RETROSPECTIVE EVALUATION OF PRE-OPERATIVE IMAGING AND FACTORS AFFECTING LOCALISATION AND SURGICAL OUTCOME IN PRIMARY HYPERPARATHYROIDISM

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DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF SURGERY

UNIVERSITI SAINS MALAYSIA

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Acknowledgement

First and foremost, I would like to express my deepest gratitude to Allah the Almighty for showering me his blessing throughout my research work to complete the research successfully.

I would like to express my greatest appreciation to Associate Professor Dr. Zaidi Bin Zakaria (Head of Department, General Surgery) and my research supervisor Dr. Rosnelifaizur Bin Ramely for the guidance and support. I would also like to extend my appreciation to my co-supervisor Dr. Sadhana Sadar Mahamad, the Department of General Surgery, Breast and Endocrine Unit in Hospital Putrajaya for the advice and allowing me to conduct my study at their centre. Their time and effort are greatly appreciated.

Last but not least, I would like to express my sincere gratitude to my parents and family, my colleagues both in Hospital Universiti Sains Malaysia and Hospital Putrajaya, The Human Research Ethics Committee of USM (JEPeM), the Medical Research and Ethics Committee, Ministry of Health for the direct and indirect contribution to the completion of this study. Without all the mentioned above, none of the work would have come to fruition.

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LIST OF ABBREVIATIONS

IOPTH	Intra-operative parathyroid hormone
FN	False negative
FP	False positive
PHPT	Primary hyperparathyroidism
PPV	Positive predictive value
PTH	Parathyroid hormone
RLN	Recurrent laryngeal nerve
TP	True positive
TN	True negative

Abstrak

Pengenalan: Primary Hyperparathyroidism merupakan satu penyakit endokrin yang selalunya disebabkan oleh *parathyroid adenoma*. Pembedahan fokus dengan bantuan kemajuan pemeriksaan radiologi pra-pembedahan dan prosedur intra-pembedahan dapat memendekkan tempoh operasi dan juga hasil pembedahan. Tujuan penyelidikan ini adalah untuk mengkaji kepekaan *Ultrasonography* dan Pegimbas Sestamibi dalam mencari kedudukan *parathyroid adenoma.*

Metodologi: Data telah dikumpulkan secara retrospektif untuk pesakit yang telah menjalani pembedahan kelenjar parathyroid untuk *primary hyperparathyroidism* dari Januari 2014 hingga Disember 2018 di Hospital Putrajaya, sebuah hospital rujukan penyakit endokrin. Dermografi, data pra-pembedahan, lokasi *parathyroid adenoma* dan hasil pembedahan dicatatkan. Data telah dianalisa untuk mengkaji *sensitivity* dan *specificity* Pengimbas Ultrasonografi and Sestamibi dalam mencari lokasi *parathyroid adenoma* dan factor-faktor yang mempengaruhi penemuan.

Keputusan: Seramai 86 pesakit telah memenuhi kriteria kemasukan dan pengecualian. *Sensitivity* Pengimbas Ultrasonografi untuk menemui adenoma adalah 65% dengan *positive predictive value* (PPV) 89.7% dan ketepatan 60.5%. *Sensitivity* Pengimbas Sestamibi adalah 79.5% dengan PPV 88.6% dan ketepatan 72.1%. Gabungan Pengimbas Ultrasonografi and Sestamibi mempunyai *sensitivity* 90.5% dan PPV 97.4% dengan ketepatan 88.4%. Berat adenoma dan tahap hormon parathyroid (PTH) pra-pembedahan tidak mempengaruhi penemuan adenoma menggunakan Pengimbas Sestamibi, tetapi adenoma yang lebih berat dan tahap PTH pra-pembedahan mempunyai pengaruh terhadap penemuan adenoma (p=0.021).

Kesimpulan: Gabungan pengimbasan membantu menaikkan *sensitivity* penemuan adenoma parathyroid. Adenoma yang lebih berat dan tahap PTH lebih tinggi mempengaruhi penemuan adenoma menggunakan Pengimbas Ultrasonografi tetapi tidak untuk Pengimbas Sestamibi.

Kata kunci: hyperparathyroidisma primer, Ultrasonografi, Pengimbas Sestamibi

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ABSTRACT

Introduction: Primary hyperparathyroidism is an endocrine disease that is most commonly caused by parathyroid adenoma. Focused surgery with the aid of the advancement of pre-operative localisation together with intro-operative adjuncts allows shorter operative time and improve surgical outcome. This study aims to evaluate the sensitivity of ultrasonography and Sestamibi scan for correct localisation of parathyroid adenoma.

