease was made.

2.4 Statistical analysis

Data analysis was carried out using SAS version 9.4 for Windows and STATA version 14.2. Descriptive statistics were conducted and categorical variables were summarized by frequency and percentage, whilst continuous variables were described according to the median and interquartile range (IQR). The associations between preoperative calcium levels and histological outcome, surgery and histological outcome, and between SG/MG disease and adenoma/hyperplasia were determined by the Mann-Whitney U Test and Chi-squared or Fisher's exact test, as appropriate. Where both imaging tests were carried out, the degree of agreement between neck USS and Tc-99 Sestamibi SPECT scan in the identification of SG versus MG disease was determined by Cohen's kappa with a standard error (SE). The sensitivity and specificity of the individual imaging modalities and their combination in predicting SG and MG disease are reported. P-values of 0.05 were the threshold used for statistical significance for all tests.

CHAPTER 3: RESULTS

3.1 Patient characteristics and preoperative biochemistry

A total of 252 patients underwent parathyroidectomy during the study period and were included in the study. Table 1 shows the demographic characteristics, pre-operative biochemistry and histopathology findings in SG vs MG disease. The median age (IQR) of the study patients at surgery was 60.0 (51.0 – 70.0) years and this did not differ between SG and MG disease. The majority of study patients were female (n = 195, 77.4%), regardless of whether SG or MG disease was diagnosed. Histologically proven SG disease was found in 83.3% of patients (Table 1) and adenoma was the causative pathology in 91.0% of these patients. Histologically proven MG disease was found in 13.1% of patients and hyperplasia was the causative pathology in 87.9% of these patients. Nine patients had no glands identified on histology, i.e. tissue mistaken for parathyroid tissue was removed at time of surgery.

One or more blood results were recorded for 212 patients (15.9% missing data). The median (IQR) days' duration between preoperative results and surgery was 38 (18 – 69) days. The median (IQR) preoperative calcium level in the study patients was 2.68 (2.57 – 2.80) mmol/L and 68.6% (n = 142) had hypercalcaemia (Table 1). The median calcium level was significantly higher in SG vs MG patients (p = 0.03). PTH levels showed a median (IQR) level of 118.6 (88 – 175) pg/mL, with 93% of patients having PTH levels above the normal range of 15.0 – 68.3 pg/mL, and none below the normal range. Also, PTH levels were significantly higher in MG vs SG disease patients (p = 0.007). Vitamin D levels were only available in 51% of study patients (n = 128) and did not show any significant differences between SG and MG disease.

3.2 Localization of disease with preoperative imaging

Of the 252 patients in this study, 94% (n = 237) had at least one type of preoperative imaging done. A neck USS (Table 2) was performed in 71.8% (n = 181) patients. Within these 181 patients, 76.8% were found to have SG disease, 7.2% MG disease and 16.0% had no glands identified. A Tc-99 Sestamibi SPECT scan was done on 75.4% (n = 190) patients, identifying SG and MG disease in 76.8% and 5.3% respectively. No glands were seen in 17.9% of patients. Combined imaging was done in 53.2% (n = 134) patients. The following results were obtained: 80.6% SG, 12.7% MG and no glands in 6.7% of patients.

Table 1. Patient demographics, pre-operative clinical characteristics and histopathology in Single gland (SG) vs Multigland (MG) disease

Parameters	Total	SG	MG	P value*
Study patients, n (%)	**252 (100%)**	**210 (83.3%)**	**33 (13.1%)**	
Glands identified	**243 (96.4%)**			
Age, years	60.0 (51.0 – 70.0)	60.0 (51.0 – 70.0)	59.0 (48.0 – 67.0)	0.41
Female, n (%)	195 (77.4%)	165 (78.6%)	24 (72.7%)	0.50
Calcium, mmol/L	2.68 (2.57 – 2.80)	2.70 (2.58 – 2.83)	2.64 (2.49 – 2.71)	**0.03**
Calcium level categories (n = 207)				
Normocalcaemia, n (%)	65 (31.4%)	50 (29.6%)	11 (37.9%)	0.39
Hypercalcaemia, n (%)	142 (68.6%)	119 (70.4%)	18 (62.1%)	
PTH, pg/mL	118.6 (88.0 – 175.0)	116.1 (87.1 – 166.8)	142.0 (108.0 - 1102)	**0.007**
Vitamin D ng/mL	22.1 (16.8 – 28.5)	21.9 (16.5 – 28.5)	23.6 (19.8 – 28.5)	0.56
Histopathology, n (%)				
Adenoma	199 (79.0%)	191 (91.0%)	8 (24.2%)	**<0.0001**
Hyperplasia	42(16.7%)	17 (8.1%)	29 (87.9%)	**<0.0001**
Carcinoma	2 (0.8%)	2 (0.9%)	0	-
No glands	*9 (3.6%)*			

*Mann-Whitney test statistic for continuous variables; Chi^2/Fisher's Exact test statistic for categorical variables. Continuous variables are presented as median (interquartile range [IQR]), unless specified otherwise. Categorical variables are expressed as absolute and relative frequencies. *Abbreviations:* PTH, parathyroid hormone.

