Updates in management of Parathyroid Gland Tumors

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Abstract: Background: Primary hyperparathyroidism emerged from relative obscurity before the 1970s to become the third most common endocrine disorder in more recent times. Pathological correlates in primary hyperparathyroidism include parathyroid adenoma (80-85%) and hyperplasia (10-15%) and malignancy, which can occur in <1-5% of patients. In the past, both benign and malignant parathyroid disease would present symptomatically in affected patients. However, with the advance of routine serum calcium testing, the majority of patients with benign hyperparathyroidism are now diagnosed incidentally and asymptomatically. In addition to clinical and biochemical information, certain radiological features can help to distinguish benign from malignant parathyroid disease in the preoperative setting in all patients with primary hyperparathyroidism, radiological investigations is warranted to assess the extent of disease for treatment planning. Patients with primary hyperparathyroidism and symptoms or signs should undergo surgical removal of their parathyroid gland (s). **Aim of the Work:** The aim of this essay is to review the management of parathyroid glands tumours and the most recent updates in the parathyroid glands surgeries. **Conclusion**: Parathyroid surgery has evolved from conventional open parathyroidectomy, with exploration of all four parathyroid glands, to minimal access open or endoscopic parathyroidectomy. This evolution was made possible by the development of high resolution radiological techniques and the development of the rapid IOPTH assay. Sonography and technetium-99m-sestamibi (99mTc-sestamibi) scintigraphy are the most commonly used imaging techniques for the demonstration of parathyroid lesions. Neck ultrasonography is a non-invasive and relatively inexpensive tool that should be considered in all patients with overt hyperparathyroidism. The recent development and adoption of 99technetium-labelled sestamibi (99mTc-sestamibi) scintigraphy has enhanced our ability to distinguish between single-gland and multigland parathyroid disease. Although not routine, CT scan of the neck and chest may also be indicated in some cases to assess for disseminated disease. Recently, some investigators described a promising method by which a 3rd-generation to 2nd-generation PTH ratio >1 can help predict whether a parathyroid tumor is more likely to be malignant in the preoperative setting (sensitivity: ~75-82%; specificity: ~97-98%).. Rapid intraoperative assay is extremely helpful in confirming the complete removal of abnormal “hyperfunctioning” parathyroid tissue (demonstrated by >50% decrease in circulating PTH level 10-15 min after surgical excision), and can help distinguish between single-gland and multi-gland disease. Patients with primary hyperparathyroidism and symptoms or signs should undergo surgical removal of their parathyroid gland (s). However. In some patients, with medical comorbidities may preclude surgery, controlling hypercalcemia alone may be the goal.

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Introduction

The parathyroid glands are small glands located in the neck near the thyroid gland. Usually, 4 parathyroid glands develop, and are responsible for maintaining normal serum calcium levels. This is essential for normal bone metabolism, muscle and nerve physiology, in the nonpathologic state. The parathyroid glands respond to low serum calcium levels by releasing parathyroid hormone (PTH), PTH increases serum calcium levels through direct action on bone and the kidneys **(1).**

The term primary hyperparathyroidism (P-HPT) refers to the inappropriate overproduction of parathyroid hormone (PTH), resulting in abnormal calcium homeostasis. High levels of PTH lead to increased renal resorption of calcium, phosphaturia, increased synthesis of 1,24 (OH)2D3 and increased bone resorption. Primary hyperparathyroidism emerged from relative obscurity before the 1970s to become the third most common endocrine disorder in more recent times **(2).**

Pathological correlates in primary hyperparathyroidism include parathyroid adenoma (80-85%) and hyperplasia (10-15%) and malignancy, which can occur in <1-5% of patients **(3).**

In addition to clinical and biochemical information, certain radiological features can help

distinguish benign from malignant parathyroid disease in the preoperative setting **(4).**

Nonetheless, in all patients with primary hyperparathyroidism, radiological investigations is warranted to assess the extent of disease for treatment planning **(5).**

Parathyroid surgery has evolved from conventional open parathyroidectomy, with exploration of all four parathyroid glands, to minimal access open or endoscopic parathyroidectomy **(6).**

Aim of the Work

The aim of this essay is to review the management of parathyroid glands tumours and the most recent updates in the parathyroid glands surgeries.

Anatomy of Parathyroid Glands

Embryological background

The parathyroid glands develop from the endoderm epithelial cells of third and fourth pharyngeal pouches in weeks 5-6 of gestation **(7).** The inferior parathyroid glands arise from a more superior pharyngeal location (third pouch) than the superior thyroids (fourth pouch). The developing glands detach from the pouches at the fifth week of development, and descend to join the thyroid gland during the seventh week. In normal development the attachment is lost and the inferior parathyroid glands take up their normal position posterior to the thyroid, deviation of the normal will result in ectopic parathyroid glands**(8).**

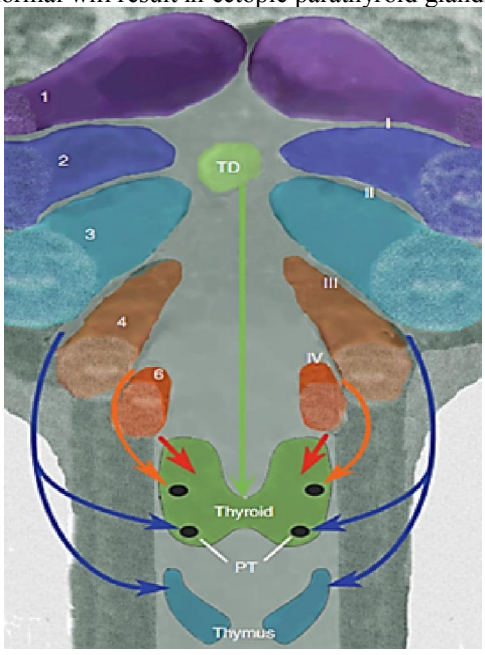

Figure (1): Embryology of the thyroid and parathyroid and their development from the pharyngeal pouches. TD = thyroglossal diverticulum, PT = parathyroid (8).

