

A Retrospective Review of Imaging and Operative Modalities Performed in Patients with Primary Hyperparathyroidism at a Mid-Volume Surgical Centre in Southeast Asia

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Abstract

Introduction: A paradigm shift appears to have occurred worldwide in surgery for primary hyperparathyroidism with the advent of sensitive preoperative imaging techniques. Preoperative imaging for parathyroid adenoma localisation was not found to be useful in a study conducted in Singapore in the 1990s. This study aimed to explore what the change has been in preoperative localisation tools compared to the previous study and if the ability of these tools to correctly localise pathologic parathyroid glands has improved. **Materials and Methods:** A retrospective review of patients who had surgery for primary hyperparathyroidism at our institution during the period 2005 to 2014 was carried out. Individuals with positive, as opposed to those with negative preoperative imaging, were compared with regard to whether they underwent limited focal or bilateral neck exploration. Length of hospital stay (LOHS) was also compared between patients who underwent limited versus bilateral exploration. **Results:** Fifty-eight patients who had preoperative imaging and surgery were evaluated. True positive rates of sestamibi, ultrasound and 4-dimensional (4D) computed tomography (CT) scans were 63.8%, 72.4% and 90%, respectively. Eighty percent of patients who had positive localisation had limited exploration. LOHS was 2.8 days (1.6, 4.8) and 4.3 days (2.1, 9.0) for limited and bilateral exploration respectively, $P = 0.011$. **Conclusion:** Our study highlights the marked change in the surgical landscape for primary hyperparathyroidism in the last 2 decades in Singapore. Improved preoperative localisation has resulted in a swing from predominantly bilateral, to limited exploration in almost all cases of primary hyperparathyroidism due to solitary adenoma. LOHS was significantly shorter in patients who had limited as compared to those who had bilateral exploration.

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Introduction

Primary hyperparathyroidism is a common cause of hypercalcaemia, particularly in the ambulatory setting with an estimated prevalence of 1 to 4 cases per 1000 persons.¹⁻³

The clinical and laboratory diagnosis of primary hyperparathyroidism is well established in the presence of elevated serum calcium paired with increased serum parathyroid hormone (PTH) and the current definitive treatment of choice for the condition is surgery. Most surgical data suggest a cure rate of 95% to 98% in experienced hands with low complication rates.⁴⁻⁶ The landscape of

surgery for primary hyperparathyroidism has changed significantly in the last 2 decades with the advent of sensitive imaging techniques. The operative strategies have become increasingly disparate and the technical terms describing parathyroid operations also differ. Though an assortment of diverse parathyroidectomy procedures are often described as “minimally invasive”, the precise surgical technique that qualifies for the term is controversial.⁷ In general, limited exploration (LE) surgeries may include focal exploration which involves examination and excision of 1 parathyroid gland only or a unilateral exploration that examines the 2

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parathyroid glands located on one side of the neck. Bilateral exploration (BE) examines all 4 parathyroid glands.⁸ Though the outcome of a preoperative localisation procedure generally does not influence the decision to operate but simply directs whether to perform a BE or a LE, an ongoing debate has centred on the optimal preoperative localisation method to be employed to identify the adenomatous gland(s).

Preoperative imaging to localise parathyroid glands before intended surgery was not found to be useful in a study conducted 15 years ago at our institution, a large tertiary teaching hospital.⁹ The study had included patients with primary as well as tertiary hyperparathyroidism. Preoperative localisation in patients with primary hyperparathyroidism in that study conducted during 1990 to 1996, was correct only in 2 of 11 patients by ultrasound (US) scan, 6 of 15 patients by Technetium (99mTc) sestamibi (MIBI) scintigraphy and 12 of 29 patients by computed tomography (CT). These less than satisfactory rates were reflected in the then prevailing practice of bilateral neck exploration surgery in all patients.