Table 2. SG and MG disease according to imaging modalities

Variable	Total (n=252)	Histology outcome		
		SG (n = 210)	MG (n = 33)	No glands (n = 9)
Neck USS done, n (%)	**181 (71.8%)**	**155 (73.8%)**	**20 (60.6%)**	**6 (66.7%)**
No glands	29 (16.0%)	26 (16.8%)	2 (10%)	**1 (11.1%)**
SG disease	139 (76.8%)	**120 (77.4%)**	14 (42.4%)	5 (55.6%)
MG disease	13 (7.2%)	9 (5.8%)	**4 (12.1%)**	0 (0%)
Tc-99 Sestamibi SPECT done, n (%)	**190 (75.4%)**	**167 (79.5%)**	**16 (48.5%)**	**7 (77.8%)**
No glands	34 (17.9%)	29 (17.4%)	4 (25.0%)	**1 (11.1%)**
SG disease	146 (76.8%)	**129 (77.2%)**	11 (68.8%)	6 (66.7%)
MG disease	10 (5.3%)	9 (5.4%)	**1 (6.3%)**	0 (0%)
Both USS and Tc-99 Sestamibi SPECT, n (%)	**134 (53.2%)**	**118 (56.2%)**	**12 (36.4%)**	**4 (44.4%)**
No glands	9 (6.7%)	9 (7.6%)	0 (0%)	**0 (0%)**
SG disease	108 (80.6%)	**94 (79.7%)**	10 (83.3%)	4 (100%)
MG disease	17 (12.7%)	15 (12.7%)	**2 (16.7%)**	0 (0%)

Abbreviations: MG, multigland; SG, single gland; USS, ultrasound.

To determine the degree of agreement between the neck USS and the Tc-99 Sestamibi SPECT scan in identifying SG and MG disease, Cohen's Kappa (SE) was calculated to be 0.139 (0.07). This is considered to be poor agreement. For these 134 patients who had both the neck USS and the Tc-99 Sestamibi SPECT scan done, the sensitivity and specificity of each imaging modality and their combination in successfully identifying SG or MG disease is shown in Table 3. Evidently, preoperative imaging was only reasonably sensitive in detecting SG disease and not at all sensitive in the detection of MG disease, albeit reliably specific in the latter.

Table 3. Sensitivity and specificity of individual and combined imaging modalities

Imaging modality (n = 134)	To identify SG		To identify MG	
	Sensitivity % (95% CI)	Specificity % (95% CI)	Sensitivity % (95% CI)	Specificity % (95% CI)
Neck USS	77.1 (68.5 – 84.4)	31.3 (11.0 – 58.7)	16.7 (2.1 – 48.4)	95.1 (89.6 – 98.2)
Tc-99 Sest. SPECT	72.9 (63.9 – 80.7)	31.3 (11.0 – 58.7)	0.0 (0.0 – 26.5)	92.6 (86.5 – 96.6)
Both modalities	79.7 (71.3 – 86.5)	12.5 (1.6 – 38.4)	16.7 (2.1 – 48.4)	87.7 (80.5 – 93.0)

Abbreviations: Sest, Sestamibi; USS, ultrasound.

3.3 Surgical approach

The 252 patients had a total of 266 surgeries: one patient had 3 surgeries and 12 patients had 2 surgeries each. We considered only first surgeries, as these relate directly to the pre-operative imaging data. Minimally invasive or unilateral surgery was only done in 44.8% (n = 113) of patients, while the rest had bilateral neck explorations. SG disease as determined by histological outcome was found in 74.1% (n = 103) of patients who underwent bilateral four gland exploration.

3.4 Post-operative calcium levels

As six monthly post-operative serum calcium levels were only obtained in 21 patients, thus 91.7% had this data missing, the incidence of postoperative normocalcaemia and, therefore, surgical cure rates at six months could not be determined retrospectively. Nevertheless, the serum calcium levels immediately postoperatively were available in 157 patients with SG disease (74.8%) and in 27 patients with MG disease (81.8%). In these 157 patients, preoperative hypercalcaemia was present in 109 patients with SG disease (69.4%) and was significantly reduced to only 15 patients (9.6%) postoperatively (p = 0.02), as shown in Figure 1. In the 27 patients with MG disease and postoperative calcium levels available, hypercalcaemia was present in 16 patients (59.3%) preoperatively and only one patient (3.7%) remained hypercalcaemic postoperatively, although this reduction was not statistically significant (p= 0.60).

