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Management of Primary Hyperparathyroidism: 'Past, Present and Future'

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1. Introduction

Over the years the disease known as primary hyperparathyroidism has undergone a dramatic change in the clinical spectrum ranging from a symptomatic disease to an asymptomatic disease. In spite of the current understanding of the disease perspective, the mainstay of treatment is still surgical.

The standard treatment advocated and practiced for years could be considered as a source control operation involving routine bilateral exploration of the neck with an attempt to identify and eliminate the offending gland or glands. These surgeries were elaborate, time consuming and the success rates depended on the experience of the surgeon. Of late, certain novel and more patient-friendly techniques such as minimally invasive surgery and targeted selective gland excision are being performed with reportedly excellent outcomes.

This chapter reviews and discusses the surgical aspects of parathyroid surgery including the evolution of surgery from the 'conventional bilateral cervical exploration' to recent advances such as 'minimally invasive surgery' and 'focused parathyroidectomy'. The clinical features of primary hyperparathyroidism and indications for parathyroidectomy are also described, followed by a review of surgical techniques currently being practiced.

2. Anatomy

2.1 The surgical anatomy of the parathyroid glands

A good surgeon should also be an excellent anatomist. The ultimate triumph of the surgical management of primary hyperparathyroidism is often based on the surgeon's knowledge of the normal anatomical relationships and more so about the important embryologic variations of the parathyroid anatomy.

Practically everyone has at least four parathyroid glands, but their number can vary between 2 to 6. [Figure 1]. Thus in about 80% of cases there are symmetrically four (2 on either side) and in 5-13% of the cases they may be supernumerary (Hooghe et al., 1992). For example, in an autopsy study of 503 cases, in 84% there were four glands, 3% of the cases had only three glands, and in 13% there were supernumerary glands. The supernumerary gland was often a fifth gland tucked away in the thymus (Akerström et al., 1984).

The parathyroid glands are oval shaped, well encapsulated and smooth, often the size of a split pea, and yellow, pink or tan in colour weighing around 20-40 mg each. Normal parathyroid glands measure approximately 6 mm in length, 3-4 mm in transverse diameter, and 1-2 mm in anteroposterior diameter. In addition to the yellowish tinge, these small glands are often camouflaged by a covering of fat making it difficult to identify them during surgery and may be confused with surrounding fat. The parathyroid gland usually weighs around $29.5 \text{ mg} \pm 17.8$ (mean \pm standard deviation), with a reported upper limit of 65 mg (Dufour & Wilkerson, 1983). However, the weight of the normal parathyroid glands removed at surgery in patients with primary hyperparathyroidism may be greater than that reported in autopsy studies (Yao et al., 2004).

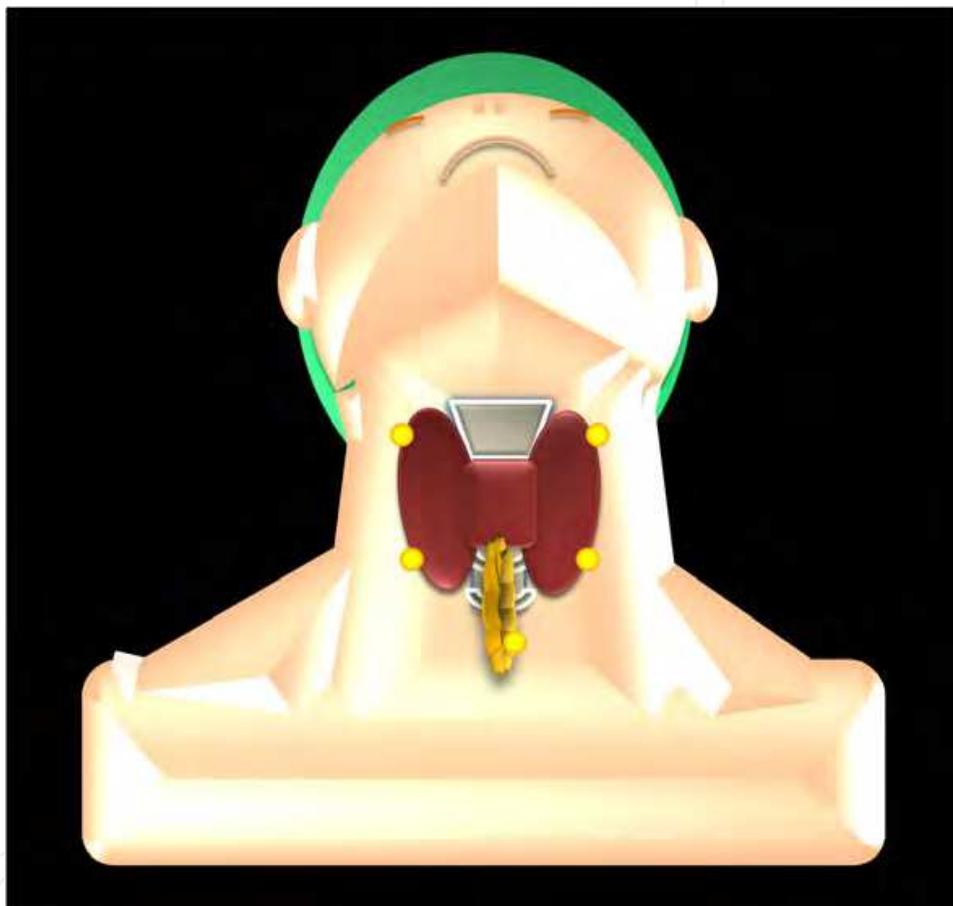


Fig. 1. The normal location of paired parathyroids and a supernumerary fifth gland within the thymus.

The inferior parathyroid gland derives its blood supply from the inferior thyroid artery. In about 10% of patients, the inferior thyroid artery may be absent, in which case the superior thyroid artery supplies the inferior parathyroids (Delattre et al, 1982). The superior parathyroid gland is also usually supplied by the inferior thyroid artery or from an anastomosing artery joining the superior and inferior parathyroid arteries. In about 20-45% of cases, the superior parathyroid glands receive their blood supply from a posterior branch of the superior thyroid artery (Bonjer & Bruining, 1997; Nobori et al., 1994). There often exists a good collateral arterial supply from the tracheal vessels and therefore adequate parathyroid function persists even if all four major thyroid arteries are ligated.

About 15-19 % of the glands can be found in ectopic locations and distant from the thyroid lobes, mostly posterior alongside the esophagus, in the upper anterior mediastinum encapsulated in the thymus, and within the carotid sheath or even rarely (0.5-4%) embedded within the thyroid itself. (Wang, 1981; Feliciano, 1992). The ectopic or aberrant locations of the parathyroid gland are related to discrepancies during embryological development and descent.

Key points-1

- In 80% of cases parathyroids are normal in position, symmetrical and paired.
- About 20% of the parathyroids are ectopic.
- 65mg is the upper normal weight limit for a single gland.
- Supernumerary glands may be commonly found within thymus ("*para-thymus*").
- Collateral blood supply from tracheal vessels is protective to the parathyroids.
- Intra-thyroidal location of the parathyroid is rare.

2.2 Applied surgical embryology of the parathyroids

Although functionally independent, the development of thyroid, parathyroid and the thymus are closely related to one another. The parathyroid glands develop from the cranial portions of the third and fourth pharyngeal (branchial) pouches on either side of the embryo and are therefore designated as *parathyroid glands III* and *parathyroid glands IV* respectively. Since these pouches are bilateral they should normally yield four parathyroid glands.

The **parathyroid III (the future inferior parathyroids)** and the thymus arise from the third branchial pouch from its dorsal and ventral wings respectively [figure2]. The downward descent of the thymus pulls the parathyroid III along with it. But parathyroids usually halt at the dorsal surface and outside the fibrous capsule of the thyroid gland while the thymus descends further beyond. This embryonic descent therefore places the parathyroid IIIs inferior to the parathyroid IVs in the neck, thereby designating them as inferior and superior parathyroids respectively. Discrepancies in this course of normal descent can cause the parathyroid IIIs to be situated at levels higher up in the neck (sometimes referred to as '*undescended parathymus*').