Methods: Data were retrospectively collected for patients that underwent parathyroidectomy for primary hyperparathyroidism between January 2014 to December 2018 in Hospital Putrajaya, a single high-volume endocrine centre. Patient included underwent both ultrasonography and Tc-Sestamibi scan. Demographics, pre-operative data, intra-operative gland location and surgical outcome were recorded. Data were analysed to assess the sensitivity and specificity of ultrasonography and Tc-Sestamibi scan for localising parathyroid adenoma as well as factors and that influences correct detection.

Results: 86 patients fulfilled the inclusion and exclusion criteria. The sensitivity of ultrasound to detect adenoma was 65% with positive predictive value (PPV) and accuracy of 89.7% and 60.5% accuracy. Sestamibi scan had a sensitivity of 79.5% with PPV and accuracy of 88.6% and 72.1% respectively. Combining scan showed a sensitivity and PPV of 90.5% and 97.4% respectively with an accuracy of 88.4%. Adenoma weight and

pre-operative PTH levels have no association of detectability by Sestamibi scan however on ultrasound, heavier adenomas and higher PTH levels influence detectability (p=0.021)

Conclusion: Dual modality of pre-operative localisation increases the sensitivity of parathyroid adenoma detection. Heavier adenomas and higher pre-operative PTH levels influence detection by ultrasound however has no influence on detectability by Sestamibi scan.

Keyword: Primary hyperparathyroidism, Ultrasonography, Sestamibi Scan

CHAPTER 1:
INTRODUCTION

Primary hyperparathyroidism is an endocrine disease that is most commonly caused by parathyroid adenoma. Autonomous hypersecretion of parathyroid hormone (PTH) from one or more parathyroid gland causes hypercalcaemia and may present as incidental findings of raised serum calcium or by symptoms clinically. Symptoms associated with hypercalcaemia include constipation, renal calculi and bony pain. Diagnosis of primary hyperparathyroidism is made by raised serum calcium with an inappropriately high serum PTH. (Clarke, 2013)

Commonly 1 out of the 4 parathyroid glands would have hypersecretion of PTH from the parathyroid adenoma. Surgical excision of parathyroid adenoma remains the mainstay management of primary hyperparathyroidism resulting in long term cure and reversal of symptoms. Bilateral neck exploration was the traditional approach, allowing visualisation of all parathyroid glands and removing one or more grossly enlarged glands. (Fraser et al., 2009)

However with the advancement of pre-operative localisation using either ultrasound, CT scan or parathyroid scintigraphy such as Sestamibi scans, together with the utilisation of intra-operative PTH (IOPTH) monitoring, unilateral approach is feasible and would reduce operative time and complications involved such as post-operative hypocalcaemia and risk of recurrent laryngeal nerve injury. Focused surgery with the guidance of IOPTH allows the surgeon to confirm removal of hypersecreting parathyroid glands and predict operative success. (Fraser et al., 2009)

Literature review done found limited data regarding the accuracy of pre-operative localisation in Malaysia or Asian region. Purpose of this study is to assess the pre-

operative localisation of parathyroid adenoma as well as surgical outcome in Malaysia, based on a single high-volume endocrine centre.

Literature review

Literature review done showed scarce studies on use of ultrasound and parathyroid scintigraphy for pre-operative localisation of parathyroid adenoma in the Malaysia or Asian region. A retrospective study done by *Borumandi et al* published in the British Journal of Oral and Maxillofacial Surgery in 2019 investigated factors that improve the detectability and surgical outcome of parathyroidectomy in primary hyperparathyroidism. In 117 patients that were included, the study showed the sensitivity of ultrasound and Sestamibi scan for detecting parathyroid adenoma were 80% and 92% respectively. Regarding the influence on detectability, it was noted that pre-operative Parathyroid hormone (PTH) had no significant influence in detectability, however heavier glands were detected more accurately by Sestamibi scans. (Borumandi et al., 2019)

In another study published by European Journal of Endocrinology in 2015 by *Guerin et al*, they found Scintigraphy Sestamibi scan had a sensitivity of 93.3% for detecting parathyroid adenoma versus 84.4% by ultrasonography. They noted Sestamibi scan were superior to ultrasonography specifically in adenomas that were in posterior locations due to ectopia and in cases where patients previously underwent thyroidectomy which could cause difficulty in image interpretations. (Guerin et al., 2015)