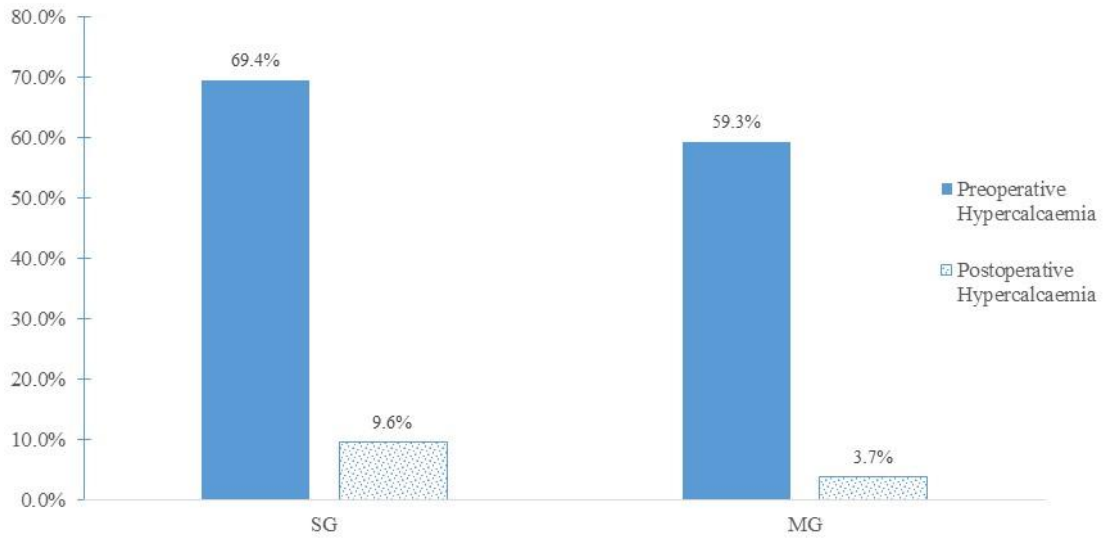

Figure 1. Reduction in hypercalcaemia postoperatively

3.5 Post-operative PTH levels

In patients with SG disease who had both pre- and immediate postoperative PTH levels measured (n = 155), there was a marked decrease in median PTH level postoperatively. Where 92.2% of SG patients had pre-operative PTH levels above the normal range of 68.3 pg/mL compared to only 10.3% post-operatively, this did not reach statistical significance (p = 0.16; Figure 2). The latter may be explained by the eight patients who actually had an increase in post-operative PTH levels; of these eight patients, one also became hypercalcaemic post-operatively. In MG patients with both pre- and post-operative PTH levels available (n = 27), there was a statistically significant decrease in median PTH level post-operatively (p < 0.001). Moreover, 92.6% of MG patients had PTH levels above 68.3 pg/mL pre-operatively compared to only 22% post-operatively, with all patients showing a decrease.