The **parathyroid IV glands (the future superior parathyroids)** and the ultimobranchial bodies are derived from the fourth pharyngeal pouch and migrate together. The superior parathyroid glands travel with the ultimobranchial bodies and consequently migrate a shorter distance than the inferior glands. They therefore remain in contact with the posterior part of the middle third of the thyroid lobes and are in a comparatively more constant position in the neck.

Key points-2

- The superior parathyroids are more constant in location.
- The inferior parathyroids are more prone to become ectopic.
- The superior parathyroid glands are typically located about 1 cm superior to the intersection of the inferior thyroid artery and the recurrent laryngeal nerve.[along the posterior border of the thyroid].

- The inferior glands are commonly found near the lower pole of the thyroid more often in an anterior plane.

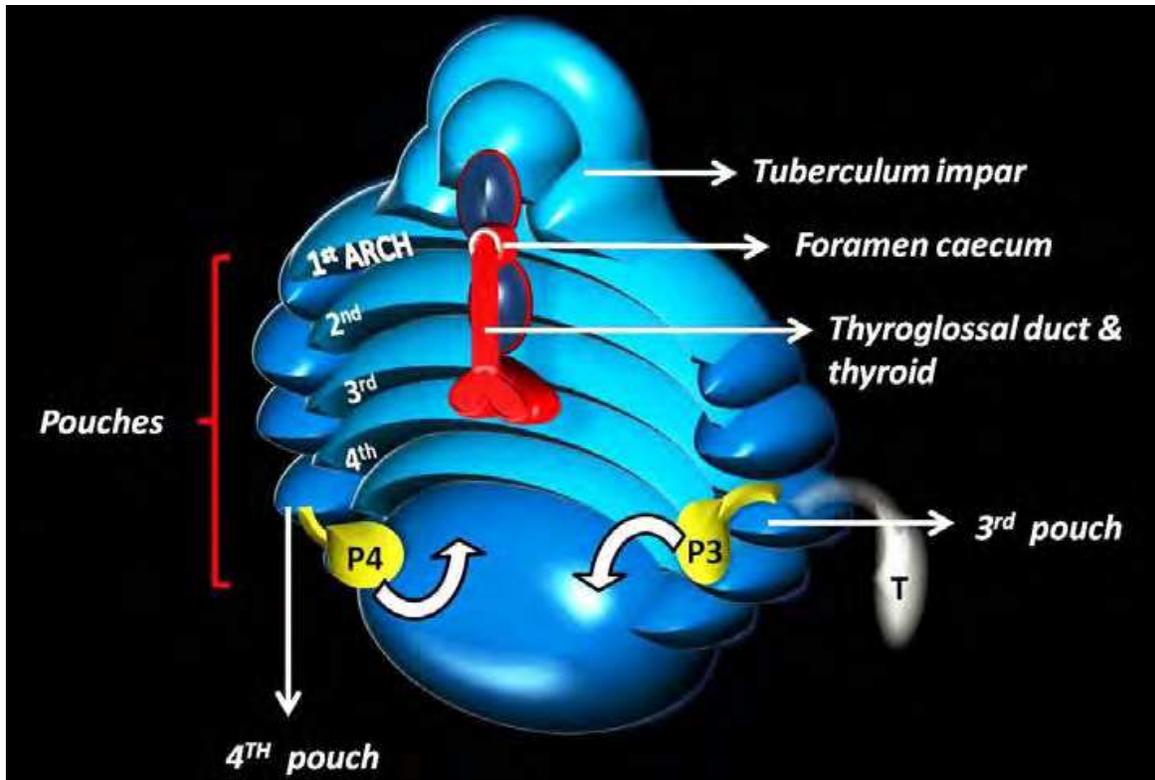


Fig. 2. The developing branchial complex demonstrating the parathyroid III (P3) and thymus (T) budding from the third branchial pouch on the dorsal and ventral aspects respectively. Pathways of parathyroids III (P3) and IV (P4) denoted by arrows.

3. Primary hyperparathyroidism

Primary hyperparathyroidism (PHPT) is a hypercalcaemic state caused by excessive unregulated production of parathyroid hormone, resulting in defective calcium homeostasis. The secretion of parathyroid hormone is regulated directly by the plasma concentration of ionized calcium. The exact cause of spontaneous hyperfunctioning of the parathyroids is unknown and it is often recognized due to peripheral or systemic effects of the excess hormone.

PHPT can be regarded as a relatively recent disease owing to the fact that the parathyroid glands were the last major organ to be recognized in humans. (Elaraj & Clark, 2008). Ivar Sandström, a Swedish medical student, in 1879 was the first to describe the parathyroid glands. (Eknoyan, 1995)

3.1 The spectrum of parathyroid disease

Parathyroid disease usually manifests in three forms namely **primary**, **secondary** and **tertiary** hyperparathyroidism. **Primary hyperparathyroidism (PHPT)** is a relatively common endocrine disorder and is the commonest reason for surgical exploration. The other two forms are consequences of other disease processes.

TYPE	CAUSE	TREATMENT
Primary HPT	Unregulated overproduction of parathyroid hormone resulting in abnormal calcium homeostasis, due to adenoma, hyperplasia or carcinoma, familial syndromes(MEN 1 or MEN 2a), familial isolated hyperparathyroidism (FIHPT) etc.	Surgery: open / minimal access Parathyroidectomy
Secondary HPT	Excessive production of parathyroid hormone secondary to a chronic abnormal stimulus such as chronic renal failure and vitamin D deficiency.	Primarily medical management
Tertiary HPT	Autonomous hypersecretion of parathyroid hormone causing hypercalcaemia often seen in chronic secondary hyperparathyroidism (prolonged compensatory stimulation) and often after renal transplantation.	Total parathyroidectomy with auto transplantation, subtotal parathyroidectomy

Table 1. The spectrum of hyperparathyroidism

3.2 Incidence

There is a wide variation in the incidence of PHPT geographically. This variation is most markedly seen in between the western world and developing countries. It is a common endocrine disease in countries where hypercalcaemia is detected at an early stage due to routine biochemical screening (Bilezikian et al, 2002). The exact incidence of PHPT is difficult to define since many patients remain asymptomatic and the reported incidence varies according to the population studied. In the United States, the incidence of primary hyperparathyroidism is 2 to 3 per 1000 women and approximately 1 per 1000 men. The incidence increases to 2% after the age of 55 years. It is more commonly seen in postmenopausal woman older than 50 years. With the advent of multichannel biochemical screening in the 1970s, the incidence of PHPT increased around the world especially in western countries and this brought to light the existence of the entity referred to as 'asymptomatic PHPT'.

3.3 Etiopathogenesis

The exact cause of primary hyperparathyroidism is not clear and may possibly due to an underlying primary pathology of the parathyroid gland itself. The pathogenesis of PHPT may be sporadic or familial. Normally the parathyroid glands are composed of chief cells, oxyphil cells, and transitional oxyphil cells mixed with adipose tissue. Chief cells secrete parathyroid hormone. Sporadic PHPT involves abnormal tissue in the parathyroid gland [figure 3].

The pathological lesions responsible for PHPT include **solitary adenomas** (>80%); **double adenomas** (2-3%) **multigland hyperplasia** (15%) and **carcinoma** (1-2%).(Kaplan et al,1992)

Inherited disorders include familial hyperparathyroidism, multiple endocrine neoplasia syndrome (MEN type 1 and 2A), and hyperparathyroidism-jaw tumor syndrome and these account for roughly about 10% of PHPT. Other suggested causes include over expression of PRAD1 oncogene and also low dose irradiation to the neck during childhood.

3.4 Double parathyroid adenomas -“fact or fiction”?

Double parathyroid adenomas account for only a small percentage of the lesions associated with PHPT. Controversy still exists as to whether double adenomas are a distinct entity or part of four gland hyperplasia presenting metachronously. There is no reliable method to accurately distinguish adenoma from hyperplasia. Some authors feel that the most reliable clinical criteria to document double adenomas, is the absence of recurrent hyperparathyroidism on follow up of at least 5 years following selective gland excision (Baloch & LiVolsi., 2001). Meanwhile some others have authoritatively documented the existence of double adenoma as a separate entity and are not simply missed cases of four-gland hyperplasia. (Abboud et al., 2005). Neonatal convulsions as the initial presentation of maternal PHPT due to double parathyroid adenomas has also been described (Zachariah & Thomas, 2010).