Anatomy

Normally, the two pairs of parathyroid glands are located along the posterior aspect of the thyroid gland. However, there can be 5 or more glands present, but it is rare to find less than 4 glands. In a Large autopsy series by Akerstrom and his colleagues, 4 glands were seen in 84% of patients and 3% of the patients had only 3 glands. There was 13% incidence of supernumerary glands. The supernumerary parathyroid glands were quite small, less than 5 mg, and were located in close proximity to normal glands, another common locations are in the thymus and in the mediastinum **(9).**

It is important to consider this numeric variation by surgeons performing parathyroid explorations.

The glands are ovoid glands weighing roughly 35-40 mg and measuring 3-8 mm in all dimensions. They have been described as flat-bean or leaf-like shaped, yellow tan or caramel in color and thus may be distinguished from the closely associated fat which is brighter, less distinct yellow**(10).**

The glands are primarily subserved by the inferior thyroid artery, which is the primary vascular supply to both upper and lower parathyroid glands in 76%-86% of cases and only in 15 % of cases, the superior parathyroid glands receive blood from the superior thyroid artery, and in 5 % of cases, from anastomoses of two thyroid arterial systems **(11).**

The venous blood of the parathyroid glands flows through the veins of the thyroid, trachea, and esophagus. The superior, median and inferior neck sympathetic nodes and stellate ganglia are sources of sympathetic innervations while parasympathetic sources are the vagus and descending branches of the hypoglossal and glossopharyngeal nerves, spinal nodes of CV–DII segments and vagal nodulous ganglia are the source of the sensitive fibers to parathyroid glands **(11).**

Etiology and Pathophysiology of Primary Hyperparathyroidism

Primary hyperparathyroidism (PHPT) is characterized by excessive secretion of parathyroid hormone (PTH) leading to hypercalcemia and a tendency toward hypophosphatemia **(12).**

Primary hyperparathyroidism (PHPT) is the most common cause of hypercalcemia in the outpatient setting. PHPT is twice to three times more common among women compared to males. The incidence is more common in subjects over 50 years of age and in postmenopausal women. The prevalence of PHPT in patients evaluated in reference centers is about 0.78% **(13).**

The parathyroid glands respond to low serum calcium levels by releasing PTH, which is an 84-amino

acid peptide. PTH increases serum calcium levels through direct action on bone and the kidneys **(14).**

It stimulates osteoclasts to resorb bone and mobilize calcium into the blood. In the kidneys, PTH acts to reduce calcium clearance and stimulates synthesis of 1, 25-dihydroxyvitamin D, which stimulates calcium absorption in the gastrointestinal tract (Figure 2).

Parathyroid disorders most commonly present with serum calcium abnormalities. The estimated incidence of primary hyperparathyroidism is approximately 25 cases per 100,000 persons per year in outpatients of Western countries, with a prevalence of one to four per 1,000 persons. Multiple endocrine neoplasia type 1 (MEN-1) and type 2 (MEN-2), which often include parathyroid neoplasia, each occur in about two per100,000 persons per year. Parathyroid cancer is rare, with an incidence of approximately four per 10 million persons per year **(14).**

Most patients suffering from primary hyperparathyroidism todays are asymptomatic, with nephrolithiasis occurring in up to 15% of patients, bone disease (formerly osteitisfbrosacystica) occurring in 2% of patients, and neuromuscular symptoms occurring rarely. Although marked symptoms are uncommon in Western countries, it is important to be aware that subtle and nonspecific symptoms may be present. Other causes of hypercalcemia are listed in Overall, 85% of patients with primary hyperparathyroidism have a single adenoma, Multiglandular hyperplasia accounts for 10% to 15% of patients with primary hyperparathyroidism, and carcinoma accounts for 1% or less. There are also uncommon familial causes, such as MEN-1 and MEN-2A; persons with these conditions may have parathyroid adenomas or asymmetric hyperplasia **(14).**

Risk factors for primary hyperparathyroidism include a history of neck radiation, age older than 50 years, and female sex; women are twice as likely as men to develop primary hyperparathyroidism. **(15).**

A solitary adenoma may involve any one of the four glands. Multigland enlargement most often results from primary parathyroid hyperplasia and less often from multiple adenomas. Hyperplasia usually involves all four glands asymmetrically, whereas multiple adenomas may involve two or possibly three glands. An adenoma and hyperplasia cannot always be reliably distinguished histologically, and the sample may be referred to as "hypercellular parathyroid" tissue. Because of this inconsistent pattern of gland involvement, and because distinguishing hyperplasia from multiple adenomas is difficult pathologically, these two entities are often histologically considered together as "multiple gland disease" **(12).**