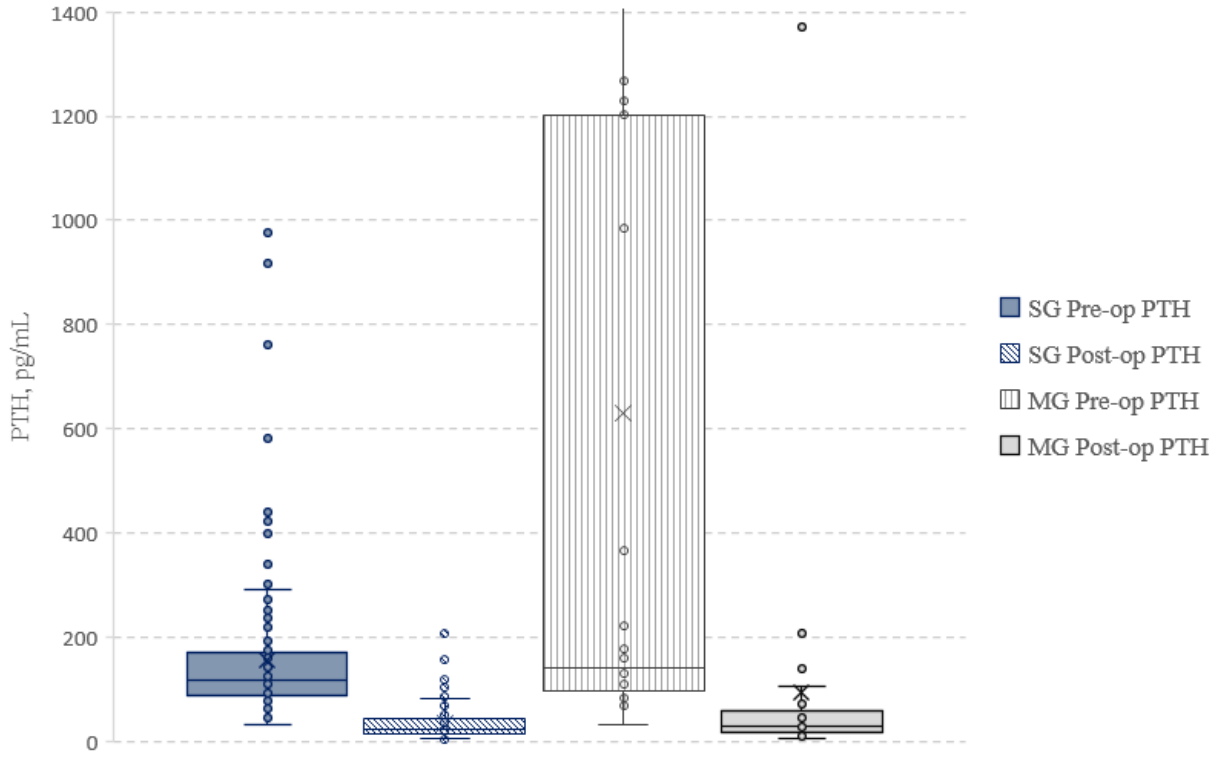

Figure 2. Reduction in PTH levels postoperatively

CHAPTER 4: DISCUSSION

Patients undergoing parathyroidectomy in this cohort, at a private academic hospital in Johannesburg, South Africa, had a similar demographic profile to what has been described in existing literature in that PHPT is mainly a disease of postmenopausal females. Likewise, SG (83.3%, n = 210) disease was the predominant cause of PHPT and characteristically due to adenomatous change.

Preoperative serum corrected calcium and PTH levels are routinely measured in the diagnostic evaluation of a patient with PHPT. Indeed, the actual diagnosis of PHPT may be questioned in the small subset of patients included in this study who did not have these results recorded. However, all patients who did have PTH levels recorded were indeed hyperparathyroid thereby confirming their diagnosis. Hypercalcaemia was present in 68.6% of the group while the normocalcaemic phenotype of PHPT was observed in as many as 31.4%. Normocalcaemia accounts for 15% of patients with PHPT. However, this study demonstrated a much higher prevalence of normocalcaemia compared to previous studies of mainly Western population groups [23]. This increase may be due to an underlying Vitamin D deficiency [24]. Most of the observed Vitamin D levels in this group were in the low normal range. However, interpretation of this is difficult given that only 51% (n = 128) had Vitamin D levels recorded. The cofounding factors accounting for this greater proportion of the normocalcaemic phentoype may be a topic to evaluate further.

The degree of hypercalcaemia was significantly higher in patients with SG disease compared to MG PHPT. Despite this statistical difference, the clinical relevance is not obvious when comparing the numerical similarity between the median calcium levels in SG 2.70 (2.58 – 2.83) mmol/L and MG disease 2.64 (2.49 – 2.71) mmol/L. Interestingly, MG disease was associated with significantly higher PTH levels unlike in existing literature where the opposite has been demonstrated [19]. Given this conflicting finding the application of preoperative biochemistry to clinical practice in predicting SG versus MG disease may be unreliable.

A minimally invasive parathyroidectomy relies upon the accurate preoperative localization of SG disease by using imaging. At least one modality of imaging was performed preoperatively in the majority of patients, a neck USS in 71.8% and a Tc-99 Sestamibi SPECT in 75.4% of the group. Just over half (53.2%) had both forms of imaging done. Analysis of the results showed a comparable sensitivity, 77.4% for neck USS and 77.2% for Tc-99 Sestamibi SPECT, for the detection of SG disease to what has been described in literature. Combined imaging resulted in a

slightly higher sensitivity (79.7%) for SG disease. However, the agreement between the two imaging modalities was poor and therefore, imaging results, should always be interpreted with caution. For example, both modalities may have concluded a preoperative localization to one side of the neck, however, it may not have been same gland. An abnormal right upper parathyroid gland may have been identified on neck ultrasound but another gland may have been interpreted as abnormal on Tc-99 Sestamibi SPECT. Therefore, imaging results must be reviewed by the operating surgeon and the concordance between different modalities established. The sensitivity of detecting MG disease was dismally poor for both neck USS and Tc-99 Sestamibi SPECT. Therefore, imaging should always be interpreted with caution. Any discordance or equivocal imaging results should favour a bilateral neck exploration.