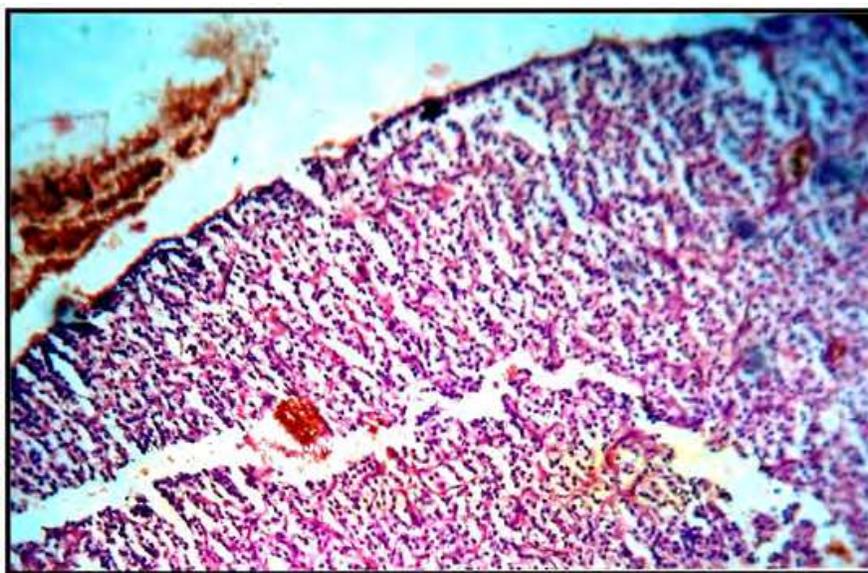


Fig. 3. Photomicrograph of a solitary parathyroid adenoma showing hypercellular parathyroid tissue, absence of fat cells and surrounding capsule (Haematoxylin & Eosin *40)

3.5 Clinical features

It is now well known or well phrased that “*The clinical presentation of PHPT has changed from a symptomatic to an asymptomatic disease*”. Patients with severe symptoms have become exceedingly rare. To make the discussion simpler, PHPT can be broadly classified into two types-namely symptomatic and asymptomatic PHPT, a view also supported by a National Institutes of Health consensus panel. (Bilezikian et al., 2002; Kearns & Thompson, 2002)

Clinical features are associated to the direct and indirect effects of excess parathyroid hormone on the skeleton, kidneys, and intestine may include bone resorption of calcium and phosphorus, enhanced intestinal absorption of calcium, renal tubular reabsorption of calcium, and hypercalciuria

3.5.1 Asymptomatic PHPT

Asymptomatic PHPT (APHPT) is the commonest form of the disease and therefore the most common clinical presentation of primary hyperparathyroidism is asymptomatic hypercalcaemia and this accounts for 75% to 80% of cases. However it should be understood that absence of any of the obvious classical clinical presentations is what is commonly referred to as asymptomatic disease. In such patients the symptoms are mild and nonspecific, often underestimated. But studies have shown that the so called asymptomatic patients will often have symptoms or metabolic complications when carefully evaluated with standardized health questionnaires. (Burney et al., 1999; Talpos et al., 2000). Patients may have weakness, fatigue, mild depression, anorexia, and often increased absence from work. These patients have mild and sometimes only intermittent hypercalcaemia. In most of these cases, the mean serum calcium concentration is less than 1.0 mg/dL (0.25 mmol/L). Truly asymptomatic PHPT is therefore rare, occurring in only 2% to 5% of patients. (Chan et al, 1995; Clark et al, 1991) The importance of APHPT is that the surgical management of asymptomatic patients has been controversial and this very aspect has encouraged the formulation of treatment guidelines.

3.5.2 Symptomatic PHPT

This was the original form of the disease and is still at large in developing countries. The signs and symptoms of hyperparathyroidism largely reflect the effects of hypercalcaemia and may involve multiple organ systems (Taniegra, 2004).

Classical symptoms of PHPT popularly summed up as "*bones, stones, abdominal groans and psychic moans*" are hardly ever encountered today. (Silverberg et al, 1999) This may be true in the western world. Conversely, in developing countries classic and severe forms of the disease are still the presenting features and asymptomatic PHPT is probably a rarity. Some of the classical radiological findings are shown in figure 4.

Bone related problems were the first to call attention to the disease and include manifestations of selective cortical bone loss. The high incidence of bone disease in patients with PHPT in developing countries has been attributed to associated vitamin D and dietary calcium deficiency (Harinarayan, 1995). The various classical clinical features are summed up in [Table 2]. Cardiovascular manifestations include hypertension, bradycardia, shortened QT interval, and left ventricular hypertrophy. It should be remembered that the symptoms may not be proportional to magnitude of hypercalcaemia.

In developing countries the scenario and spectrum of the disease are therefore different. In a systematic review of data of 858 patients with PHPT, from India, showed that majority of the patients (71.5%) were less than 40 yrs of age, (whereas patients from developed nations are diagnosed in the fifth and sixth decades) (Pradeep et al, 2011). Interestingly, 5 to 33% had a clinically palpable parathyroid gland. Also, the incidence of parathyroid carcinoma causing PHPT in the various series has been 2.6 to 6%, which is higher than in developing countries. Moreover in India, asymptomatic presentation is virtually unheard of. The symptomatic disease is identified much later after a series of management for fractures and renal stones. Another study also showed similar results, where in, 67% had bone disease, 48% had fractures, 21% had stone disease, 23% had psychiatric symptoms and 15% had peptic ulcer disease (Bhansali et al, 2005).



Fig. 4. SYMPTOMATIC PHPT: (A) Xray of the hands showing subperiosteal bone resorption over the middle phalanges (white arrows). (B) Showing “salt and pepper” appearance of the skull. (C) Showing a dental cystic lesion over the mandible.

SYMPTOMATOLOGY	ORGAN SYSTEM INVOLVED	FEATURES
Bones	Skeletal And Neuro-Muscular	Bone & Joint Pain; Osteoclastic Bone Resorption,Pseudo-gout; Chondrocalcinosis;Brown tumour, Bone cysts
Stones	Renal	Polyuria; Haematuria; Graveluria; Recurrent urinary tract infections Nephrolithiasis (35-50%); Nephrocalcinosis (rare: 3-5%) Hypercalciuria
Abdominal Groans	Gastro-Intestinal	Anorexia;Vomiting;Abdominal Cramps;Constipation;Acid Peptic Disease; Acute Pancreatitis Cholelithiasis (25-30%)
Psychic Moans	Psychological Manifestations	Depression; Poor Libido; Memory Loss,Lack of concentration

Table 2. Clinical features of classical disease

The association between pancreatitis and hyperparathyroidism was first reported in 1940 by Smith and Cooke. (Bess et al, 1980). The commonest manifestation of pancreatic disease with PHPT is the history of recurrent upper abdominal pain. A high concentration of serum calcium may be responsible for the increased incidence of gall stone disease in PHPT and this is seen especially in developing countries

4. Making the diagnosis of primary hyperparathyroidism

4.1 Laboratory diagnosis

The diagnosis of PHPT is based on the documentation of elevated serum calcium in combination with elevated serum parathyroid hormone (PTH) levels. The initial finding of an elevated serum calcium (ionized fraction) level should always raise the suspicion of PHPT and in such cases hypercalcaemia should be confirmed by a repeat test. In such cases, other causes of hypercalcaemia should be excluded (history of vitamin D intake, thiazide diuretics and family history of hypercalcaemia). Elevated parathyroid hormone levels in the presence of persistent hypercalcaemia confirms the diagnosis of primary hyperparathyroidism. In order to eliminate the variations that can occur with respect to time, blood volume, and dietary intake the PTH and serum calcium levels should be measured simultaneously.

The first generation parathyroid hormone assays is becoming obsolete. Second-generation parathyroid hormone assays (known as 'intact'), and third-generation parathyroid hormone assays (known as 'whole or bio-intact') are becoming more popular.

4.2 Additional investigations

The concentration of serum phosphate varies between 2.5 and 4.5 mg/100ml. About half the patients with PHPT have hypo-phosphataemia provided they do not have significant renal impairment. Also, 10-40% of patients have elevated levels of serum alkaline phosphatase and almost all these patients have significant bone involvement. Imaging studies have no role in the diagnosis of primary hyperparathyroidism and are mainly used for localization.