The American Journal of Surgery published a study in 2018 by *Asseeva P et al* on the value of Sestamibi scintigraphy in directing focused or minimally invasive parathyroidectomy in primary hyperparathyroidism. 90 patients were included and had both ultrasound and Parathyroid Scintigraphy and reported as uniglandular,

multiglandular or negative and was compared to intra-operative findings. The sensitivity of accurate detection of parathyroid adenoma in ultrasound and Scintigraphy Sestamibi scan were 91.7% and 93.1% respectively. They noted that a concordance between ultrasonography and scintigraphy has the highest specificity for directing focused surgery, as opposed to ultrasonography alone. (Asseeva et al., 2019)

Another study published in the European Annals of Otorhinolaryngology, Head and Neck diseases in 2020 by C. de Maissin et al evaluated the performance of ultrasonography and 99mTc-sestamibi scintigraphy in primary hyperparathyroidism. In their study, 273 patients were retrospectively reviewed between January 2008 to November 2017 who underwent both ultrasonography and Tc-Sestamibi scan and noted a 81% sensitivity when used together for parathyroid adenoma localisation with a 96% positive predictive value. (de Maissin et al., 2020)

The advancement of pre-operative localisation with the use of intra-operative parathyroid hormone monitoring (IOPTH) as an adjunct has shifted the practice of bilateral neck exploration towards a more minimally invasive procedure. This has benefited in terms of patient safety as well as increasing success rate. Parathyroid hormone having a short half-life of around 5 minutes would be a good marker for correct removal of parathyroid adenoma as the levels would significantly drop following removal. *Patel K et al* published an article in Surgical Oncology Clinics of North America comparing different criteria and protocols used for IOPTH monitoring including Miami criterion, Halle Criterion, Rome as well as Vienna Criterion. It was noted that the Miami Criterion was a simple but highly sensitive and specific criteria using the decay of PTH levels of > 50% from highest baseline within 10 minutes of removal of the parathyroid adenoma. The sensitivity and specificity of Miami criteria were 98% and 94% respectively, thus was used as the criteria for my study. (Patel et al., 2016)

Study aim and rationale

Traditionally, primary hyperparathyroidism secondary to parathyroid adenoma was managed by surgically exploring bilateral neck and individually examining all 4 parathyroid glands, subsequently excising the most abnormal looking gland. This approach increases the risk for intra-operative and post-operative complications such as bleeding and injury to surrounding structures, mainly recurrent laryngeal nerve. This also increases the risk of inadvertently resecting a normal parathyroid gland, as well as longer operative time. A more focus approach would reduce all these risks, subsequently benefiting patient with smaller incision, shorter anaesthesia period, faster recovery and ultimately better surgical outcome.

The aim of this study is to assess the sensitivity and specificity of pre-operative localisation of parathyroid adenoma as well as surgical outcome, based on data from a single high-volume endocrine centre in Malaysia. With advancement of pre-operative localisation of parathyroid adenoma, a more focused approach could be offered, giving way to a more minimally invasive surgery. Parathyroid glands are small glands that may be difficult to distinguish from surrounding tissue, mimicking thyroid nodule or lymph node especially to the less experienced surgeons. With its location closely related to the recurrent laryngeal nerve, bilateral neck exploration would increase the risk of nerve injury. Both patient and surgeons would benefit from this approach with accurate pre-operative localisation to guide exploration

CHAPTER 2:

STUDY PROTOCOL

2.1 Document submitted for ethical approval

RESEARCH PROPOSAL FOR MEDICAL AND HEALTH SCIENCES

Research title

Retrospective evaluation of pre-operative imaging and factors affecting localisation and surgical outcome in primary hyperparathyroidism

Principal investigator:

Dr. Shahrul Fariz Bin Ramli (MMC no. 53903)

Institution: Universiti Sains Malaysia

Co-researcher:

Dr. Rosnelifaizur Bin Ramely (MMC no. 39506)

Institution: Universiti Sains Malaysia

Dr. Sadhana Sadar Mahamad (MMC no. 37629)

Institution: Hospital Putrajaya

Sponsorship: Self sponsor

Introduction

Primary hyperparathyroidism is an endocrine disease that is most commonly caused by parathyroid adenoma. Autonomous hypersecretion of parathyroid hormone (PTH) from one or more parathyroid gland causes hypercalcaemia and may present as incidental findings of raised serum calcium or by symptoms clinically. Diagnosis of primary hyperparathyroidism is made by raised serum calcium with an inappropriately high serum PTH. (Clarke, 2013)