Despite the predominance of SG disease and acceptable preoperative localization technique accuracy only 44.8% (n=113) of the cohort had a minimally invasive parathyroidectomy. And most patients, 74.1% (n=103) who had a bilateral neck exploration only had SG disease on final histopathological review. Reasons favoring a bilateral four gland exploration in patients deemed to have SG disease preoperatively should perhaps be explored further. However, this was a review of patients accumulated over a period of just under ten years. By a temporal analysis, a greater reliance on minimally invasive surgery for SG disease over time and with increasing surgical experience may have been demonstrated. However, a recent retrospective study in the Collaborative Endocrine Surgery Quality Improvement Program (CESQIP) included more than 5000 patients undergoing first parathyroidectomy and demonstrated that despite excellent preoperative localization to SG disease up to 40% of the patients still had a four gland exploration, mainly according to the discretion of the surgeon (25).

Surgical cure between the two operative approaches based on preoperative localization of disease could not be determined given the large number of missing six month postoperative calcium levels. Nevertheless, analysis of serum calcium levels immediately postoperative showed an undeniable reduction in the number of patients who remained hypercalcaemic. Likewise, PTH levels dropped dramatically postoperatively. This demonstrates the effectiveness of parathyroidectomy in reversing the biochemicaly changes in patients with PHPT. With such a rapid and immediate objective measure of success this may explain why patients are not followed up to six months post surgery.

This study does, however, have limitations. Firstly, it is a retrospective study and therefore not all data points were available for each study patient. Moreover, this study cannot comment whether there was any association between symptomatology and SG/MG disease as this information was not available retrospectively. Secondly, this is a single centre study and all patients were operated on by a single surgeon and thus not reflect the clinical approach at the study site as a whole.

CHAPTER 5: CONCLUSION

The biochemical changes characteristic of PHPT namely, hypercalcaemia and hyperparathyroidism, are rapidly reversed with parathyroidectomy. A bilateral neck exploration remains the gold standard surgical approach. However, given the predominance of single gland disease, a minimally invasive parathyroidectomy based on the cautious interpretation of reliable preoperative localization studies is equally advocated.

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APPENDIX 1: Approved Protocol

MMED PROTOCOL

Single gland versus multigland disease in primary hyperparathyroidism at the Wits Donald Gordon Medical Centre in Johannesburg, South Africa.

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Introduction

Primary hyperparathyroidism (PHPT) is an endocrine disorder caused by excessive parathyroid hormone (PTH) secretion by autonomously functioning parathyroid tissue. It is characterized by hypercalcaemia and an elevated or inappropriately normal PTH serum level.

The clinical presentation of PHPT used to be a symptomatic primarily renal and/or skeletal disease. However, it has evolved over recent decades to be typically asymptomatic, especially in developed countries where serum calcium levels are routinely measured. As a result, the incidence rate of PHPT has increased dramatically since the 1970s[25] and the 1990s heralded a progressive decline in the incidence possibly due to a plateau effect [26]. Nonetheless, a study published from Scotland in 2009 showed that the prevalence of PHPT continued to increase significantly from 1.82 per 1000 in 1997 to 6.72 per 1000 population in 2006 [27].

Gender, age and race differences in the prevalence of PHPT are well documented in the literature. Studies have reported that PHPT is predominantly a disease of middle aged females [28]. Moreover, Yeh et al. reported in 2013 that in a racially mixed population in Southern California race confers significant variability in the incidence and prevalence of PHPT [29]. The prevalence of PHPT was statistically higher amongst blacks (92 women, 46 men) when compared to whites (81 women, 29 men) of a similar age. PHPT in this study was mainly a disease of older black women. Moreover, lower vitamin D levels may have a contributory role in this underlying racial difference due to the resulting stimulation of PTH secretion [30].

Several studies from developing countries [31-34] have reported a different pattern of clinical disease. In 2013 a South African study by Paruk et al. [34] retrospectively analysed records of 28 patients with PHPT at the Inkosi Albert Luthuli Central Hospital in Durban and reported a predominantly symptomatic presentation (93%) consistent with more advanced disease progression at the time of diagnosis. Twenty-one patients complained of bone pain and this was frequently associated with radiological abnormalities (47%). Associated morbidity arose from renal disease, dyspepsia and neurological symptoms. Despite this difference in symptomatology between developing and developed countries, middle aged females remained the most commonly affected group. This study was, however, limited by a small sample size, bias towards a greater morbidity of disease in keeping with tertiary referral centres in South Africa and the lack of preoperative vitamin D levels. Associated vitamin D deficiency confounds disease severity in PHPT [35].