Advances in imaging modalities along with changes in institutional practices with respect to diagnostic workup for primary hyperparathyroidism in the last 2 decades and a shift towards minimally invasive surgery have resulted in a greater reliance on preoperative imaging and localisation.¹⁰ The ability of preoperative localisation methods to correctly identify pathologic parathyroid glands has been very variable depending on the patient population studied (single adenoma versus multiple gland disease), technique employed (MIBI vs US or CT) and experience of the operator and centre, with sensitivities ranging from 34% to 100% in published studies.¹¹ Sensitivity of US has been shown to range from 48.3% to 96.2%, and for MIBI scintigraphy from 61.4% to 94%.¹² Four-dimensional (4D)-CT is a relatively new multiphase imaging modality in which the first 3 “dimensions” are multiplanar CT axial acquisitions with coronal and sagittal reformations. The fourth “dimension” of 4D-CT is change in enhancement over time in non-contrast enhanced, arterial, and delayed (venous) phase imaging. 4D-CT has been reported to be more sensitive than sonography and scintigraphy for preoperative localisation of parathyroid adenomas.¹³

Tertiary hyperparathyroidism has the same biochemical characteristics as primary hyperparathyroidism. However, unlike primary hyperparathyroidism which is mostly due to a single adenoma and which would benefit from limited explorative or minimally invasive surgery, tertiary hyperparathyroidism usually has a preceding long standing secondary hyperparathyroidism phase, most often occurring in the setting of end-stage renal failure and is almost always due to multiple gland hyperplasia. Open surgery is thus required for all patients with tertiary hyperparathyroidism

and thus, the value of preoperative imaging in it is limited.

The primary aim of our study was to understand whether there has been a change in preoperative localisation tools used for primary hyperparathyroidism in Singapore compared to 2 decades ago and to assess the extent to which the ability of these imaging tools to correctly localise pathologic parathyroid glands has improved. Our secondary aim was to explore whether there was a difference in surgical approach employed when imaging was positive with either US scan, MIBI scintigraphy or 4D-CT as compared to when it was negative and to see whether there was a difference in the length of postoperative hospitalisation stay between the patients who underwent either of the 2 surgeries viz limited focal versus BE. We also evaluated the biochemical cure rate achieved with either of the 2 operative modalities.

Materials and Methods

The study was done with prior ethics approval from the Centralised Institutional Review Board of our institution (CIRB 2014/480/C) and in accordance with Good Clinical Practice and the World Medical Association’s Declaration of Helsinki. The CIRB approval included a waiver of informed consent.

Patients who had parathyroidectomy during the period 2005 to 2014 were identified from the surgical archives of our institution. Only those patients with confirmed primary hyperparathyroidism (as diagnosed by preoperative serum calcium levels more than the upper range of normal at our laboratory with a concomitant elevated or inappropriately normal PTH level, and calculated fractional excretion of calcium in the urine of more than 1%) were included in the analysis. Patients with secondary and tertiary hyperparathyroidism were excluded for the reasons explained above. Since the general practice at our institution (as is elsewhere in Singapore) is to perform subtotal/total parathyroidectomy for patients with multiple endocrine neoplasia (MEN) irrespective of preoperative imaging findings, those with MEN as well as those who did not have preoperative localisation imaging were excluded. This resulted in 58 patients who could be analysed (Fig. 1).

Case records and operative notes were reviewed to obtain information about the imaging modality performed, duration between initial biochemical diagnosis and the surgery, and the type of parathyroid surgery performed (LE vs BE). A MIBI scan with US scan was denoted as primary imaging. 4D-CT was considered as secondary imaging. Imaging was considered positive when findings that were in line with established characteristics for parathyroid adenomas on US scan, MIBI scan or 4D-CT were clearly seen and reported.¹⁴⁻¹⁶ Imaging was considered concordant when both MIBI scan and sonography showed evidence of parathyroid adenoma

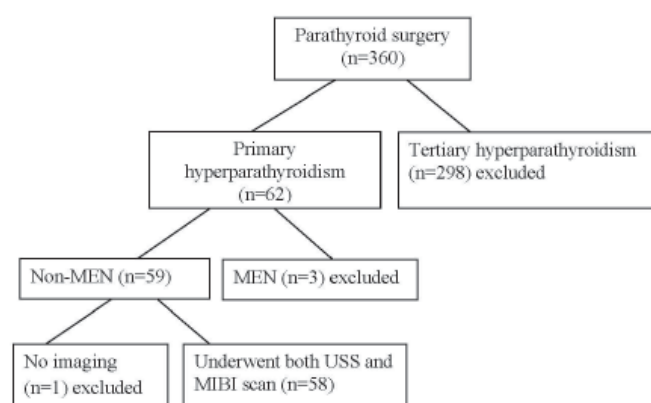


Fig. 1. Enumeration of patients.

and denoted as discordant when there was evidence of it by 1 modality and not by the other. The ability of preoperative localisation imaging in identifying pathological parathyroid gland(s) was evaluated by examining postoperative pathology reports with true positivity defined as congruent findings on imaging (identification of adenoma on US scan, MIBI scan or 4D-CT) and histopathology.