Commonly 1 out of the 4 parathyroid glands would have hypersecretion of PTH from the parathyroid adenoma. Surgical excision of parathyroid adenoma remains the mainstay management of primary hyperparathyroidism resulting in long term cure and reversal of symptoms. Bilateral neck exploration was the traditional approach, allowing visualisation of all parathyroid glands and removing one or more grossly enlarged glands. (Fraser et al., 2009)

However with the advancement of pre-operative localisation using either ultrasound, CT scan or parathyroid scintigraphy such as Sestamibi scans, together with the utilisation of intra-operative PTH (IOPTH) monitoring, unilateral approach is feasible and would reduce operative time and complications involved such as post-operative hypocalcaemia and risk of recurrent laryngeal nerve injury. Focused surgery with guidance of IOPTH allows surgeon to confirm removal of hypersecreting parathyroid glands and predict operative success. (Fraser et al., 2009)

Literature review done found limited data regarding the accuracy of pre-operative localisation in Malaysia or Asian region. Purpose of this study is to assess the pre-operative localisation of parathyroid adenoma as well as surgical outcome in Malaysia, based on a single high-volume endocrine centre.

Problem statement & study rationale

Why are you conducting this study?

Traditionally, primary hyperparathyroidism secondary to parathyroid adenoma was managed by surgically exploring bilateral neck and individually examining all 4 parathyroid glands, subsequently excising the most abnormal looking gland. This approach increases the risk for intra-operative and post-operative complications such as bleeding and injury to surrounding structures, mainly recurrent laryngeal nerve. This also increases the risk of inadvertently resecting a normal parathyroid gland, as well as longer operative time. A more focus approach would reduce all these risks, subsequently benefiting patient with smaller incision, shorter anaesthesia period, faster recovery and ultimately better surgical outcome.

The aim of this study is to assess the sensitivity and specificity of pre-operative localisation of parathyroid adenoma as well as surgical outcome, based on data from a single high-volume endocrine centre in Malaysia.

What is the importance of your study findings?

With advancement of pre-operative localisation of parathyroid adenoma, a more focused approach could be offered, giving way to a more minimally invasive surgery. Parathyroid glands are small glands that may be difficult to distinguish from surrounding tissue, mimicking thyroid nodule or lymph node especially to the less experienced surgeons. With its location closely related to the recurrent laryngeal nerve, bilateral neck exploration would increase the risk of nerve injury. Both patient and surgeons would benefit from this approach with accurate pre-operative localisation to guide exploration.

Research Question(s)

What are the questions that you derived based on your problem statement that you would like to answer with this study?

1. Does pre-operative localisation with dual modality (Ultrasound and Sestamibi Scan) increases the detectability of parathyroid adenoma?
2. Does serum PTH levels or weight of the parathyroid gland influence the detectability of parathyroid adenoma pre-operatively?

Objective

Primary:

1. To review the accurate detection of pre-operative localisation of parathyroid adenoma using both Ultrasound and Sestamibi Scan versus intra-operative findings

Secondary:

1. To evaluate associations between the weight of the parathyroid adenoma gland and accurate detectability of parathyroid adenoma pre-operatively
2. To evaluate association between PTH levels and the accurate detectability of parathyroid adenoma pre-operatively
3. To review the post-operative outcomes regarding PTH level reductions, maintenance of normal calcium post operatively, proportion of recurrent laryngeal nerve (RLN) injury in bilateral neck exploration versus focused neck exploration and length of hospital stay
4. To review the number of patients that utilise IOPTH monitoring

Literature review

Literature review done showed scarce studies on use of ultrasound and parathyroid scintigraphy for pre-operative localisation of parathyroid adenoma in the Malaysia or Asian region. A retrospective study done by *Borumandi et al* published in the British Journal of Oral and Maxillofacial Surgery in 2019 investigated factors that improve the detectability and surgical outcome of parathyroidectomy in primary hyperparathyroidism. In 117 patients that were included, the study showed the sensitivity of ultrasound and Sestamibi scan for detecting parathyroid adenoma were 80% and 92% respectively. Regarding the influence on detectability, it was noted that pre-operative Parathyroid hormone (PTH) had no significant influence in detectability, however heavier glands were detected more accurately by Sestamibi scans. (Borumandi et al., 2019)