In a much earlier retrospective South African study of 100 patients, a high rate of complicated disease from PHPT was evident [36]. More than half of PHPT patients (57%) had nephrolithiasis, 27% had associated renal dysfunction and 38% bone disease. Furthermore, 20% had peptic ulcer disease and a high rate (23%) of neuropsychiatric symptoms were reported.

PHPT is a biochemical diagnosis and the only curative treatment remains parathyroidectomy – thus the surgical removal of the pathological autonomously functioning parathyroid gland(s) [5, 37]. To aid operative preparation and to allow for a minimally invasive parathyroidectomy (MIP) preoperative localization by imaging is essential [38]. MIP does have numerous advantages, however, bilateral neck exploration with visualization of all four parathyroid glands remains the gold standard for parathyroid surgery [39].

Preoperative localization usually employs the combination of neck ultrasonography with a sestamibi nuclear scan which results in a high sensitivity of parathyroid adenoma detection thereby allowing for a focused neck exploration to remove the abnormal gland [40, 41]. However, this minimally invasive or focused approach is not suitable in all PHPT patients as a single, isolated parathyroid adenoma accounts for only 80-87% of cases. The remaining cases of PHPT are caused by multiglandular disease including double adenomas (2-5%), and multiple gland hyperplasia (6%) [2]; such patients would require bilateral neck exploration to ensure surgical cure. The incidence of hyperplasia has been reported in another study to be slightly higher (10-15%) than aforementioned [42].

Therefore, predicting whether the patient has single- or multigland parathyroid disease is important as it influences the surgeon's preoperative planning in determining which patients are candidates for a minimally invasive approach. Kebebew's group [19] retrospectively analysed preoperative clinical, biochemical and imaging studies of 238 patients to determine single gland versus multigland pathology in PHPT patients. In total 83 patients (35%) had bilateral neck exploration, 103 (43%) had a unilateral neck exploration, and the remaining 52 (22%) patients had focused neck exploration. The corresponding pathology was: 179 (75.2%) had a single adenoma, 51 (21.4%) had asymmetrical four gland hyperplasia and 8 (3.4%) had double adenomas. The curative rate, based on postoperative normo- or hypocalcaemia was 99.2% after follow up for 2 to 3 weeks postoperatively. A single adenoma was significantly associated with higher preoperative calcium (2.8 vs 2.6 mmol/L respectively, $p = 0.03$) and PTH (22 vs 13 pmol/L respectively; $p = 0.04$) levels when compared to multigland hyperplasia. In addition, neck ultrasonography and sestamibi scans were more likely to be positive in single adenomas ($p < 0.001$). The authors concluded that preoperative studies can be used to reliably predict the presence of a single adenoma, thereby allowing for a minimally invasive surgical approach to parathyroidectomy. The preoperative predictors of single gland disease used in a scoring system in this study include: a total serum calcium ≥ 3 mmol/L, PTH level ≥ 2 times normal upper limit, neck ultrasound result positive for a single enlarged parathyroid gland, Sestamibi scan result positive for a single enlarged parathyroid gland, and concordant Sestamibi and ultrasound scan results for one parathyroid gland on the same side of the neck. A score of 3 or more positively predicted single gland disease in 100% of cases.

Recently, McHenry and Shi [13] studied a cohort of 549 patients with PHPT who underwent parathyroidectomy by a single surgeon over a period of more than two decades until 2017. In total

85% of patients had a single adenoma, 8% had a double adenoma, 7% had hyperplasia and 1% had parathyroid carcinoma. Compared to patients with a single adenoma, patients with hyperplasia showed no statistical differences in clinical presentation, preoperative calcium or PTH levels. Nonetheless, patients with hyperplasia were significantly more likely to have negative neck ultrasounds and sestamibi scans ($p < 0.001$) – 91% of patients with hyperplasia vs 2% of patients with adenomas had negative ultrasound and sestamibi scans. Both ultrasound and sestamibi scans were unable to identify multiglandular disease in all patients with hyperplasia. They concluded that preoperative studies are not always reliable in identifying multigland disease.