The impact of positive versus negative imaging was evaluated with regards to the type of surgery that was subsequently performed i.e. LE versus BE. Time interval from the identification of hypercalcaemia to surgery was compared between patients who had positive versus those who had negative primary imaging.

Biochemical cure rate was defined as normocalcaemia at 6-months postoperatively. Inpatient and outpatient notes were reviewed in order to calculate the length of hospital stay (LOHS) and the proportion of patients who achieved biochemical cure.

Statistical analysis was performed using IBM® SPSS® version 21. Parametric variables were expressed in mean $\pm$ standard deviation (SD). Non-parametric variables were expressed in median (25th to 75th percentile). The independent samples t-test was used in all the comparisons that were performed on parametric data and had *P* values generated. Skewness and kurtosis were explored using histograms. Skewness and/or kurtosis that is more than ± 1 suggests a non-normality in distribution. This non-normality was evident in the time interval from the identification of hypercalcaemia to surgery as well as the length of postoperative hospitalisation stay. Hence, log-transformation of these values was performed to convert them to a normal distribution before utilising parametric statistics viz independent samples t-test to ascertain the differences between groups.

Results

Descriptive statistics of the patient population and their biochemical parameters are provided in Table 1.

The standard practice at our institution in the last decade has been to perform concomitant MIBI scintigraphy and US scanning in all patients who are referred for parathyroid imaging for primary hyperparathyroidism. Patients in whom primary (initial) imaging (MIBI and US scans) failed to localise a pathologic parathyroid gland(s) or those in whom it is deemed necessary to clarify the findings of primary imaging are offered the imaging modality of 4D-CT. This practice of referring for 4D-CT however, appears to be a very recent development. Thus, of the 58 patients who were analysed, 12 had negative primary imaging and 9 amongst this group went on to have 4D-CT performed. All 9 of these patients had the parathyroid adenoma identified by 4D-CT. In 1 individual who had concordant positive US and MIBI scans, 4D-CT was done to clarify the findings of the primary imaging because both US and MIBI scans had suggested the presence of an intrathyroidal adenoma.

MIBI scan, US scan and 4D-CT had true positive rates of 63.8%, 72.4% and 90%, respectively (Table 2).

The ability of imaging techniques to identify pathological parathyroid gland(s) has improved compared to the previous study (Table 3). MIBI scintigraphy, and particularly US scan, had markedly improved performance.

Table 1. Baseline Characteristics of Patients (n = 58)

Baseline Characteristics	Values
Gender	
Female	60.3%
Male	39.7%
Ethnicity	
Chinese	84.5%
Malay	3.4%
Indian	5.2%
Other	6.9%
Mean age	58 $\pm$ 15 years
Mean calcium	2.84 $\pm$ 0.21 mmol/L
Median parathyroid hormone	19.6 pmol/l (11.4 to 28.2)
Mean 25-hydroxyvitamin D	22.3 $\pm$ 10.5 mcg/L
Clinical presentation/s	
Asymptomatic	41.4%
Gastrointestinal symptoms	24.1%
Renal stones	24.1%
Osteoporosis	19.0%
Musculoskeletal symptoms	20.7%

Table 2. Ability of Imaging Modalities to Correctly Localise Pathologic Parathyroid Glands

	MIBI Scintigraphy (n = 58)	US Scan (n = 58)	4D-CT (n = 10)
True positive localisation	63.8%	72.4%	90%
False positive localisation	3.4%	3.4%	10%
False negative localisation	32.8%	24.1%	0%

4D-CT: 4-dimensional computerised tomography; MIBI: Methoxyisobutylisonitrile; US: Ultrasound

Table 3. True Positive Rates of Imaging Modalities in Previous and Current Studies

	True Positive Rates in Previous Study*	True Positive Rates in Current Study
MIBI scintigraphy	40.0%	63.8%
US scan	18.2%	72.4%
CT	41.4%	Not applicable
4D-CT	Not applicable	90.0%

4D-CT: 4-dimensional computerised tomography; MIBI: Methoxyisobutylisonitrile; US: Ultrasound

*Koong HN, Choong LH, Soo KC. The role for preoperative localisation techniques in surgery for hyperparathyroidism. Ann Acad Med Singapore 1998;27:192-5.

An enumeration of the type of preoperative imaging modality and surgical approach employed is provided in Figure 2.

A total of 79.3% (n = 46) of patients had a positive MIBI and/or positive US scans; 94.8% of patients (n = 55) had a positive MIBI and/or positive US scans and/or positive 4D-CT of which 80% (n = 44) had LE. Of the 46 patients who had positive MIBI and/or positive US scans, concordant findings were obtained in 37 patients. Surgeons were even more likely to perform LE when the MIBI and US scans showed concordant results. Thirty-three (89.2%) of the 37 patients who had concordant MIBI and US scan findings in our series went on to have LE. Of the remaining 4 patients who actually had concordant results on US and

MIBI scans and could have probably undergone LE, 1 had 4D-CT imaging that suggested bilateral involvement, 2 had concomitant thyroid nodules necessitating thyroidectomy, and in 1 patient, MIBI and US scans concordantly suggested bilateral involvement. Conversely, most patients with discordant imaging underwent BE. Of the total 9 patients who had discordant results on MIBI and US scans, 5 went on to have BE. Of the remaining 4, 3 had negative MIBI but positive US scan and underwent LE due to the surgeon's decision to trust the positive US scan finding as confirmatory of localisation. The fourth patient had an on-surgical table US scan that confirmed the earlier positive MIBI scan finding and therefore also underwent a LE.

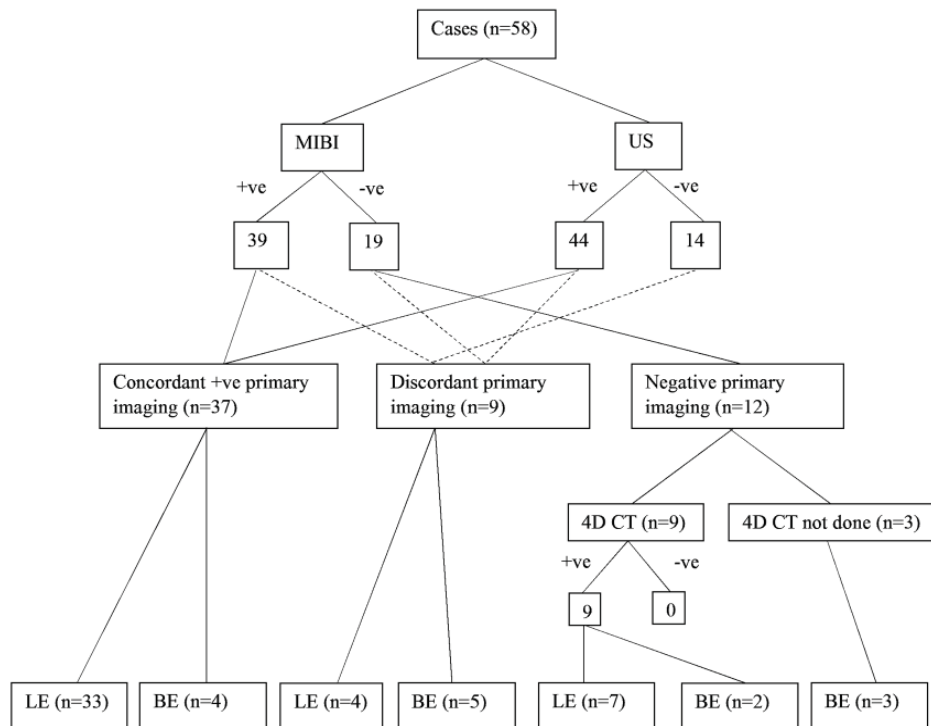


Fig. 2. Preoperative localisation imaging and type of surgery.

Table 4. Impact of Localisation Method on Type of Surgery

	Positive Localisation (n = 55)	Negative Localisation (n = 3)
Limited focal neck exploration	80%	0%
Bilateral neck exploration	20%	100%

Seven out of the 9 patients who had negative primary imaging and subsequently had a parathyroid adenoma identified by 4D-CT went on to have LE. Of the 2 who had BE, 1 patient had multinodular goitre and therefore underwent concomitant thyroidectomy through an open surgery and in the other case, the BE was a discretionary decision by the operating surgeon. The impact of localisation method on type of surgery is shown in Table 4.

The surgical methodologies employed were based on the principles of the anatomic basis of parathyroid surgery.¹⁷ Frozen section confirmation of parathyroid tissue was performed for all specimens excised.

The mean time from detection of hypercalcaemia to surgery was 14.1 weeks (4.9 to 40.8) in those who had positive primary imaging as compared to those whose primary imaging was negative, in whom the mean time to surgery was 31.5 weeks (6.1 to 162.0); $P = 0.053$.

Biochemical cure rate was achieved in all but 1 of the 58 patients (98.3%). Of the 57 patients who were cured, 96.5% ($n = 55$) had single adenoma and 3.5% ($n = 2$) had multiple gland hyperplasia. Forty-three out of 44 patients who had LE achieved biochemical cure. In the 1 patient who did not achieve biochemical cure in the LE group, an apparent adenoma was identified and was surgically removed at the initial operation. Histology showed hyperplasia. However, despite repeat surgery with bilateral neck exploration in an attempt to remove all parathyroid tissue, this patient remained hypercalcaemic. So it can be assumed that the failure to attain biochemical cure in this patient was not likely due to the initial operative modality chosen but to a false localisation of potentially persistent pathology. All 14 of the patients who underwent BE achieved biochemical cure.

The mean calcium at 1-month postoperatively and at 6-months postoperatively were 2.30 mmol/L (SD: 0.14) and 2.30 mmol/L (SD: 0.11) respectively.

LOHS was 2.8 days (1.6, 4.8) and 4.3 days (2.1, 9.0) for limited and bilateral neck surgery respectively, $P = 0.011$. Fifty percent of limited neck exploration surgery patients versus 6% of bilateral neck surgery patients were able to be discharged within 2 days of surgery, $P = 0.001$.

Discussion

Our study demonstrates that even in a mid-volume¹⁸

multiple-surgeon operative centre such as ours with a yearly total parathyroid surgical case volume of approximately 20 to 80, a major practice shift has occurred in the landscape of surgery for primary hyperparathyroidism. From a time when the oft-quoted dictum that the best localisation procedure for primary hyperparathyroidism was to localise a good surgeon, the ongoing improvement that has occurred in the sensitivity and specificity of MIBI and US scans, and the refinement of CT techniques have resulted in changes in even the type of surgery that is performed. The study from our centre in the 1990s had concluded that preoperative imaging to localise parathyroid glands was not useful.⁹ This was the case noted in surgeries for both primary hyperparathyroidism as well as secondary and tertiary hyperparathyroidism. The extent of the procedure performed then was based on frozen section irrespective of the preoperative radiologic diagnosis. It has to be noted that sestamibi scanning had just been introduced at our hospital a mere 4 years prior to the publication of the above study.¹⁹

It was apparent from our retrospective review that compared to the previous study, the prevailing practice at our institution in the last decade has changed such that concomitant MIBI and US scan are performed as primary imaging for hyperparathyroidism. This also appears to be the favoured approach amongst surgeons in the United States as was revealed in a nationwide survey.⁸ Concomitant use of MIBI and US scanning has been shown through several studies to give a combined sensitivity of more than 90% in detecting parathyroid adenomas.²⁰ All of the patients who had concordant MIBI and US imaging in our current study had the parathyroid adenoma correctly identified upon surgery.

A significant majority of patients had conventional planar CT scan as their primary imaging modality in the previous study.⁹ This could have been a reflection of the fact that CT was more readily available than the other imaging modalities at that time. Localisation by CT was found to be correct only in 41.4% of patients in the above study.⁹ This is not surprising since published studies during that era reported low detection rates of parathyroid adenomas with conventional CT imaging.²¹ The authors of the study also did not find CT to be useful in differentiating between hyperplastic and adenomatous parathyroid glands. Unlike conventional CT that was not found to be useful in differentiating superior versus inferior parathyroid glands, the sensitivity of 4D-CT for the localisation of a single hyperfunctioning parathyroid gland to a quadrant in the neck is 73% to 97%.²² Though 4D-CT may have value as a primary imaging modality,²³ it has to be noted that the thyroid-specific radiation dose associated with 4D-CT is 50 times that of MIBI scanning.^{24,25} MIBI and US scanning hence probably should remain the primary imaging modality in the workup of primary hyperparathyroidism. It would be

appropriate for 4D-CT to be considered for patients with negative primary imaging. The use of 4D-CT was shown to result in an increased rate of successful localised focused parathyroid exploration in patients in whom localisation by MIBI or US scanning had failed.²⁶ 4D-CT is a relatively new modality that has become available in our institution. This novel modality correctly localised pathologic parathyroid glands in 90% of our cases. This preliminary finding of a very high true positive rate holds significant promise for the use of 4D-CT especially as a second-line imaging modality.

There has been a swing in practice from bilateral to limited unilateral/focal neck exploration surgery in those patients who have had a single adenoma identified on preoperative imaging. In our study, 80% of the patients who had positive imaging findings underwent LE. There are, however, potential issues that have to be addressed when considering LE. This type of surgery relies on successful localisation of the pathological gland preoperatively. Because of the increased risk for morbidity and failure in reoperation, the current consensus calls for 2 concordant imaging studies localising the hyperfunctioning parathyroid tissue before a LE is considered.²⁷ Discordant primary imaging should ideally be dealt with by BE though this is necessarily not always followed as was seen in our series. Parathyroidectomy success rates however, have been found to be similar in patients with MIBI scan-only or USS-only positive preoperative imaging compared to those with concordant ultrasound/MIBI imaging in a recent study.¹⁵ Whether the success rate noted in this one study can be replicated by others needs to be seen. Patients with bilateral parathyroid hyperplasia as well as those who have negative preoperative imaging should also ideally be managed by BE.

The advantages of LE that have been demonstrated in a high-volume, single-surgeon setting are reduced operative duration, reduced LOHS, reduced overall cost and greater patient satisfaction.²⁸ Our study shows that these findings are true in a mid-volume, multiple-surgeon setting with those patients who underwent LE having significantly shorter postoperative hospitalisation stay compared to those who had BE.

Our study has some limitations. The findings are from a retrospective study of a series of patients presenting to a large tertiary teaching hospital and the operations were performed by multiple surgeons. This meant that though the surgical methods employed were uniform, there were some variations in decisions made as to whether LEs or BEs should be performed. Data collection for the study was made on the premise that all parathyroidectomy operations done at our institution would have been accurately recorded

in the surgical archives. There was also a potential for error in transcription of laboratory data. However, this was mitigated by cross-referencing the manual case notes with electronic patient records. The sample size was relatively small; however, this is reflective of the primary hyperparathyroidism surgical case load not only at our institution but in most mid-volume surgical centres. Our study was not designed as a prospective controlled head-to-head comparison of the various imaging modalities and therefore, the true positive rates found should be interpreted appropriately. Since all patients in our series underwent some form of preoperative imaging, we could not explore the cost effectiveness of the preoperative imaging approach against non-image guided bilateral neck exploration. This has been evaluated previously in 2 studies both of which showed cost savings for preoperative imaging with minimally invasive surgery over bilateral neck exploration.²⁹⁻³¹

Despite these limitations, our findings are consistent with those reported from larger studies conducted at high-volume surgical centres. The mid-volume multiple-surgeon setting is replicative of most centres that perform parathyroidectomies and we consider that the findings are likely to be replicated in other such centres that have dedicated nuclear medicine departments and trained ultrasonographers. The surgical technique that was predominantly used in our setting was that of a limited focal approach with a less than 2.5 cm incision under general anaesthesia. Whether this represents a true minimally invasive parathyroidectomy (MIP) is debatable. However, we have not attempted to denote our surgical approach as MIP and prefer to call it “limited image directed focal exploration”. Our biochemical cure rates with this approach for primary hyperparathyroidism in those patients who had positive primary imaging were comparable to that achieved by bilateral neck exploration.

Conclusion

Our study done at a mid-volume multiple-surgeon centre shows a marked change in the surgical landscape for primary hyperparathyroidism in the last 2 decades in Singapore. Improved imaging techniques have resulted in significantly enhanced preoperative localisation of the pathologic parathyroid gland and have also led to a dramatic swing from bilateral neck explorative predominance to limited focal exploration in almost all cases of primary hyperparathyroidism presenting with a solitary adenoma. Comparable cure rates were achieved with both operative modalities with hospitalisation stay being shorter for those patients who had LE as compared to those who had bilateral neck exploration.

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