Recently a new clinical phenotype of PHPT has been identified known as **normocalcemic PHPT**. **Eucalcemic primary hyperparathyroidism** may represent the earliest manifestation of primary hyperparathyroidism. As for now more information is needed on this entity to consider its routine evaluation in PHPT (Peacock et al, 2005; Lowe et al, 2007).

5. The surgical management of PHPT

Surgery provides the only available cure for primary hyperparathyroidism. Although operative management is clearly indicated for all patients with symptomatic PHPT (classic symptoms or complications of PHPT), the role of surgery for asymptomatic PHPT is still controversial.

5.1 Decision making: "Current indications and guidelines"

There is no doubt patients with **symptomatic PHPT** should undergo surgery as there is enough evidence of symptomatic improvement and reversal of the effects of PHPT (such as

improvement in bone density, reduction in fractures, reduced frequency of kidney stones, and improvements in some neurocognitive elements and sense of well being).

Controversy still exists as whether patients with **asymptomatic PHPT** should undergo surgery. Data increasingly appears to support parathyroidectomy in all patients with PHPT because it is associated with a quantifiable improvement in health related quality of life. (Sheldon et al, 2002).

However, among the so called ‘asymptomatic patients’ only about 2-5% are truly asymptomatic. In order to address this issue and set down guidelines, three conferences have been held on the management of asymptomatic PHPT during the past 18 years. The most recent conference (the third) was held in 2008 from which summary of guidelines are available for reference. Important aspects based on the current guidelines for surgical intervention and for medical surveillance, for patients with asymptomatic hyperparathyroidism are listed in table 3. (Bilezikian et al, 2009). As for now the surgical treatment should definitely be based on these guidelines.

FACTOR	CRITERIA
Asymptomatic	No Kidney Stones, Nephrocalcinosis, Fractures, Or Other Symptoms
Age	<50 years
Serum Calcium	>1 mg/dl Above Normal Upper Limit Of Normal
Creatinine Clearance	<60 ml/Min
Bone Mineral Density (BMD)	T-Score<-2.5 At Lumbar Spine, Hip, Or Forearm
24 hr Urine Calcium	Not Indicated (Hypercalciuria By Itself Is Not Considered An Indication For Surgery)
Asymptomatic PHPT who do not meet above criteria(1,2,3,4,5,6)	Medical surveillance (Can be safely managed without surgery) Monitor: serum calcium levels biannually Serum creatinine levels-annually BMD 1-2 years at three sites

Table 3. Current guidelines for surgical management of asymptomatic PHPT

5.2 Pre-operative localization: “Chasing the target”

Once we have confirmed the diagnosis of primary hyperparathyroidism from the laboratory and clinical information, the next and one of the most important step is to identify the source of the disease process.

In the past the only way of identifying an abnormal gland was at the time of bilateral neck exploration and the best tool available was an experienced surgeon!! This is aptly reflected in the words of Doppmann *“in my opinion, the only localizing study indicated in a patient with untreated hyperparathyroidism is to localize an experienced parathyroid surgeon.”*(Doppmann, 1986).

The argument was that, in the hands of an experienced parathyroid surgeon, 95% to 97% of the cases could be resolved by a single neck exploration. Thus, in the past, the only indication for preoperative localization was re-exploration following an unsuccessful parathyroidectomy. The various modalities for preoperative location are listed in table.

IMAGING MODALITY	COMMENTS
Ultrasonography (USG)	Cheap & non invasive, no radiation, can localize upto 80% of adenomas. Not very useful for ectopic parathyroids USG guided FNAC can help confirm an adenoma preoperatively Reported accuracy 75%-80%
Computed Tomography Scan(CT)	Expensive. Useful for localizing ectopic glands Thin-section contrast-enhanced CT is reported to have a sensitivity ranging from 46% to 87%.
Magnetic Resonance Imaging (T2-Weighted MRI)	Expensive. Useful for localizing ectopic glands Sensitivity of MRI is about 65% to 80%
Tc99m Sestamibi Scanning	The 'trend setter' and breakthrough investigation. "The preoperative localization investigation of choice in parathyroid disease" positive sestamibi does not improve surgical outcome Negative sestamibi scan is a predictor of those patients that are less likely to be cured.(Allendorf et al,2003) Combined with single photon-emission computed tomography (SPECT) can localize 90% of adenomas including ectopics.(Ho Shon et al,2001)
Combined USG + Tc99m Sestamibi Scanning	Ultrasound scan (USG) and Technetium (Tc ^{99m}) sestamibi scanning are combined, localization of a parathyroid adenoma is accurate in over 95% of cases (Miura et al,2002) Allows preoperative skin marking of the parathyroid position.

Table 4. Techniques of preoperative localization.

The interest in preoperative localization techniques is being given even more importance now, as more and more minimal access techniques are being developed for parathyroidectomy. Therefore it would be logical if the offending gland could be accurately localized as a part of preoperative planning. Preoperative localization would be advantageous for a single gland disease, but its utility in multi-gland disease is questionable. At present no single method of parathyroid localization matches to the unguided neck exploration by an experienced surgeon.

Key points-3

- Preoperative localization studies help plan the operative approach in patients who have biochemically confirmed diagnosis of primary hyperparathyroidism.
- Imaging studies are mainly used for localization and they have no role in the diagnosis.
- A single site positive imaging result does not rule out the possibility of multiglandular disease.
- Tc-99m sestamibi-SPECT scanning has been shown to be the best imaging modality to localize parathyroid adenomas.

5.3 Parathyroidectomy: “The dawn of a new concept”

Felix Mandl performed the first successful parathyroidectomy in Vienna in 1925. (Mandl, 1925). Thereafter and for a considerably long time the standard accepted procedure was wide exposure, for bilateral neck exploration and evaluation of all the four parathyroids.

The surgical treatment for PHPT has undergone a dramatic change in the last decade owing to the development of better localization techniques. The standard treatment advocated and practiced for years could be considered as a source control operation involving routine bilateral exploration of the neck with an attempt to identify and eliminate the offending gland or glands. These surgeries were elaborate, time consuming and the success rates depended on the experience of the surgeon. When performed by experienced surgeons, cure rates with parathyroidectomy are 95% to 98%, and complication rates are 1% to 2%. (Schell & Dudley, 2003; Clark, 1997) Of late, certain novel and more patient -friendly techniques such as minimally invasive surgery and targeted selective gland excision are being performed with reportedly excellent outcomes.

The present era of ‘minimal access surgery’ has made considerable progress in the field of parathyroid surgery too. The recent trend is to develop procedures that require significantly smaller incisions for performing the same procedure. The routinely performed parathyroid exploration which made use of the large Kocher cervicotomy can be now be conveniently referred to as the, ‘conventional’ or ‘standard parathyroidectomy’. Any other surgical method or access entailing a smaller incision could therefore be referred to as minimal access parathyroidectomy (**MAP**) or minimally invasive parathyroidectomy (**MIP**).

The protocol of bilateral neck exploration was challenged initially in the 1980s, when a unilateral approach was advocated in an attempt to avoid the need for contralateral exploration and its associated risks (Wang, 1985; Tibblin, et al., 1982; Russell et al., 1990).

There was a dramatic change in concept following the introduction of Tc^{99m}-sestamibi parathyroid scanning especially with reports such as simultaneous sestamibi and ultrasound of the neck could localize an enlarged parathyroid gland with almost 95% accuracy. The rationale was that if the abnormal parathyroids could be localized accurately then they could be appropriately targeted and removed through very small incisions, thereby offering the proclaimed advantageous of minimally invasive surgery in a general perspective. This thought paved the way for developing minimal-access parathyroid surgeries.

Many studies have shown that minimally invasive parathyroidectomy offers advantages like reduced hospital costs, shorter hospital stays, a lower incidence of hypocalcemia, and

equally high cure rates with lower complication rates (Udelsman R, 2002; Bergenfelz et al., 2002; Goldstein et al., 2000).

An average Kochers collar incision was usually about 8-10cm long. With time surgeons learned to perform the conventional bilateral exploration utilizing smaller incisions of about 4.1 cm (Brunaud et al, 2003). The point at which the procedure becomes a minimal-access operation probably is best defined by the length of the incision. It has been suggested that the procedure can be referred to as MAP when the incision length is less than 2.5cm for a patient with BMI of less than 30.

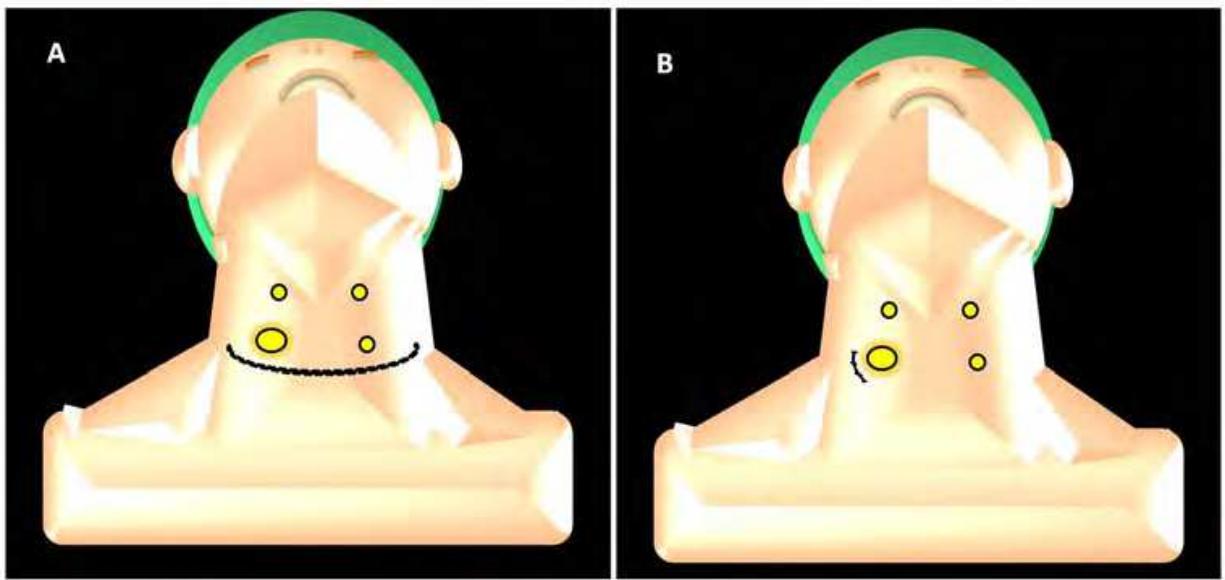


Fig. 5. Schematic representation comparing length of incisions of conventional (A) and minimally invasive parathyroidectomy (B).

5.4 Types of minimal access surgeries for parathyroid -“An overview of assortments”

5.4.1 Unilateral neck exploration (UNE)

The feasibility of unilateral neck exploration is based on the fact that that 85-90% of patients have single gland disease which could be preoperatively accurately localized by ^{99m}Tc sestamibi scanning and/or ultrasound. Therefore such patients require excision of only one gland to achieve a cure. The unilateral approach to the solitary parathyroid adenoma was advocated by Wang and later refined by Tibblin et al.

A meta-analysis of ^{99m}Tc sestamibi scanning has revealed a sensitivity and specificity of 90.7% and 98.8% respectively suggesting that the majority of patients may be suitable for unilateral exploration (Denham & Norman, 1998). A prospective randomized trial compared unilateral versus bilateral neck exploration in 91 patients. There was no statistically significant difference in the incidence of multiglandular disease, costs, or cure rate (95.1% vs. 97.5%) between unilateral versus bilateral exploration. However patients who underwent unilateral neck exploration had a lower incidence of biochemical and early severe symptomatic hypocalcaemia compared to patients who underwent bilateral exploration (Bergenfelz et al, 2002).

In another series of 184 patients who underwent scan-directed UNE, long term cure rates of 98.4% were reported (Sidhu et al, 2003)

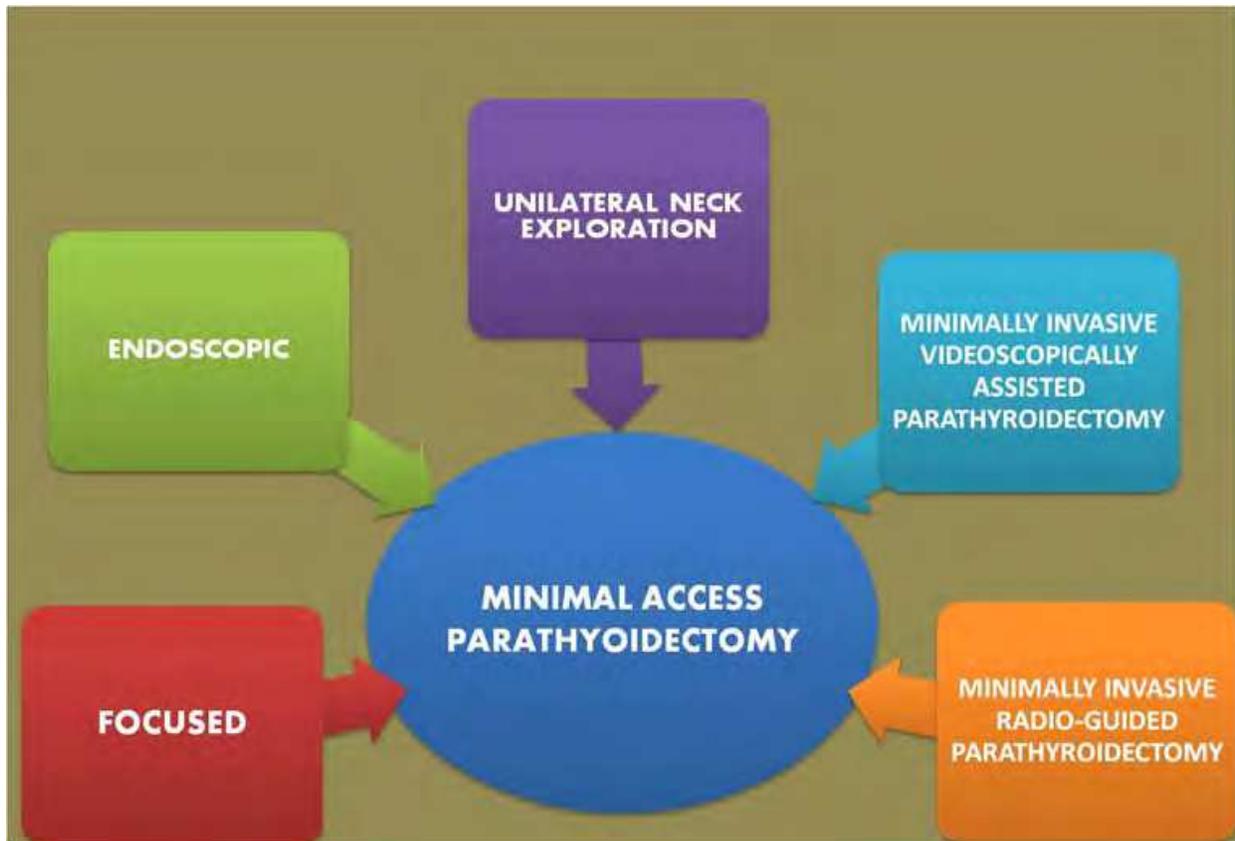


Fig. 6. Chart showing types of minimal access procedures for parathyroidectomy

5.4.2 Focused parathyroidectomy (FNE)

Also known as focused neck exploration (FNE). FNE can be performed as a day-case surgery and either under general anesthesia, cervical block, local anesthesia and sedation (Agarwal et al, 2002). Following 150 MIPs, 74 patients were discharged the same day and a further 70 were discharged the following day (within 23 h) (Mihai et al, 2007).

The technique usually makes use of a small (2cm) lateral incision to enter the space between the lateral border of the strap muscles and sternomastoid and thereby reach the lateral border of the thyroid gland and gain direct access to the parathyroid bearing areas. An FNE can be performed in as little as 12 minutes (Delbridge, 2003) and is achieved fully maintaining the principles, established with conventional parathyroid surgery.

Similar conclusions were drawn from a retrospective study comparing 255 focused lateral approaches to 401 bilateral neck explorations, where there was no significant difference in surgical success (99% versus 97%) or complication rates (1.2% versus 3%). However a favorable reduction in the operating time from 2.4 hours to 1.3 hours for MIP was demonstrated.

As with FNE the obvious advantages are that these explorations are suitable for those patients who may otherwise be high risk candidates for general anesthesia.

5.4.3 Endoscopic parathyroidectomy / Minimally invasive endoscopic parathyroidectomy (MIEP)

Minimally invasive endoscopic parathyroidectomy (MIEP) is now regarded as a feasible surgical procedure. Early work on endoscopic approach to parathyroid disease was first described by Gagner. (Gagner, 1996)

The neck is obviously a small area, and therefore the major technical challenge of an endoscopic approach to parathyroidectomy was creation of enough working space to obtain adequate exposure and freedom of movement.

Enthusiasts have tried and tested various approaches including a three-port lateral approach along the anterior border of the sternomastoid muscle (Henry et al,1999) to a midline suprasternal port and two lateral ports on the same or opposite sides of the neck, in front or behind the sternomastoid muscle (Gauger et al, 1999). Irrespective of the port placement, the technique is essentially an endoscopic lateral approach. [Figure 7& 8] An axillary approach has also been described, inserting three trocars through the axilla. This completely avoids any scars in the neck or anterior chest.

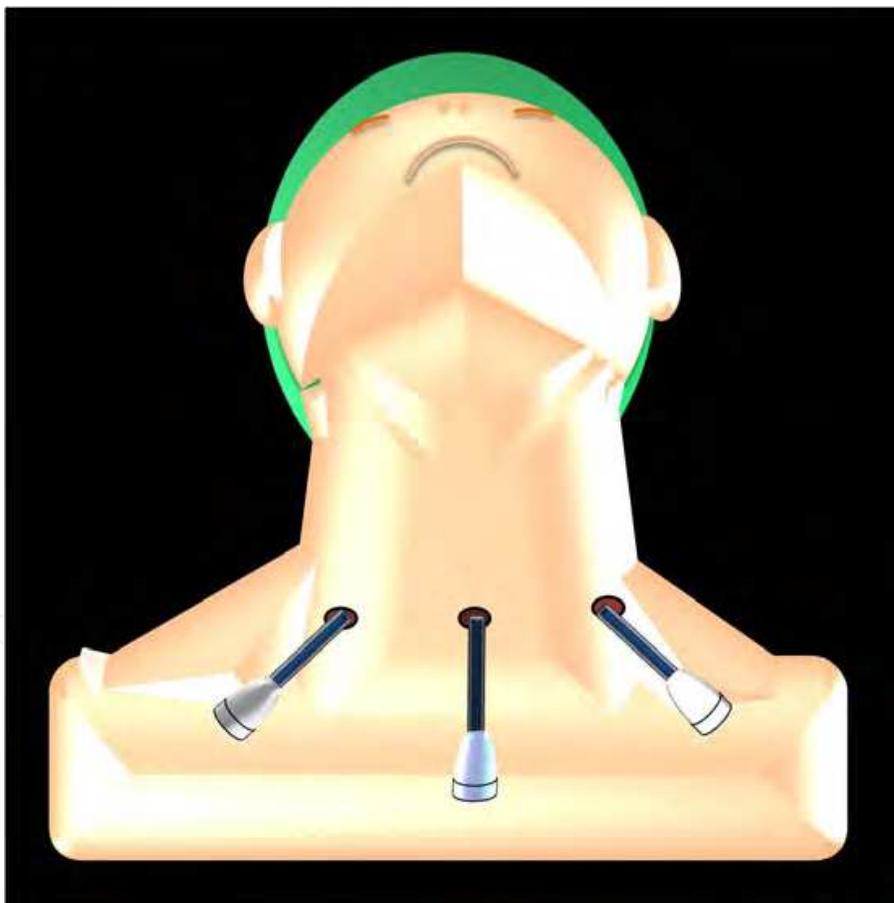


Fig. 7. Port positions in endoscopic parathyroidectomy using central access technique

5.4.4 Minimally invasive videoscopically assisted parathyroidectomy (MIVAP)

Miccoli P et al developed and described this gaseless procedure in 1998. The localized adenoma is approached via a 1.5 cm suprasternal incision, through which 5 mm endoscope

is inserted, dissection is carried out with 2 mm spatulas and forceps. The rest of the operation follows the standard principles of open parathyroid surgery, with recurrent laryngeal nerve (RLN) identification and ligation of the parathyroid vascular pedicle. MIVAP offers advantages over the endoscopic approach, with the preservation of tactile contact and a considerably smaller incision.

5.4.5 Minimally invasive radio-guided parathyroidectomy (MIRP) – (*gamma probe assisted parathyroidectomy*)

A hand held gamma probe is used to determine the position of the incision and guide the dissection (20 mCi of Technetium 99m sestamibi is injected intravenously, two to four hours prior to the surgery) the principle is similar that of sentinel lymph node biopsy.

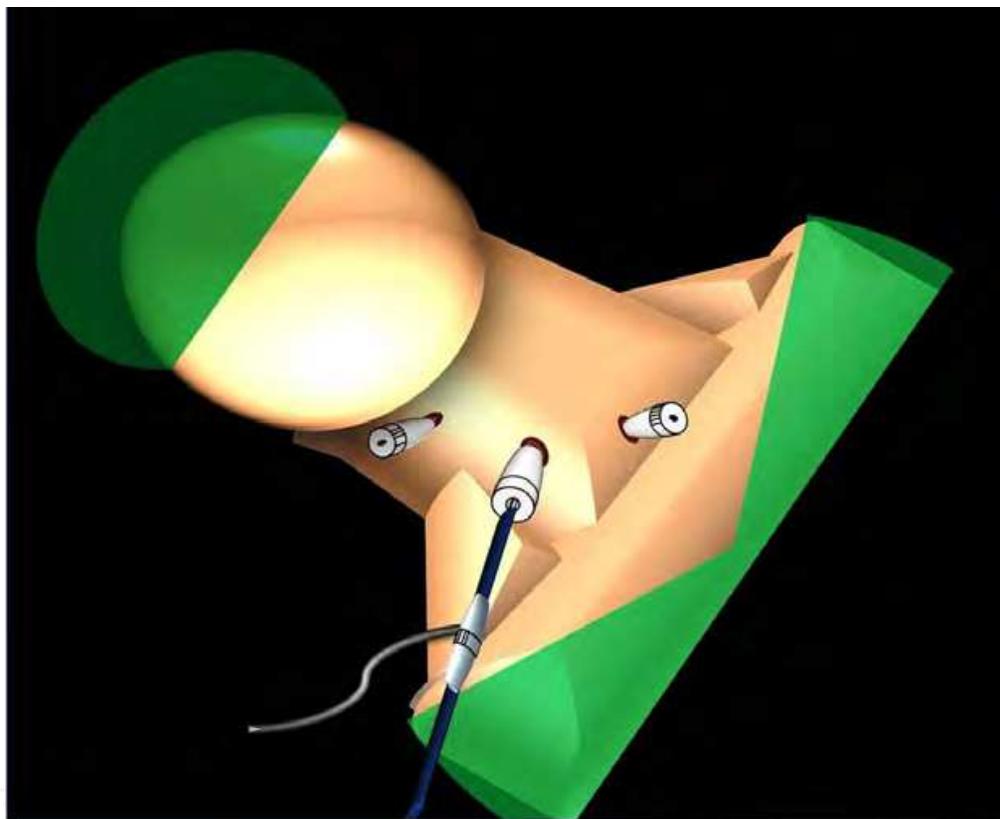


Fig. 8. Schematic representation of endoscopic parathyroidectomy: lateral access technique

With the continued improvements in parathyroid imaging techniques, minimally invasive parathyroidectomy is rapidly becoming the procedure of choice in patients with PHPT.

5.4.6 Intra-operative PTH (IOPTH) measurement

IOPTH measurements were first introduced in 1990, and represent an alternative to four-gland visualization. (Irvin GL., 1999) This is regarded as an important advancement in the development of unilateral surgery, replacing the need for visualisation of all glands, and has been referred to as biochemical “frozen section”. During surgery, blood is drawn for PTH assays before (baseline) and after the excision of a hyperfunctioning gland. The removal of the diseased hyperfunctioning parathyroid tissue is predicted by a fall of PTH by more than

50% of its preoperative (baseline) value, within 10 to 15 minutes. Studies have reported that a 50% reduction from pre-excision PTH values within 5-10 minutes of adenoma excision can accurately predict post-operative normocalcaemia. (Inabnet et al, 1999). In other words, a decrease of more than 50% from the baseline value at 5-10 minutes after resection is suggestive of a single gland disease (solitary adenoma). However, if such a drop does not occur, then the possibility of multi gland disease is likely, and a conversion to bilateral neck exploration should be considered.

OUTCOMES	COMMENTS
Cure rates	Similar cure rates between MAP and conventional parathyroidectomy 95%-100%
Complications	Similar complication rates between minimal access parathyroidectomy and conventional parathyroidectomy (Starker et al 2011) Recurrent laryngeal nerve injury and transient hypoparathyroidism <1% Post operative haemorrhage (0.2%-0.5%)
Cosmesis	Definitive evidence of smaller scars Some opine that centrally placed scars appear better than lateral scars Concern of central scar more prone to keloid formation Axillary approach avoids unsightly scars in visible areas of the neck & torso
Hospital stay	Shorter hospital stay < 23 hrs Day case surgery especially if performed under local anaesthesia

Table 5. Overview of outcomes in minimal access parathyroidectomy

The disadvantages described include its cost, and interaction with anesthetic drug propofol (which should be stopped 5-10 minutes before blood sampling). The full potential of IOPTH needs further study. The role of intra-operative radioguided technique is controversial. Some are of the opinion that radioguided techniques rarely provide any additional information over the sestamibi scan itself and should not be routinely used during parathyroid operations.

All patients may not be candidates for directed or targeted minimal access approaches. Patients with multigland disease, MEN-related hyperplasia, and renal disease may not be suitable candidates for MAP. Whether the long term outcomes of MAP will be comparable to the best results obtainable with a conventional bilateral exploration remains to be proven.

KEY POINTS-4

- Since majority of the patients have only a single-gland disease, bilateral neck exploration is not routinely necessary, in all patients.
- The term MAP/MIP should be reserved for parathyroidectomies performed through incisions less than 2.5 cm.

- Cure rates are equivalent to those of a bilateral neck exploration for single gland disease.
- Advantages include avoidance of general anaesthesia and overnight admission, good cosmesis.
- Minimal access approach may be best suited for single adenomatous disease.
- Surgical expertise is still an important factor.

6. Conventional parathyroidectomy: “Identification and dissection of the parathyroid glands”

The three important goals in parathyroid surgery are-

1. Recognizing the normal from abnormal parathyroids.
2. Identifying and protecting recurrent laryngeal nerves.
3. Searching for parathyroids in predictable locations.

The initial operative steps are similar to that for thyroidectomy. The corresponding thyroid lobe is elevated and the structures lying under this region are carefully inspected first. The normal parathyroids and the fat in this region may appear similar initially and moreover the parathyroids may be covered by a globule or layer of adipose tissue.

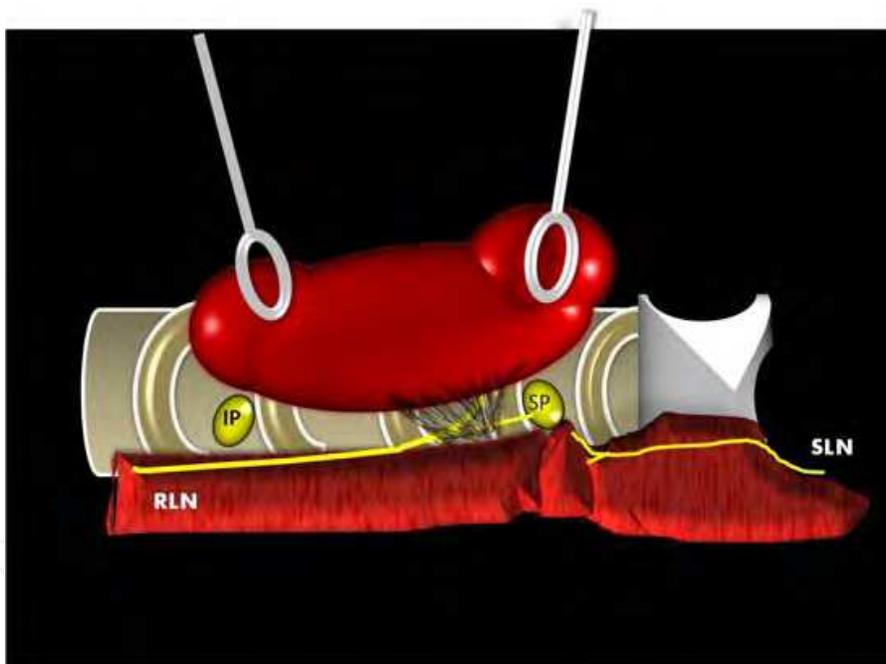


Fig. 9. Schematic representation of the expected anatomy during conventional parathyroidectomy. The thyroid lobe is mobilized. The recurrent laryngeal nerve (RLN) lies in the trachea-oesophageal groove. The commonest position of the superior parathyroid gland (SP) is posterior to the superior or middle third of the thyroid lobe and that of the inferior parathyroid gland (IP) is anterior, lateral, or posterior to the inferior third of the thyroid lobe with the nerve passing obliquely between them.

A small pledget can be used to tease away cobweb like fascia lying in close proximity to the posterolateral surface of the elevated thyroid lobe. This will most often bring into view the locations of the superior and inferior parathyroids. The presence of globular fat deposits

might create some amount of confusion. The normal parathyroids are soft and can be present in different shapes and may be sometimes very much flattened like a disc by the overlying fascial layer. Once the fascia is teased away the glands will appear to be more globular. The gland will also have a network of fine capillaries on the surface [figure 10] and a biopsy might cause it to bleed (in contrast to fat). Lymph nodes and thyroid nodules may add to confusion too but these are often palpably firm.

The recurrent laryngeal nerve typically runs in the tracheo-esophageal groove with the superior parathyroids more anteriorly and inferior parathyroids more posterior in relation to this nerve. Capsular rupture of the abnormal gland should be avoided to prevent implantation of parathyroid cells in the operative site. Histological confirmation by frozen section examination is often valuable.

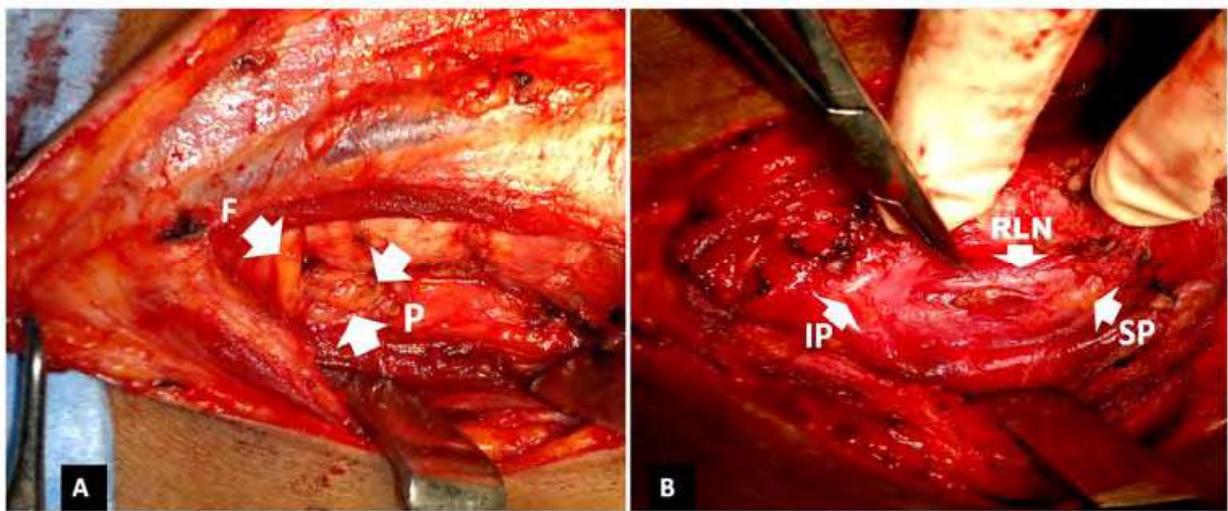


Fig. 10. (A) Operative photograph showing the parathyroid (P) which can be differentiated from fat (F) by the presence of fine blood vessels on the surface of the gland. (B) Operative photograph depicting normal relationships between recurrent laryngeal nerve (RLN), and superior(SP) and inferior parathyroid(IP) glands.

7. Ectopic parathyroids: “The hunt for the elusive parathyroids”

Sometimes, all the parathyroid glands cannot be identified readily. A systematic search is performed; based on the knowledge of the path of descent of superior and inferior parathyroid glands. The table gives a brief description of the places to look for in such cases.

The superior parathyroid glands are normally located on the posterior aspect of the superior or middle third of the thyroid lobe in more than 90% of the cases. The location of an ectopic superior parathyroid gland may be above the upper pole of the thyroid lobe (<1%); posterior to the pharynx or esophagus, in either the neck or the superior mediastinum (1%-4%); or intrathyroidal (<3%) (Eslamy & Ziessman, 2008).

The ectopic inferior parathyroid glands may be found, inferior to the lower pole of the thyroid lobe, either in the thyrothymic ligament or associated with the cervical portion of the thymus (26%); on or adjacent to the posterior aspect of the middle third of the thyroid lobe (7%); in the anterior mediastinum (4%-5%); intrathyroidal (<3%); or along the carotid sheath (<1%-2%).

Gland	Where to look for
Superior parathyroids	adjacent to the superior thyroid vessels the carotid sheath or posterior to the esophagus or pharynx (retroesophageal) the capsule of the thyroid gland
Inferior parathyroids	thyrothymic ligament. the thymus anterior mediastinum carotid sheath capsule of the thyroid

Table 7. Locations of ectopic parathyroids

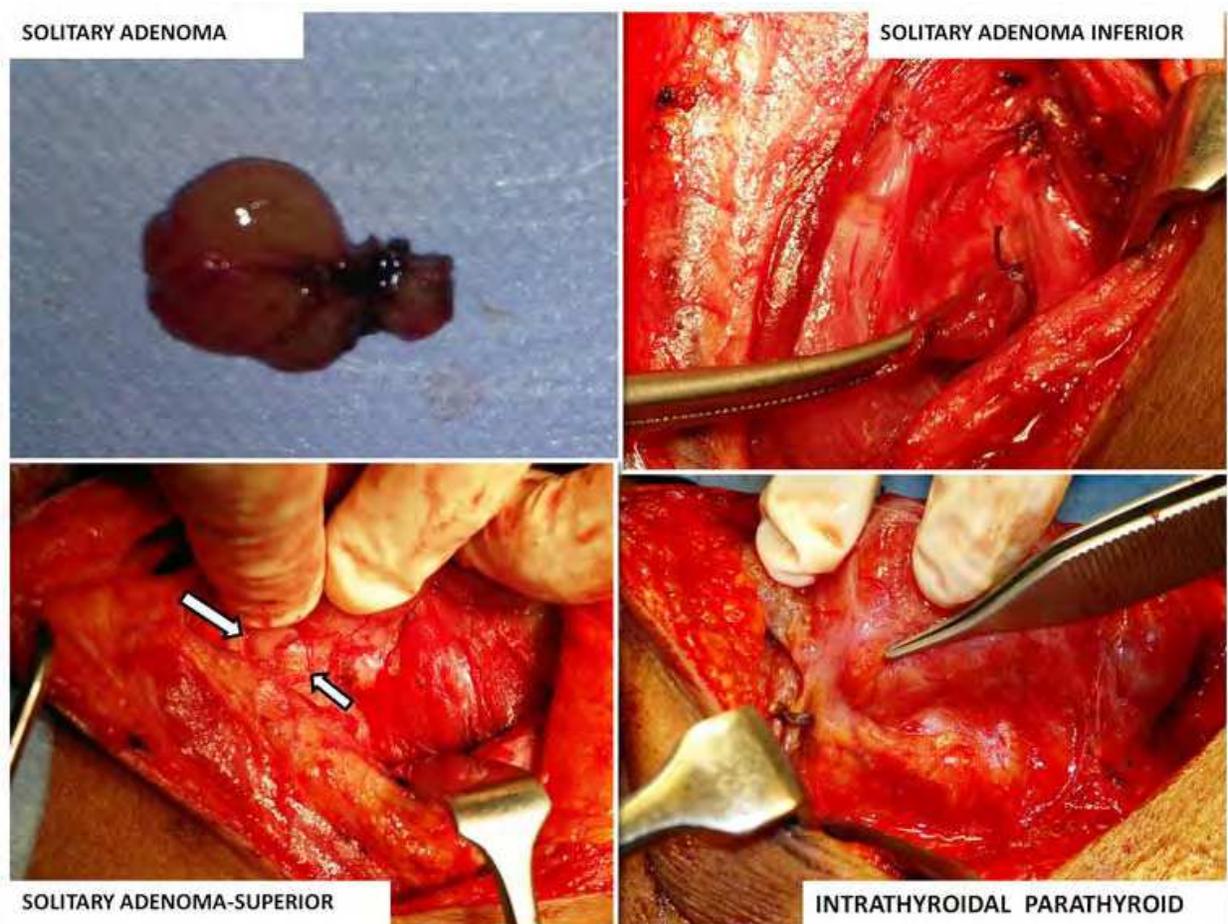


Fig. 11.

8. Conclusion - “The future”

As the patients are often asymptomatic, the diagnosis of primary hyperparathyroidism is based principally on laboratory findings of elevated serum calcium and serum parathyroid hormone levels. Asymptomatic disease is the commonest form of presentation in the developed nations. Symptomatic disease is very common in developing parts of the world.

Surgery is the only, definitive treatment for symptomatic disease. Since majority of cases of primary hyperparathyroidism, are due to a single parathyroid adenoma, selective gland excision is a better option. This should be facilitated with appropriate preoperative localization techniques such as with (Tc^{99m}) sestamibi scanning alone or combined with other modalities wherever possible. Intra-operative parathyroid hormonal monitoring may be a useful adjunct and can predict possibility of multigland disease and the need for converting the procedure to a bilateral neck exploration. The new surgical procedures are here to stay. Minimally access parathyroid surgery is feasible and should probably be increasingly offered to select group of patients. Conversion to bilateral neck exploration should not be regarded as a complication.

The final statement is that: "the success of both conventional and minimal access parathyroidectomy is dependent on the surgeon's hard earned experience and nothing can substitute that. "

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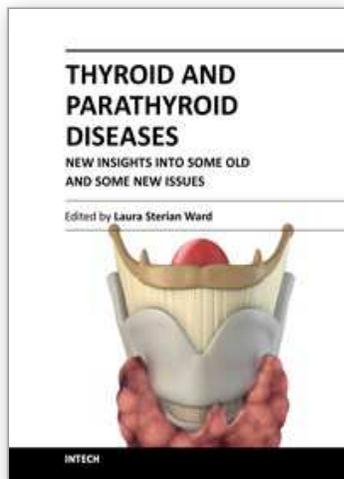
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Edited by Dr. Laura Ward

ISBN 978-953-51-0221-2

Hard cover, 318 pages

Publisher InTech

Published online 07, March, 2012

Published in print edition March, 2012

This book was designed to meet the requirements of all who wish to acquire profound knowledge of basic, clinical, psychiatric and laboratory concepts as well as surgical techniques regarding thyroid and parathyroid glands. It was divided into three main sections: 1. Evaluating the Thyroid Gland and its Diseases includes basic and clinical information on the most novel and quivering issues in the area. 2. Psychiatric Disturbances Associated to Thyroid Diseases addresses common psychiatric disturbances commonly encountered in the clinical practice. 3. Treatment of Thyroid and Parathyroid Diseases discusses the management of thyroid and parathyroid diseases including new technologies.

How to reference

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Sanoop K. Zachariah (2012). Management of Primary Hyperparathyroidism: 'Past, Present and Future', Thyroid and Parathyroid Diseases - New Insights into Some Old and Some New Issues, Dr. Laura Ward (Ed.), ISBN: 978-953-51-0221-2, InTech, Available from: <http://www.intechopen.com/books/thyroid-and-parathyroid-diseases-new-insights-into-some-old-and-some-new-issues/-management-of-primary-hyperparathyroidism-past-present-and-future->

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