Parathyroidectomy is associated with cure rates of more than 95% [43]. However, operative failures may occur leading to persistent or recurrent hyperparathyroidism. Persistent hyperparathyroidism is defined as hypercalcaemia occurring within six months of initial operation. Recurrent hyperparathyroidism refers to development of hypercalcaemia after six months of parathyroidectomy. Surgical cure implies normocalcaemia after a six month period. Both persistent and recurrent hyperparathyroidism require re-exploration to remove the autonomously functioning parathyroid tissue which may have been a missed ectopic or supernumerary adenoma, missed multiglandular disease, or an inadequate excision of hyperplastic tissue [44]. Recurrent and persistent hyperparathyroidism carry two main complications. First, the patient is at persistent risk of target organ damage from hypercalcaemia and may continue to be troubled by symptoms. Second, reoperation is more technically challenging for the surgeon and carries a greater risk of operative complications. Missed hyperplastic multiglandular disease has been reported as a cause of operative failure in up to 40% of reoperative cases [45, 46]. This multiglandular pathology was often missed on preoperative imaging [47].

In 2010 Chen's group [48] reviewed 159 patients with persistent and recurrent hyperparathyroidism who underwent reoperation. The study reported that at reoperation 84 (53%) patients had a missed adenoma and 75 (47%) patients had missed multigland hyperplasia. In the same year Lew et al. [49] followed up 723 patients for at least six months after a focused or minimally invasive parathyroidectomy. Intraoperative parathyroid hormone testing was used in all of the operations. At six months after surgery 97.1% of patients were cured biochemically. This high cure rate achieved with a focused surgical approach was attributed to the use of intraoperative PTH monitoring – using this adjunct 33 patients were converted to bilateral neck exploration allowing multigland disease to be recognised and surgically removed.

A commonly observed complication postoperatively is hypocalcaemia. Hypocalcaemia may lead to unpleasant symptoms such as paraesthesias ("pins and needles"). Life threatening hypocalcaemia may result in laryngospasm, tetany and cardiac arrhythmias. Mittendorf et al. [50] reported a 41.6% incidence of hypocalcaemia postoperatively. Two main risk factors for post-operative hypocalcaemia were identified including reoperation and patients undergoing surgery for multigland disease. Patients with multigland disease were more likely to have a lower postoperative calcium level compared to patients with single adenomas (7.95 mg/dl and 8.49 mg/dl respectively, $p = 0.036$).

To conclude, PHPT is a common cause of hypercalcaemia. Cure of PHPT is achieved by surgical excision of all abnormally autonomously functioning parathyroid tissue. Such abnormal tissue may be confined to a single gland or to multiple parathyroid foci. The possibility of multigland disease must always be considered in the perioperative management of a patient with PHPT. Literature has shown that the preoperative assessment of parathyroid pathology based on predictors such as clinical presentation, biochemistry and imaging studies should not always be relied upon, especially in the setting of multiglandular disease. Missed multiglandular parathyroid disease leads to undesirable suboptimal surgical cure rates.

Aims and Objectives

Study Aim

To determine whether single- versus multigland parathyroid disease was accurately predicted preoperatively in patients with PHPT undergoing parathyroidectomy at the WDGMC.

Study objectives

The objectives of this retrospective study on a cohort of patients undergoing parathyroidectomy for PHPT at the WDGMC are to:

1. Determine the incidence of single- versus multigland disease
2. Compare the clinical variation and the preoperative biochemical profile in single- versus multigland PHPT specifically considering serum calcium, PTH and vitamin D levels
3. Determine the radiological description of disease according to neck ultrasound and sestamibi – including the sensitivity and specificity, and predictive values of each imaging modality in determining single- versus multigland disease preoperatively
4. Describe associated thyroid disease – focusing on its possible effect on imaging reliability
5. Describe operative approach (unilateral (focused) or bilateral neck exploration) – based on preoperative assessment of single- or multigland disease; and to review associated intraoperative findings

6. Determine and compare postoperative outcomes, focusing on the incidence of immediate post parathyroidectomy hypocalcaemia, between single- and multigland disease
7. To determine the cure rate (according to six monthly serum calcium levels) between each operative approach.

Methodology

A retrospective non-interventional study will be undertaken on patients with PHPT who underwent parathyroidectomy by a single surgeon (Dr Alan Cairns) at the WDGMC over a period of 14 October 2008 to 18 January 2018. This study will be conducted using an existing REDcap database that the WDGMC research centre has already established on the same cohort of patients. This REDcap database was created for another study titled 'Minimally Invasive Parathyroidectomy for Primary Hyperparathyroidism at the WDGMC,' led by Principal Investigator Dr Stephen Brachmeyer. Ethical clearance was obtained prior to the data collection (clearance certificate number M170826). Permission to do use this database has been obtained from Dr Stephen Brachmeyer (appendix A).

Patients included in this database were sourced from pathology reports of all parathyroid surgical specimens sent to Professor Simon Nayler of the Pathology Practice of Gritzmann and Thatcher. The corresponding patient's files were then obtained from the responsible surgeon. Pathology reports of 283 patients were identified, however, only 252 patient files were retrievable and reviewed to create the Redcap database. The remaining patient files could not be found.