In another study published by European Journal of Endocrinology in 2015 by *Guerin et al*, they found Scintigraphy Sestamibi scan had a sensitivity of 93.3% for detecting parathyroid adenoma versus 84.4% by ultrasonography. They noted Sestamibi scan were superior to ultrasonography specifically in adenomas that were in posterior locations due to ectopia and in cases where patients previously underwent thyroidectomy which could cause difficulty in image interpretations. (Guerin et al., 2015)

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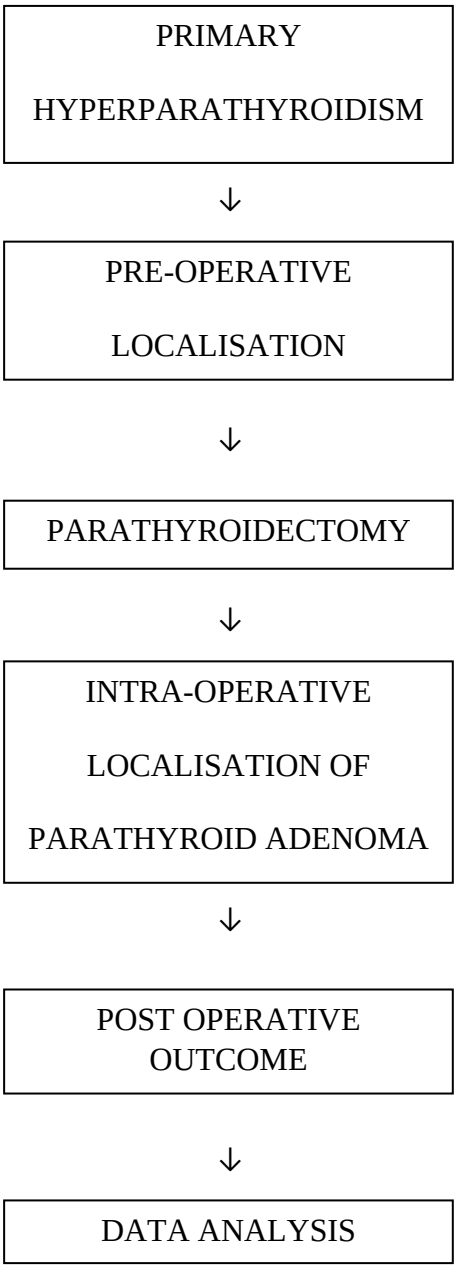
scan were 91.7% and 93.1% respectively. They noted that a concordance between ultrasonography and scintigraphy has the highest specificity for directing focused surgery, as opposed to ultrasonography alone. (Asseeva et al., 2019)

The advancement of pre-operative localisation with the use of intra-operative parathyroid hormone monitoring (IOPTH) as an adjunct has shifted the practice of bilateral neck exploration towards a more minimally invasive procedure. This has benefited in terms of patient safety as well as increasing success rate. Parathyroid hormone having a short half-life of around 5 minutes would be a good marker for correct removal of parathyroid adenoma as the levels would significantly drop following removal.

In my study, were available, IOPTH monitoring was used to further aid in confirming the correct parathyroid gland to increase surgical success rate as well to minimise unnecessary contralateral neck exploration. Many studies have been done to compare the criteria and protocol to be used. *Patel K et al* published an article in Surgical Oncology Clinics of North America comparing different criteria and protocols used for IOPTH monitoring including Miami criterion, Halle Criterion, Rome as well as Vienna Criterion. It was noted that the Miami Criterion was a simple but highly sensitive and specific criteria using the decay of PTH levels of > 50% from highest baseline within 10 minutes of removal of the parathyroid adenoma. The sensitivity and specificity of Miami criteria were 98% and 94% respectively, thus was used as the criteria for my study. (de Maissin et al., 2020)

Conceptional framework



Research design

This is a retrospective study to assess the accuracy of pre-operative localisation of parathyroid adenoma using both Ultrasound and Sestamibi Scan in patients who underwent parathyroidectomy for primary hyperthyroidism in Hospital Putrajaya.

Study area

Data collection will be done at Hospital Putrajaya as a tertiary endocrine referral centre with high volumes of thyroid, parathyroid and adrenal cases.

Study population

Participants involved are patients who underwent parathyroidectomy for primary hyperparathyroidism in Hospital Putrajaya between January 2014 and December 2018 that fulfil the inclusion and exclusion criteria.

Subject criteria

Inclusion criteria

1. Patients presented with primary hyperparathyroidism who underwent parathyroidectomy (focused or bilateral neck exploration)
2. Pre-operative imaging done for localisation of parathyroid adenoma with both Ultrasound and Sestamibi Scan

Exclusion criteria

1. Secondary / tertiary hyperparathyroidism
2. Parathyroid carcinoma

3. Multiple Endocrine Neoplasia (MEN)
4. Recurrent disease
5. Concurrent thyroid surgery
6. Multi-gland adenoma
7. Incomplete data

Sample size estimation

Sample size for this study was determined by using two proportion formula based on primary objective as this will be the main focus for this study. The total samples in which the corrected samples obtained after included the 10% drop out rate [Total sample size = calculated sample size + (0.2xcalculated sample size)]. The detail calculation and output from PS Power and Sample Size Calculations Version 3.0 software is as follows;

Based on primary objective: to determine the accurate detection of pre-operative localisation of parathyroid adenoma versus intra-operative findings.

P0: proportion of patients detected intra-operative localisation of parathyroid adenoma = 0.41 (expert opinion)

P1: proportion of patients detected pre-operative localisation of parathyroid adenoma (by Sestamibi) = 0.72 (Borumandi.F et al, 2019)

Corrected sample size, n=(39x2) + 10% dropout

$$= 78 + 8 = 86$$

Thus, the total samples required in this study will be 86 patients

Research tool

Data of patients who underwent parathyroidectomy will be collected directly from 'Operating Theatre' book census. Further data regarding patient's background history, pre-operative investigations as well as post-operative follow up will be taken from FISIEN, a computerised database from Hospital Putrajaya.

Data collection method

Data will be retrospectively collected on patients who underwent parathyroidectomy for primary hyperparathyroidism between January 2014 and December 2018 in a single endocrine centre. Pre-operative data that include symptoms, serum calcium, serum PTH and vitamin D levels as well as imaging for pre-operative localisations documented. Localisation of parathyroid adenoma is done using both ultrasound and Sestamibi Scan. Patients with clear localisation of parathyroid adenoma (both Ultrasound and Sestamibi Scan show similar results) underwent focused unilateral neck exploration while patients with discordance in adenoma localisations proceeded with bilateral neck exploration. Comparison made between pre-operative localisation and intra-operative findings with adjunct use of intra-operative PTH monitoring (where available) to further aid detection of the hyperfunctioning parathyroid adenoma.

Where available, intra-operative PTH (IOPTH) monitoring will be used, using the *Modified Miami Criteria* (decay ≥50% from highest baseline within 10 minutes after resection). When there is no drop or does not fulfil the criteria, further neck exploration done and test repeated. Location of parathyroid adenoma recorded and compared with pre-operative localisations.

Patients were followed up for a minimum of 6 months and post-operative calcium levels recorded. Indirect laryngoscopy was done in all patients pre-operatively, however only done post-operatively to assess recurrent laryngeal nerve injury in patients who were suspected clinically (presented with post-operative hoarseness of voice or dysphagia).

Handling privacy & confidentiality issue

Data will be collected using a proforma sheet and will be stored in a personal computer which only the Primary Investigator has access to. Data will be kept for a period of two years after completion and submission before personally disposing the data.

No personal information of subjects will be disclosed in the event of any future publication, and relevant permission (Director General of Health, Malaysia) would be obtained prior to publication.

Data collection proforma

Patient ID:		**Age:**	
Race:		**Sex:**	Male/Female
Type of Surgery:	○ Focused ○ BE	**Date of Surgery:**	-- /--/---- (dd/mm/yyyy)
PREOPERATIVE			
Symptoms:	○ Asymptomatic ○ Symptomatic: Specify:	**Blood investigations:**	○ Calcium: ○ PTH: ○ PO_4: ○ Vitamin D:
Imaging:	○ Ultrasound :		
	○ Sestamibi :		
	○ CT :		
	○ Others :		
Clear Localization:	○ Yes ○ No		

INTRAOPERATIVE			
Specimen weight : _____ g Operation time : _____ mins Gland location : _____	**IOPTH:** **(where available)**	Induction	
		Identification of gland	
		10 mins post excision	
		20 mins post excision	

POSTOPERATIVE				
Length of hospital stay: _____ days				
Calcium Level	o Day 1 post op		**Recurrent Laryngeal Nerve Injury**:	o Yes o No
	o 3 months			
	o 6 months			

Operational definition

Focused surgery: only 1 side of the neck explored

Bilateral neck exploration: both side of neck explored

Clear localisation: both ultrasonography and Sestamibi scan showing adenoma on same side of neck

Length of stay: post-operative length of stay

Surgical outcome:

1. Correct localisation of parathyroid adenoma
2. Normalisation of serum calcium levels
3. Number of cases with recurrent laryngeal nerve injury

Community benefits

1. With the advancement of pre-operative imaging to localise parathyroid adenoma, a more focused and minimally invasive surgery could be offered to patients, thus reducing the risk and complications of neck exploration
2. Correct pre-operative localisation would increase the success rate of surgery, reducing risk of re-operation and re-exploration due to incomplete excision or incorrectly identifying the parathyroid adenoma
3. Any evidence of increased success rate of surgery due to high detection rate by dual modality may influence the guidelines to recommend the use of both ultrasound and Sestamibi scan as standard care, ultimately benefiting the patients

Declaration of conflict of interest

There is no conflict of interest

Ethical consideration and approval

I will adhere to the principles of the Declaration of Helsinki and the Malaysian Good Clinical Practice Guidelines while carrying out this research.

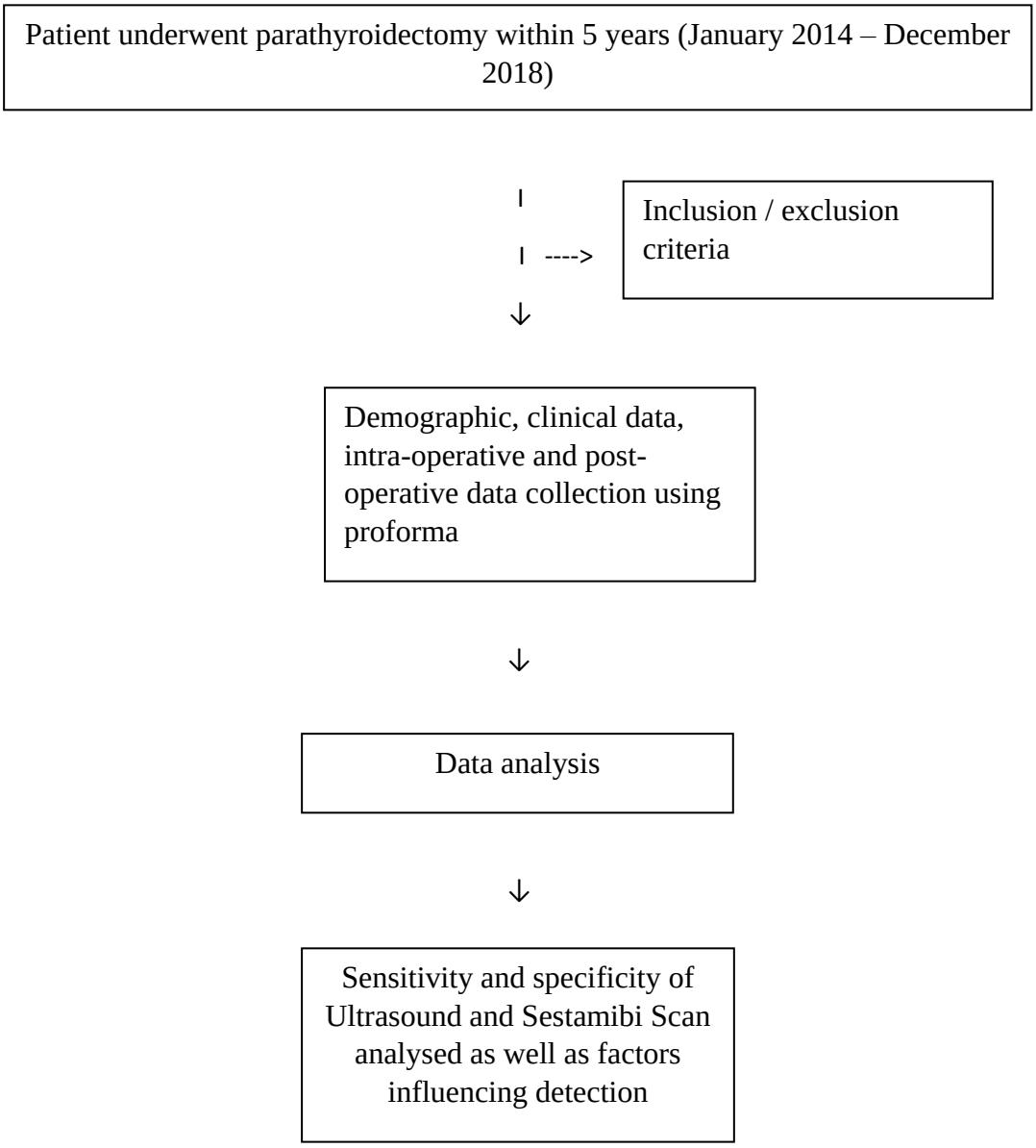
Ethical approval would be obtained from MREC, as well as from JEPEM (Jawatankuasa Etika Penyelidikan Manusia USM).

Approval from JEPEM is currently still pending.

Data analysis

Data analysis will be done using SPSS version 23.0 software. Based on the objective, chi square test will be used to determine the accuracy of pre-operative localisation of parathyroid adenoma versus intra-operative findings. While Independent t-test will be used to determine the association of parathyroid gland weight and PTH levels with the detectability of parathyroid adenoma respectively. Multiple regression will be used for determining post-operative outcomes including PTH level reduction, maintenance of normal serum calcium levels, proportion of recurrent laryngeal nerve (RLN) injury in bilateral neck exploration versus focused approach and length of hospital stay post-operatively.

Study Flowchart



Gantt chart

Date / Activities	2019				2020										
Month	S	O	N	D	J	F	M	A	M	J	J	A	S	O	N
Proposal presentation															
Ethics approval															
Data collection															
Data analysis and report presentation															
Submission of draft and revision															
Submission of final research															

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2.2 Ethical approval letters

Jawatankuasa Etika
Penyelidikan Manusia USM (JEPeM)

Human Research Ethics Committee USM (HREC)

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7th September 2020

Dr. Shahrul Fariz Ramli
Department of Surgery
School of Medical Sciences
Universiti Sains Malaysia
16150 Kubang Kerian, Kelantan.

JEPeM Code : USM/JEPeM/20050284
Protocol Title : Retrospective Evaluation of Pre-Operative Imaging and Factors Affecting Localisation and Surgical Outcome in Primary Hyperparathyroidism.

Dear Dr.,

We wish to inform you that your study protocol has been reviewed and is hereby granted approval for implementation by the Jawatankuasa Etika Penyelidikan Manusia Universiti Sains Malaysia (JEPeM-USM). Your study has been assigned study protocol code **USM/JEPeM/20050284**, which should be used for all communications to JEPeM-USM in relation to this study. This ethical approval is valid from **7th September 2020** until **6th September 2021.**

Study Site: Hospital Putrajaya.

The following researchers are also involved in this study:

1. Dr. Rosnelifaizur Ramely
2. Dr. Sadhana Sadar Mahamad

The following documents have been approved for use in the study.

1. Research Proposal

In addition to the above mentioned document, the following technical documents were included in the review on which this approval was based:

1. Data Collection Proforma

While the study is in progress, we request you to submit to us the following documents:

1. Application for renewal of ethical approval 60 days before the expiration date of this approval through submission of **JEPeM-USM FORM 3(B) 2019: Continuing Review Application Form.**
2. Any changes in the protocol, especially those that may adversely affect the safety of the participants during the conduct of the trial including changes in personnel, must be submitted or reported using **JEPeM-USM FORM 3(A) 2019: Study Protocol Amendment Submission Form.**
3. Revisions in the informed consent form using the **JEPeM-USM FORM 3(A) 2019: Study Protocol Amendment Submission Form.**
4. Reports of adverse events including from other study sites (national, international) using the **JEPeM-USM FORM 3(G) 2019: Adverse Events Report.**
5. Notice of early termination of the study and reasons for such using **JEPeM-USM FORM 3(E) 2019.**
6. Any event which may have ethical significance.

7. Any information which is needed by the JEPeM-USM to do ongoing review.
8. Notice of time of completion of the study using **JEPeM-USM FORM 3(C) 2019: Final Report Form.**

Please note that forms may be downloaded from the JEPeM-USM website: **www.jepem.kk.usm.my**

JEPeM-USM is in compliance with the Declaration of Helsinki, International Conference on Harmonization (ICH) Guidelines, Good Clinical Practice (GCP) Standards, Council for International Organizations of Medical Sciences (CIOMS) Guidelines, World Health Organization (WHO) Standards and Operational Guidance for Ethics Review of Health-Related Research and Surveying and Evaluating Ethical Review Practices, EC/IRB Standard Operating Procedures (SOPs), and Local Regulations and Standards in Ethical Review.

Thank you.