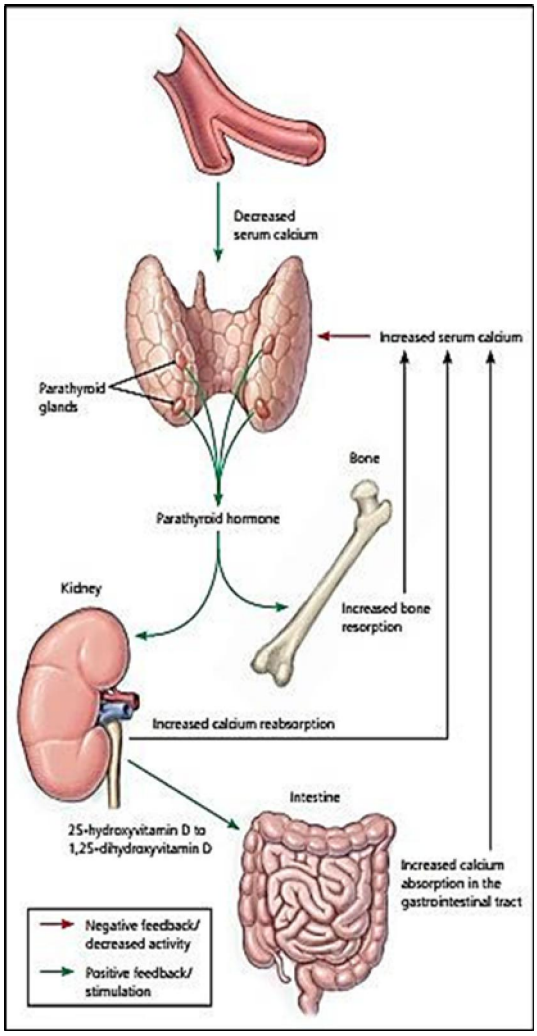

Figure (2): Control of mineral metabolism by parathyroid hormone (PTH). Calcium-sensing receptors of parathyroid cells respond to serum calcium level and change with increased release (hypocalcemia) or suppression (hypercalcemia) of PTH. PTH stimulates bone resorption, which increases serum calcium and phosphorus. In the kidney, PTH stimulates reabsorption of calcium and promotes phosphorus excretion. PTH also helps convert 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D in the kidneys, which then increases intestinal transport of calcium and phosphorus (14).

Parathyroid adenoma either occurs in the normal anatomical location of parathyroid glands, frequently in the lower ones, or can be found in ectopic sites (e.g. thymus, thyroid, and esophagus) in about 10% of cases. Ectopic parathyroid glands can significantly impact morbidity and clinical outcomes primarily due to failure during parathyroid exploration and subsequent requirement for reoperation **(16).**

Grossly, adenomas have an oval or kidney shape, red-brown color and soft consistency. Sometimes, they are multilobated, an occurrence which occasionally requires their incomplete excision. The size ranges from less than 1 cm to over 3 cm, while the weight varies from 150 mg to several grams. Large adenomas (>800mg) replace the entire gland and foci of cystic changes are common. Microadenomas, weighing less than 0.1 g, are also well documented. Larger adenomas are generally associated with higher levels of calcium and PTH and are more likely to be symptomatic **(17).**

Microscopically, Diagnostic criteria for adenoma include a pushing border, lack of intralesional fibro-adipose tissue, absence of lobular growth and complete circumscription with a rim of normal parathyroid at the periphery; the latter observed in only 50–60% of cases. Microadenomas are typically non-encapsulated, whereas larger adenomas often have a fibrous capsule. The cells of adenomas are arranged in cords, nests, sheets, and follicles and frequently are arranged around blood vessels. The nuclei are generally rounded with dense chromatin; they are usually larger than those of the normal parathyroid cells. Scattered pleomorphic and hyperchromatic nuclei, as well as multinucleate cells, are relatively common **(12).**

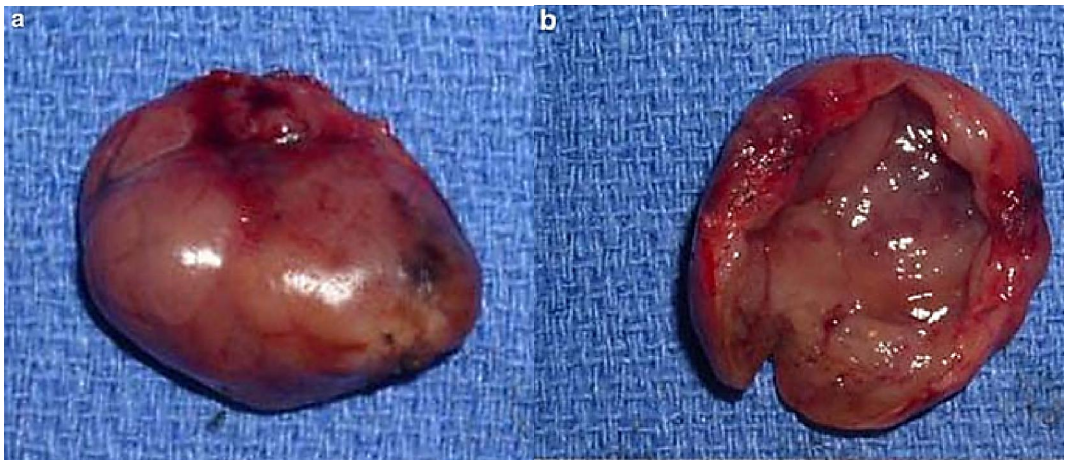

Figure (3): Gross specimen of a cystic parathyroid adenoma. (a) Exterior view shows a smooth surface with minimal hemorrhage and no significant adhesions. The specimen ‘‘shelled out’’ easily. (b) The mass is opened to demonstrate a smooth cyst wall lining **(13).**

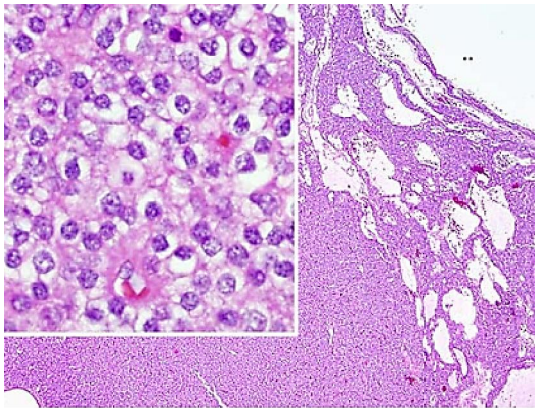

Figure (4): The low-power portion of this H & E stained section shows the hyper cellular parathyroid adenoma with a cystic lumen. High power examination depicts the proliferative parathyroid tissue to be composed of a population of chief cells.

Parathyroid carcinoma (PTCA) was first described in 1904 by De Quervain. PTCA is an exceptionally rare malignancy, with a clinical presentation similar to benign PHPT in many cases. Parathyroid carcinoma accounts for less than 4% of cases of parathyroid disease and is seen in 0.5–1% of HPT cases. Grossly, parathyroid carcinomas are large tumors that invade the surroundings of tissues of neck, thyroid and peri-esophageal tissues. By light microscopy, they are characterized by broad fibrous bands and composed predominantly of chief cells **(14).**

The only reliable indicators of malignancy are vascular invasion, perineural space invasion, capsular penetration with growth into surrounding tissues and distant metastases. In adenomas, which have been biopsied, trapping and pseudo invasion can be present, simulating a carcinoma. Histological clues include the presence of hemosiderin-laden macrophages, granulation tissue and the finding of linear areas of scarring **(12).**

Diagnostic Procedures of Parathyroid Gland Tumors

The concept of the “parathyroid incidentaloma” appeared in medical practice. It owes its emergence in the first place to ultrasound (US), magnetic resonance imaging (MRI), and computed tomography (CT) imaging. Modern surgical treatment of parathyroid

pathology is based on accurate topical diagnosis of pathologic focus. That influences the choice of the method and technique of surgical intervention. All methods of topical diagnosis of abnormal parathyroid glands can be divided into three conditional groups: noninvasive preoperative, invasive preoperative, and intraoperative diagnostic methods**(18).**

Techniques like single photon emission computed tomography [SPECT], positron emission tomography [PET], and intraoperative gamma detection are used now more and more frequently in clinical practice **(19).**

Table (1): These methods differ from each other in their main diagnostic parameters (sensitivity and specificity). Some of these methods give objective results, while others are less objective, being operator-dependent (20).

Noninvasive preoperative	Invasive preoperative	Intraoperative
▪ **Ultrasound** ▪ **Thermography** ▪ **Scanning with ^{131}I or ^{99m}Tc** ▪ **Scintigraphy with ^{201}Tl – ^{99m}Tc** ▪ **Scintigraphy with ^{99m}Tc-sestamibi** ▪ **SPECT** ▪ **CT** ▪ **MRI** ▪ **PET**	▪ Fine needle aspiration biopsy (FNAB) with Cytology. ▪ Determination of PTH and thyroglobulin in needle washout. ▪ Selective arteriography and subtraction angiography. ▪ Selective venous blood sampling with PTH test. ▪ Selenium-methionine arterial injection.	▪ Ultrasound. ▪ Intravenous infusion of toluidine or methylene Blue. ▪ Cyclic adenosine monophosphate urine test. ▪ Quick intraoperative blood PTH test. ▪ Gamma detection.

Ultrasound Examination (US):

US recommended as a first-line method in the diagnosis of PHPT. The majority of authors emphasize the advantages of US, which is a noninvasiveness approach, which gives the opportunity to utilize it repeatedly in the same patient at different stages of examination and treatment **(21).**

Many authors emphasize that the main problem of sonography is a significant number of both false-negative and false-positive results. The sensitivity of US varies depending on the experience and skill of the specialist, the class of scanner, types and frequencies of probes, and the size and location of the parathyroid glands. In addition, detection of abnormal parathyroid glands is difficult in obese patients. showed that the sensitivity of parathyroid US conducted by an experienced specialist is higher as compared with that of a general practitioner in an outpatient department (79 vs. 33 % respectively) **(22).**

US is necessary in patients with concomitant pathology of parathyroid glands and other neck organs. Many studies have shown that the incidence of thyroid cancer in patients with parathyroid adenoma is about 2%. Therefore, US of the thyroid and parathyroid glands aims to exclude thyroid nodules prior to the surgery on the parathyroids**(23).**

Computed Tomography and Magnetic Resonance Imaging (CT):

CT of the neck and mediastinum is used to specify the localization of pathologic parathyroid glands together with the methods of radionuclide diagnostics and US. CT is a more objective (though less sensitive) diagnostic method (as compared with US) in revealing enlarged and orthotopically located parathyroid glands.

Additionally, CT is a more informative method (as compared with US) for topical diagnosis of the ectopias, adenomas, and hyperplastic parathyroid glands in areas inaccessible to US. CT is advantageous in providing more complete information not only about organs under study and relations between the pathologic process and surrounding tissues but also about the condition of the adjacent organs **(24).**

MRI has advantages over CT: Radiation load is absent, X-ray contrast agents are not needed, and artifacts are rare. Its expensiveness is the greatest difficulty slowing its implementation. The principal indication for MRI (as for CT) is an ectopia of a pathologic parathyroid gland – initially, location of the tumor in the mediastinum, preliminarily revealed with a 99m Tc-sestamibi scan **(25).**

Radionuclide Imaging (RNI):

The majority of scientists have confirmed that scintigraphy with ^{99}mTcsestamibi is the most informative in revealing pathologically changed parathyroid glands. The continuation of this research has led to the discovery that isotope clearance rates in the thyroid and parathyroid glands are different. Mononuclide technology has achieved good results to general surprise. This gave Taillifer et al., a chance to create a new dual-phase technology of scintigraphy with 99mTc-sestamibi **(26).**

Single-Photon Emission Computed Tomography (SPECT) and Positron Emission Tomography (PET) have been created on principles of scintigraphy with radionuclides and computer technologies. We can confidently claim that the principle of functional and anatomic determination of tissues, which underlies scintigraphy, has good prospects in endocrine surgery. It allows for the finding and obviation (removing, destroying, evaporating, freezing, blocking the circulation, etc.) of the foci of PTH hypersecretion with minimal injury to adjacent tissues ***(26).***

Indications for Radionuclide Imaging

It is necessary to notice that indications for performance of radionuclide diagnostic procedures are strictly limited. The majority of publications recommend that radionuclide methods should be used only for topical diagnosis, and not for revealing or confirming PHPT. These methods are applied only in patients with already known hyperparathyroidism diagnosed by clinical observation and laboratory tests. It means that the patient must undergo at least two preliminary laboratory studies: determination of PTH and ionized calcium (Ca^{2+}) levels in blood serum ***(26).***

The indications for RNI in patients with hyperparathyroidism are the following:

- Primary hyperparathyroidism confirmed by laboratory research;
- Recurrent and persistent hyperparathyroidism;
- Suspicion of a parathyroid tumor;
- Differential diagnosis of mediastinal masses;
- Planning and controlling the surgical treatment of hyperparathyroidism;
- Osseous form of hyperparathyroidism: osteoporosis of unclear etiology, fibrocystic osteodystrophy, frequent pathologic bone fractures;
- Recurrent and coral-like kidney stones;
- Differential diagnosis of PHPT and SHPT;
- Assessment of multiple lesions of the parathyroid glands ***(26).***

Treatment Modalities of Parathyroid Gland Tumors

Management of primary hyperparathyroidism:

Patients with serum calcium levels of 12.14 mg/dL (33.5 mmol/L) may not require immediate treatment if this elevation is chronically well tolerated. However, an acute rise in calcium levels may lead to dehydration or cardiovascular or neurologic complications, which require more aggressive measures. In addition, patients with serum calcium levels of >14 mg/dL (3.5 mmol/L) require treatment, regardless of symptoms. Thus, patients with severe hyperparathyroidism-induced hypercalcemia should be hospitalized, and urinary catheterization and central venous pressure monitoring should be considered. Initial treatment should include intravenous saline solution to gradually replace lost fluids and increase urinary calcium excretion **(27).**

Once fluid repletion is accomplished, loop diuretics may be used to decrease renal calcium reabsorption and promote urinary excretion. Calcitonin 200 IU once every 8 h may help to decrease albumin-adjusted calcium. Bisphosphonates, corticosteroids, calcium chelators, or dialysis are occasionally indicated in severe cases ***(27).***

Patients must be closely monitored for complications caused by aggressive diuresis, including hypokalemia, hypomagnesemia, and acute renal insufficiency ***(2).***

However, parathyroidectomy is the only curative therapy, with a success rate of 95–98%. To prevent the progression of systemic complications of PHPT ***(28).***

The NIH's 2008 modified guidelines recommend surgery for asymptomatic patients who have a serum calcium that is >1.0 mg/dL (0.25 mmol/L) above the upper limit of normal, a CrCl of <60 mL/min, a T-score of ≤ 2.5 at any site, a previous low-trauma fracture, or an age of <50 years ***(29).***

Surgical options (Parathyroidectomy):

Anaesthesia

Either general or local anesthesia can be used for patients undergoing parathyroidectomy. Local anesthesia, via a subcutaneous injection of 1% lidocaine over the intended incision and along the anterior and the posterior borders of the sternocleidomastoid muscle, ipsilateral or bilateral, is used for patient preference or comorbidities. For complications such as technical complications or toxic reactions to lidocaine, unexpected findings, or patient discomfort, general anesthesia should be considered ***(30).***

Techniques

Parathyroidectomy may be performed using different techniques.

1-The standard procedure

for PHPT is bilateral neck exploration, performed under general anesthesia, which is the best choice for patients with inherited hyperparathyroidism or multigland disease. Subtotal parathyroidectomy (i.e., removal of 3.5 glands) or total parathyroidectomy with autotransplantation of parathyroid tissue at a distant site (e.g., the forearm or sternocleidomastoid muscle) may be performed. A transverse incision of 2–4 cm in length above the sternal notch is made, following the skin lines across the anterior neck. The tracheoesophageal groove, the paraesophageal area, the carotid sheath, and the thymus should be explored if a gland is missing. Cervical thymectomy can be performed if a gland is missing in the first surgery, but mediastinum exploration should only be performed in patients who have a gland clearly localized to the mediastinum ***(31).***

2-Minimally invasive parathyroidectomy (MIP)

MIP allows patients to undergo focused parathyroidectomy and has the benefits of a smaller incision, a shorter operation duration, a shorter length of hospital stay, and fewer complications; it is also more cost-effective than the standard four-gland exploration. A small incision is usually made ipsilateral to the preoperative localized adenoma. MIP surgery can be performed through central or lateral neck incisions and has a 97% success rate with minimal morbidity and no procedure-specific complications ***(32).***

Preoperative localization is critical in this situation, because most of the neck is not explored, given the focused nature of the procedure ***(33).***

3-Endscopic parathyroidectomy

Video-guided (endoscopic) parathyroidectomy is comparable to MIP in operative success, incision length, postoperative pain, cosmetic results, and complication rates. This approach facilitates recognition of recurrent laryngeal nerve and blood vessels surrounding the parathyroid glands, but it is slower. It is contraindicated in patients with previous neck surgery, negative preoperative localization, or a large goiter, or in patients who need local anesthesia ***(34).***

Video-guided parathyroidectomy can be performed by using several techniques. The anterior approach permits bilateral exploration and does not need gas insufflation. Camera and endoscopic instruments can be used through a 10–15-mm incision just above the sternal notch. The lateral approach uses camera and endoscopic instruments through one 5-mm and two 2-mm incisions near the sternocleidomastoid muscle, allowing the surgeon to visualize the glands located posteriorly in the tracheoesophageal groove. The lateral approach requires low pressures of gas insufflation of the neck to avoid significant subcutaneous emphysema ***(35).***

Post-parathyroidectomy management:

It is vital to ensure that there is no expanding hematoma in the surgical wound. Antiemetics should be used to limit nausea and vomiting, which can lead to suture dislodgement. The majority of endocrine surgeons prescribe oral calcium supplements for a few weeks or vitamin D supplements in patients with very low postoperative PTH or a high risk of postoperative hungry bone syndrome. Patients should be re-evaluated 1-2 weeks after discharge to check the surgical site and serum calcium and PTH levels. Serum calcium and PTH levels should be reassessed after 6 months to confirm cure, and then annually to ensure that they remain normal and that abnormal tissue has not regrown. A follow-up bone density test is suggested at 1 year after surgery to guide the treatment of bone loss ***(31).***

Complications:

Despite a low incidence rate of 1%, bleeding and hematoma formation are fatal complications of neck surgery, as a rapidly expanding hematoma can lead to venous congestion and airway compromise. Careful intraoperative hemostasis is vital, as well as immediate bedside evacuation with subsequent exploration and closure. Temporary or permanent recurrent laryngeal nerve injury and hoarseness are caused mainly by errors surrounding the varied anatomy of the recurrent laryngeal nerve and its relationship to the thyroid gland**. (36).**

Transient or permanent hypoparathyroidism and hypocalcemia occur frequently after subtotal or total parathyroidectomy because of ischemic injury to healthy parathyroid gland (s). Preservation of one gland is sufficient to maintain normocalcemia. The immediate primary treatment of postoperative biochemical hypocalcemia is calcium and/or vitamin D supplementation. Appropriate patient education on the symptoms of hypocalcemia and the liberal use of calcium replacement therapy is necessary prior to discharge **(37).**

Parathyroid cryopreservation can be used in patients who have a high risk of severe postoperative hypocalcemia. Persistent or recurrent disease has an incidence ranging from 1% to 10%. Following parathyroidectomy, hypercalcemia within 6 months is defined as persistent disease and hypercalcemia after 6 months is defined as recurrent disease. Persistent or recurrent disease may be caused by surgeon inexperience, incomplete exploration, or supernumerary glands. Preoperative parathyroid surgery in these cases presents a challenge, as dense scar tissue and distorted tissue planes obscure intraoperative localization ***(29).***

Medical therapy options:

In patients who are not candidates for surgery or those unwilling to undergo parathyroidectomy, treatment recommendations include annual serum calcium and creatinine testing and BMD measurement every 1–2 years. Patients should be encouraged to maintain a normal intake of calcium. Medical management includes:

1) Bisphosphonates and hormone replacement therapy to decrease bone turnover and improve BMD, although they do not decrease serum calcium or PTH levels **(38).**

2) Cinacalcet to reduce serum calcium and PTH levels and raises serum phosphorus levels, although it does not reduce bone turnover or improve BMD ***(38).***

3) Vitamin D should be measured and replaced if the pre-parathyroidectomy vitamin D level is <20 ng/mL or <50 nmol/L ***(39).***

Management of Parathyroid carcinoma

Surgical treatment:-

Surgery is the primary mode of therapy. Complete surgical resection with microscopically negative margins is the recommended treatment and offers the best chance of cure. Successful resection is dependent on preoperative suspicion and intraoperative recognition. Upon intraoperative recognition of malignant features, the surgeon should elect to perform en bloc resection of any involved tissues without compromising the tumor capsule. This may or may not include the thyroid, as taking out the adjacent thyroid lobe in itself has been recommended but not shown to improve survival ***(19).***

Parathyroid cancer has a high recurrence rate in up to 49–60% of cases after the initial operation. In cases of recurrence, surgical resection is still the primary mode of therapy ***(40).***

However, reoperation is rarely curative and eventual relapse is likely. Typically, these patients require repeated operations that predispose them to up to 60% life-time accumulated surgical risks from all subsequent surgical interventions ***(19).***

Initial neck exploration

Standard procedure:

En bloc resection is defined as careful removal of the parathyroid lesion while preserving its capsule and resecting all tissues immediately involved with the parathyroid cancer, which can include the ipsilateral thyroid lobe, the trachea, and/or the esophageal wall. Any suspicious or enlarged ipsilateral regional lymph nodes should also be removed, especially those draining the central neck compartment. When the recurrent laryngeal nerve is involved, most surgeons recommend resection to ensure adequate tumor resection, especially if the nerve is not functioning preoperatively. En bloc resection offers the best chance at complete removal of cancerous tissue while reducing risks of tumor spillage ***(41).***

Contraindications:

In untreated hypercalcemic crisis, surgery should be delayed until the metabolic derangement is medically treated. Patients with florid metastatic disease are less likely to derive a large benefit from local surgical resection unless the amount of tumor cytoreduction is enough to decrease the hypercalcemic effects of hyperparathyroidism **(41).**

Complications:

Poor outcomes are related to incomplete resection, tumor seeding, and cancer persistence or recurrence. Surgical complications include recurrent laryngeal nerve injury, esophageal injury, tracheal injury, neck hematoma, and wound infection. Metabolic complications that can occur after resection include hypocalcemia and hypophosphatemia. Perioperative mortality was estimated to be 1.8% in one series **(19).**

Reoperation

Standard procedure:

For localized regional recurrent tumors, we recommend cervical and/or mediastinal exploration with wide resection. Finding a recurrent tumor in a reoperative neck is challenging due to the presence of scar tissue and distorted anatomical planes. Locoregional injection of methylene blue dye may enhance resectability by silhouetting the tumor against the background of difficult neck anatomy. If technically feasible, metastatectomy is recommended for localized distant metastasis, which has been shown to help control hypercalcemia**(19).**

Contraindications:

The same contraindications exist as noted above for initial neck exploration.

Complications:

The types of complications in neck reoperation are the same as aslistes above for initial neck exploration. However, complication rates are 3–5 times higher than for the initial operation **(19).**

Many patients will have multiple reoperations, thus greatly increasing their cumulative surgical complication risks up to 60% and recurrent laryngeal nerve injury rate up to 38% over the course of a patient's cancer lifespan. There are also organ-specific complications from metastatectomy such as lung resections, bone resection, etc. Metabolic complications also include hypocalcemia and hypophosphatemia **(19).**

Medical treatment of parathyrotoxicosis

Parathyrotoxicosis (also referred to as hypercalcemic crisis, parathyroid storm, acute hyperparathyroidism, or parathyroid poisoning) is a medical emergency. It is more commonly due to a functioning parathyroid carcinoma than benign parathyroid lesions. Patients in this acute state can exhibit altered mental status and profound weakness, accompanied by hypercalcemia (916 mg/dL) and azotemia. Although surgical resection is the definitive therapy for treating parathyrotoxicosis, patients should be medically stabilized before surgical intervention takes place.

Standard procedure:

Aggressive fluid resuscitation with intravenous isotonic sodium chloride fluid infusion is the first line therapy in order to restore intravascular volume and to promote renal diuresis. After restoration of intravascular space as evidenced by adequate urine output, furosemide is given to promote calcium diuresis. All calcium intake and medications such as thiazide diuretics, which can promote renal calcium reabsorption, should be discontinued. Hemodialysis may be required in patients with renal insufficiency or renal failure **(42).**

Calcimimetic agents (such as cinacalcet), and agents that block bone resorption (such as calcitonin

and bisphosphonates) can be used adjunctively to help stabilize calcium level. Goal reduction of serum calcium is by 1.5–4 mg/dL in 24 to 48 h **(42).**

Chemotherapy:-

No standard chemotherapy regimen is available. Chemotherapy is generally ineffective in the treatment of parathyroid carcinoma. No randomized trials are available to stringently evaluate the efficacy of individual chemotherapeutic agents in parathyroid carcinoma as most efficacy data is derived from case reports **(43).**

Radiation therapy:-

Parathyroid cancer is usually radio resistant; thus, no established radiotherapy protocol exists. However, anecdotal reports from contemporary single institution case series have described a reduction in cancer recurrence in patients who received radiation therapy, dosed between 40 and 70 Gy after initial surgical resection. The small number of cases precludes statistical analysis for generalizable effectiveness. Incorporation of adjuvant radiotherapy for the management of parathyroid carcinoma should be determined on an individual basis **(44).**

Palliative /Emerging therapy:-

Palliative therapy:

The primary treatment goal for inoperable metastatic parathyroid carcinoma is controlling PTH-driven hypercalcemia as it is the main cause of morbidity and mortality. Several classes of calcium lowering drugs have been used with transient results lasting for only a few days. These include mitramycin, plicamycin, gallium nitrate, intravenous bisphosphonates, and calcitonin in combination with glucocorticoid **(41).**

In one case report, gallium nitrate was effective in lowering serum calcium and PTH levels in parathyroid cancer patients who were refractory to mitramycin. However, with the advent of new drugs such as the calcimimetics, which are more effective at lowering serum calcium and PTH with lesser side effects, the aforementioned agents are gradually falling out of favor **(45).**

Emerging therapy:

Experimental immunotherapy has been successfully attempted in two inoperable metastatic parathyroid carcinoma cases. This therapeutic approach requires the induction of adaptive immunity with PTH protein fragments. In one case report, a detectable anti-PTH antibody titer, a sustained reduction in PTH and serum calcium, and a marked improvement in hypercalcemia symptoms were achieved after the second, third, and fourth immunizations, respectively. Due to the anecdotal nature of this case report, additional confirmatory work in a larger patient cohort is required to substantiate its efficacy and applicability **(46).**

Ablative therapy is another adjunct for palliation of inoperable metastatic parathyroid cancer. Ethanol ablation by ultrasound guided percutaneous injection of 98% ethanol into parathyroid tumor tissue can directly reduce PTH level and ameliorate intractable hypercalcemia. This therapy appears to have minimal side effects and can be employed serially to achieve desirable therapeutic results. However, ablation should be reserved for palliative cases only because of the potential for tumor seeding from needle tracks and complications associated with ethanol toxicity from large volume injection as well as local nerve and tissue injuries **(47).**

It is not recommended for use in the central neck region if the recurrent laryngeal nerve is still functioning in that region. Some inoperable distant metastatic lesions, such as intrahepatic and intrapulmonary lesions, are anatomically accessible by interventional radiologists and thus can be ablated transcutaneously with radiofrequency (RFA) or transcatheter arterial embolization (TAE) **(48).**

As described above, management of metastatic parathyroid carcinoma is mostly described in the form of case reports or small case series. Therefore, therapeutic options should be tailored individually **(48).**

Prognosis of Parathyroid Gland carcinoma

Survival analysis of parathyroid carcinoma patients extrapolated from various cancer databases such as SEER, NCDB, and Swedish Cancer Registry, and from longitudinal retrospective studies at single institutions showed an overall survival of 85% and 49–77% at 5 and 10 years follow-up, respectively **(32)**.

Persistent or recurrent disease occurs in more than 50% of parathyroid carcinoma patients, manifested usually by elevated serum PTH and calcium. However, these serum biomarkers remain unaffected in non-functioning parathyroid carcinoma and are thus uninformative in the detection of recurrence in those patients **(43).**

Most recurrences are locoregional. Patients with recurrence are likely to require multiple operations and thus have a high rate of surgical complications, especially recurrent laryngeal nerve injuries. Up to 25% of patients with parathyroid carcinoma develop distant metastases during the follow-up period **(49)**.

The costal margin, the retroperitoneal space is entered. The medial port incision is placed approximately 4 to 5 cm caudal to the inferior margin of the 12th rib. The lateral port is placed directly inferior to the costal margin. A 10-mm port with a "donut" balloon is placed into the middle port site.

Mortality due to functional parathyroid carcinoma is usually secondary to intractable hypercalcemia leading to progressive end-organ damage, such as renal failure. The prognosis of

parathyroid cancer is somewhat variable. In general, it has a better survival rate than most solid tumors **(50).**

There is currently no prognostic staging system. It is estimated that up to 40% of patients with parathyroid carcinoma undergo piecemeal or incomplete tumor resection, mostly attributable to lack of disease recognition either preoperatively or intraoperatively **(51).**

However, the empirical selection of a mandatory concurrent thyroidectomy is debatable. A recent retrospective review by Harari et al., showed that mortality and recurrence rates were not affected by the extent of thyroidectomy during the initial operation. This was consistent with other previously published reports of single institutional experiences **(19).**

A likely explanation for this observation is that complete removal of tumor is largely driven by accurate intraoperative assessment of the extent of invasiveness by experienced surgeons rather than the amount of tissue structures removed. Currently, there are no established criteria to triage the extent of surgical resection. The most commonly recommended procedure is en bloc resection with whichever nearby structures are involved. The completeness of initial operation has been shown to be an independent prognosticator for disease-free survival **(19).**

Conclusion:

Parathyroid surgery has evolved from conventional open parathyroidectomy, with exploration of all four parathyroid glands, to minimal access open or endoscopic parathyroidectomy. This evolution was made possible by the development of high resolution radiological techniques and the development of the rapid IOPTH assay. Sonography and technetium-99m-sestamibi (99mTc-sestamibi) scintigraphy are the most commonly used imaging techniques for the demonstration of parathyroid lesions.

Neck ultrasonography is a non-invasive and relatively inexpensive tool that should be considered in all patients with overt hyperparathyroidism. The recent development and adoption of 99technetium-labelled sestamibi (99mTc-sestamibi) scintigraphy has enhanced our ability to distinguish between single-gland and multigland parathyroid disease. Although not routine, CT scan of the neck and chest may also be indicated in some cases to assess for disseminated disease.

Recently, some investigators described a promising method by which a 3rd-generation to 2nd-generation PTH ratio >1 can help predict whether a parathyroid tumor is more likely to be malignant in the preoperative setting (sensitivity: ~75-82%; specificity: ~97-98%).

Rapid intraoperative assay is extremely helpful in confirming the complete removal of abnormal "hyperfunctioning" parathyroid tissue (demonstrated by >50% decrease in circulating PTH level 10-15 min after surgical excision), and can help distinguish between single-gland and multi-gland disease.

Parathyroidectomy is the treatment of choice for Primary hyperparathyroidism. However, In some patients, with medical comorbidities may preclude surgery, controlling hypercalcemia alone may be the goal.

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