Inclusion criteria for this study protocol include: confirmed biochemical diagnosis of PHPT and patients undergoing first parathyroidectomy. The following patients will be excluded: patients undergoing parathyroidectomy for hyperparathyroidism secondary to renal disease, and patients undergoing a repeat neck exploration for recurrent or persistent hyperparathyroidism. Each patient recorded in the existing REDcap database will be reviewed to establish whether they meet the inclusion criteria or not.

The data that will be collected from the existing database for each eligible patient includes (this is outlined in Appendix B and the complete REDcap Data Dictionary Codebook that will be used is also attached):

- Basic demographic data of age and sex
- Clinical disease of patients with PHPT

- Preoperative biochemical results of serum calcium, PTH and vitamin D
- Preoperative radiological findings according to neck ultrasound and sestamibi scan (including the description of the thyroid gland)
- Intraoperative findings as described in the surgeon's operative notes
- Pathological report of diseased parathyroid tissue excised
- Postoperative serum calcium levels (day one post operatively and at subsequent follow up visits)

Data collection for the existing data base was done by members of the WDGMC research department. No identifying patient details will be analysed. In the Data Dictionary Codebook identifying data is recorded, however, when this data is exported it will be anonymised. Only the primary investigator and members of the WDGMC research department have access to the database.

Data will be then captured in Excel and imported into STATA for statistical analysis. Statistical tests will include standard descriptive statistics, for which categorical variables will be reported using means and standard deviations or medians and ranges as appropriate, and categorical variables will be described using frequencies and proportions. Comparison testing between single gland and multigland disease variants will be conducted using the T-test or Mann-Whitney test for continuous variables (for example, age and biochemistry results) and the Chi-squared test (with Fisher's exact, where appropriate) for categorical variables (such as sex, clinical presentation, imaging and intraoperative findings). Sensitivity and specificity tests as well as predictive values will be done on neck ultrasound and sestamibi findings as preoperative diagnostic tools.

Ethical considerations

Confidentiality will be maintained and no identifying data will be divulged nor exported from the REDcap database. Data will be kept on this secure data base that only the primary investigator and WDGMC co-investigators will have access to. This is a non-interventional study and will not pose any risk of harm to patients included. There is no primary benefit to the cohort of patients studied. There will be no cost to the patients involved nor will there be a payment made to study participants. As mentioned, ethical approval (awarded to the principal investigator – Dr Stephen Brachmeyer, clearance certificate number M170826) for the existing database was obtained prior to data collection, however, this study protocol will be submitted to the Human Research Ethics

Committee (Medical) of the University of the Witwatersrand. Permission to do this study has been obtained from the Chief Executive Officer of the WDGMC (appendix C).

Timeline

	2018					2019			
Month of the Year	**May**	**June**	**July**	**Aug**	**Sept**	**Oct - Jan**	**Feb-May**	**Jun**	**Jul-Sept**
Literature search									
Reading literature									
Summarising literature									
Preparing Protocol									
Protocol Assessment					05/09/18				
Ethics application					07/09/18				
Collecting data									
Data analysis									
Writing up thesis									
Submit: marking									
Writing up paper									

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APPENDIX 2: Data collection sheet

Patient Study Number:	
Parameter	**Result**
Age (years)	
Sex	Female / Male
CLINICAL PRESENTATION	
Renal GIT Neuropsych	Bones Other:
PRE-OPERATIVE *Pre-op biochemistry* Serum Calcium: PTH: Vitamin D: *Pre-op Imaging (including thyroid gland)* USS:	Sestamibi:
INTRA-OPERATIVE **Right superior** • Location • Normal • Abnormal **Right inferior** • Location • Normal • Abnormal	**Left superior** • Location • Normal • Abnormal **Left inferior** • Location • Normal • Abnormal
HISTO-PATHOLOGICAL Gland removed: Location: Size:	Weight:
Histopathology: Adenoma Hyperplasia Carcinoma	
POST-OP Serum Calcium :	PTH:

APPENDIX 3: Ethics Clearance Certificate

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Dr Nicola MacRobert

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M180918

NAME: (Principal Investigator)	Dr Nicola MacRobert
DEPARTMENT:	Surgery Wits Donald Gordon Medical Centre
PROJECT TITLE:	Single gland versus multigland disease in primary hyperparathyroidism at the Wits Donald Gordon Medical Centre in Johannesburg, South Africa
DATE CONSIDERED:	28/09/2018
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Deidre Kruger and Dr Markus Schamm
APPROVED BY:	Dr C Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	05/10/2018

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 301, Third floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed September and will therefore be due in the month of September each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature _____ Date _____

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES