Clinics in Surgery

Review Article
Published: 02 Apr, 2019

Parathyroid Disease: A Paradigm for Disease Management

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Abstract

Hyperparathyroidism is a disorder that is frequently unrecognized until the patient has an elevated serum calcium level identified on a routine physical exam. We discuss the disease identification, symptoms and signs of hyperparathyroidism as well as management. Primary hyperparathyroidism is routinely managed by surgery. The most important aspect for surgery is the pre-operative localization of the offending gland.

This paper discusses the pre-operative imaging procedures available and a paradigm for management of primary hyperparathyroid patients for which there is no preoperative localization. Specifically, it discusses the technique of intraoperative split central venous PTH measurements that is used in surgery. This technique serves as a valuable adjunct to the surgical management of primary hyperparathyroidism.

Introduction

Hyperparathyroidism

Primary Hyperparathyroidism is a disorder of 1 or more of the bodies 4 parathyroid glands. The disease often goes unrecognized until a patient has an automated laboratory test as part of a routine physical exam for some other disorder discovers hypercalcemia. When the blood test demonstrates an elevated serum calcium level (Hypercalcemia) as well as an elevated Parathyroid Hormone (PTH), the diagnosis of Hyperparathyroidism (HPTH) is made. It is estimated that in the United States, 100,000 people develop Primary Hyperparathyroidism each year [1]. The disease is diagnosed in post-menopausal women 3 times more often than in men and usually affects people in their fifth and sixth decades of life [2]. The distinction Primary hyperparathyroidism means that the calcium disorder originates in the parathyroid glands. Primary Hyperparathyroidism is a disorder of bone and mineral metabolism manifesting in hypercalcemia because of excessive parathyroid hormone secretion from one or more parathyroid glands. A single benign parathyroid adenoma is the cause in most people [2]. Although HPTH is mostly sporadic, there are familial forms of the disease that represent 2% to 5% of the total cases. MEN1 is the most common familial cause of primary hyperparathyroidism. About 10% of MEN cases are sporadic. Secondary hyperparathyroidism is a condition in which a disease outside of the parathyroid glands causes all four of the parathyroid glands to become enlarged and hypercellular. The most common causes of secondary hyperparathyroidism are kidney failure and vitamin D deficiency. There is a delicate normal homeostatic regulation of calcium and phosphorus in the serum, intracellularly and mineral levels in bone. This regulation occurs at three major target organs, the intestine, the kidney and bone, principally via the complex integration of two hormones, parathyroid hormone and vitamin D. Frequently, there is another medical condition that lowers or wastes serum calcium followed by a compensatory increase in parathyroid hormone secretion with 4-gland parathyroid hyperplasia. Chronic Kidney Disease (CKD) is the most common cause of secondary hyperparathyroidism. Failing kidneys do not convert enough vitamin D to its active form, and they do not adequately excrete phosphate. When this happens, insoluble calcium phosphate forms in the body and removes calcium from the circulation. The secondary rise in PTH secretion associated with Chronic Renal Failure is a result of the kidneys inability to excrete the excess phosphorus. For patients with secondary hyperparathyroidism from kidney failure, the only treatment is to have a kidney transplant. Secondary hyperparathyroidism can also be seen in severe dietary calcium deficiency as well as severe Vitamin D deficiency.

Primary hyperparathyroidism has two forms; a benign enlargement of one gland called a Parathyroid Adenoma which is the most common cause and is seen in 85% of the cases. A less common cause of primary hyperparathyroidism is due to enlargement of all four glands (4 gland Hyperplasia) seen in 13% to 15% of patients. In each type, the parathyroid tissue produces

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Received Date: *25 Feb 2019*
Accepted Date: *26 Mar 2019*
Published Date: *02 Apr 2019*

Citation:
Maceri DR, Tai T. Parathyroid Disease: A Paradigm for Disease Management. Clin Surg. 2019; 4: 2385.

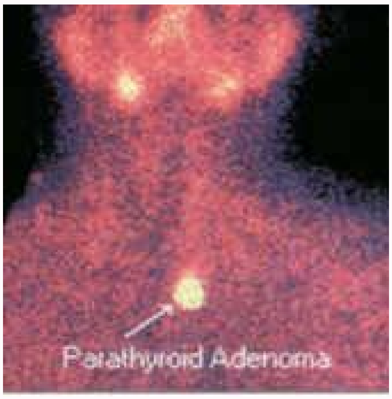

Figure 1: Sestamibi Scintigraphy (Sestamibi Scan).

Figure 2: Inferior Parathyroid Adenoma. On ultrasound, parathyroid adenomas are usually well-circumscribed, ovoid, and longitudinal in shape. They are homogeneously hypoechoic relative to the thyroid echogenicity.

excessive amounts of Parathyroid Hormone (PTH). The symptoms of hyperparathyroidism usually affect patients long after the overproduction of PTH and the onset of hypercalcemia. When a patient has symptoms, they may be mild and nonspecific.

- The range of symptoms includes:Osteoporosis leading to fragile bones and pathologic fractures
- Nephrolithiasis and nephrocalcinosis (Kidney stones)
- Excessive urination
- Abdominal pain: Constipation, possible peptic ulcers and Acute Pancreatitis
- Easy fatigability and proximal muscle weakness
- Depression and lack of focus
- Bone and joint pain

These symptoms were once chronicled as why patients came to see the doctor:

- Stones: kidney stones (most are calcium phosphate or calcium oxalate)
- Bones: Nonspecific pain in the bones and joints due to bone breakdown referred to as osteitis fibrosa cystica
- Groans: Lethargy and fatigue
- Moans: Constipation and abdominal pain
- Psychic Overtones: Confusion and depression irritability

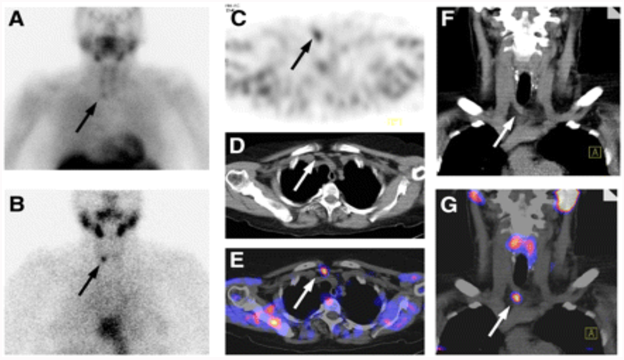

Figure 3: SPECT CT White Arrows (F) W/O Contrast with Contrast and G. **A** and **B** are Planar views (at 15 min **B** and 60 min **A**) of ^{99m} TC-MIBI scintigraphy. Planar imaging is limited by precise anatomic location and the overlapping thyroid gland. (**E**) Indicating parathyroid adenoma below right thyroid gland (arrows). (**F** and **G**) Demonstration of parathyroid adenoma (arrows) in corresponding coronal CT (**F**) and SPECT/CT (**G**) [4].

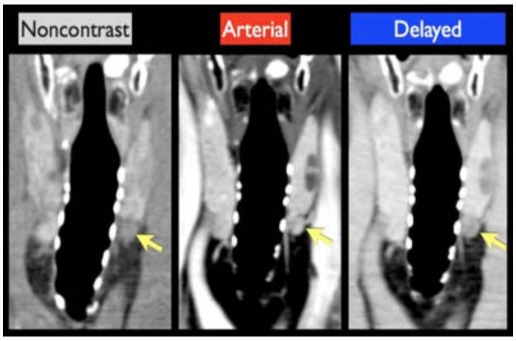

Figure 4: Four-dimensional computed tomography (4D-CT) scan. An oval shaped enhancing mass with low attenuation on non-contrast phase relative to thyroid (Yellow arrow). The greatest attenuation is in the arterial phase and rapid washout of contrast in the delayed phase Yellow arrow. There are variations in enhancement patterns and helpful morphological findings such as the polar vessel (White arrow) seen in the arterial phase [4,5].

One could add Thrones to the list of symptoms because of the frequent trips to the bathroom because of the polydipsia and polyuria.

Localization of the abnormal gland

There are normally four small parathyroid glands which are part of the endocrine system. Their function is to regulate the calcium and phosphorus in our bodies. Parathyroid glands are located in the neck behind the thyroid where they continuously monitor and regulate blood calcium levels. They are small (20 mg to 40 mg) and have a beanlike shape. They can have ectopic locations in the neck and occasionally in the chest. Ectopic parathyroid glands result from aberrant migration during early stages of embryologic development. At surgery the lack of successful identification of ectopic may lead to unsuccessful parathyroid surgery [3-5].

Abnormal Parathyroid Gland Locations

N of 37/231 16% of Patients

Ectopic Superior Location 14/231=38% (Table 1).

Ectopic Inferior Location 23/231=62% (Table 2).

More recently, (20 to 30 years) the surgical approach to Primary Hyperparathyroidism (PHPT) has shifted to Minimally Invasive Parathyroidectomy (MIP) rather than the traditional four-gland bilateral neck exploration. The success of MIP mandates the ability to localize or image the abnormal parathyroid gland prior to surgery.

Standard Imaging Techniques Include

Sestamibi scintigraphy (sestamibi scan)

Sestamibi scan (Figure 1) imaging- a nuclear medicine technique using gamma rays from the decay of Technetium (99 mTc) sestamibi. The isotope will to penetrate muscle and other tissue to view their condition and function. The Sestamibi scan will image the hyperactive gland causing hyperparathyroidism in about 80% to 90% patients. It has 98% to 100% specificity.

Dynamic ultrasonography

Dynamic ultrasound is the most frequently used imaging modality with the lowest cost and has the advantage of not using ionizing radiation in this setting. The yellow arrow points to a right (Figure 2).

SPECT CT

SPECT CT (Figure 3) is a Single Photon Emission Computed Tomography (SPECT) that uses technetium-99 Sestamibi as the radiotracer combined with X-ray-based CT to obtain planar or tomographic views. This technique is particularly helpful for pre-operative localization: The SPECT provides the 3-dimensional functional information which is fused with the CT based anatomic information [3].

4DCT

Four-Dimensional Computed Tomography (4D-CT) has increasingly been used for preoperative localization of adenomatous parathyroid glands in patients with PHPT since 2006. (This technique combines standard multiplanar CT scanning with a fourth dimension consisting of changes in contrast attenuation over time. Parathyroid 4D-CT represents the latest technology in parathyroid imaging. Parathyroid 4D-CT is not the same as a regular CT scan. There are several key differences:

The resolution of 4D-CT imaging is higher than that of any other type of parathyroid scan. In fact, abnormal parathyroid glands as small as 1 mm × 6 mm have been imaged and then gone on to be removed, resulting in successful, curative parathyroid surgery. The contrast administration and the associated timing of the scans are key differences between conventional CT and 4D-CT (Figure 4 and 5).

There are three phases in the study:

1. Non-contrast
2. The Arterial contrast phase
3. The Delayed phase

Brown et al. [6] reported that among instances in which an abnormal gland was not identified by sestamibi scanning, 4D-CT correctly identified the abnormal gland in 80% of cases (Figure 2) [7]. Similarly, in patients undergoing reoperation, 4D-CT scanning correctly identified the abnormal gland in 91% of cases, compared to 45% for sestamibi scanning (Figure 6) [7-11].

Normal and ectopic parathyroid locations

In a series of 231 patients operated on for hyperparathyroidism by Phityakorn R, and McHenry CR they found a 16% incidence of ectopic parathyroid glands and a 100% positive predictive value of sestamibi scintigraphy underscore the importance of sestamibi imaging in patients with primary hyperparathyroidism (Figure 7) [9,10].

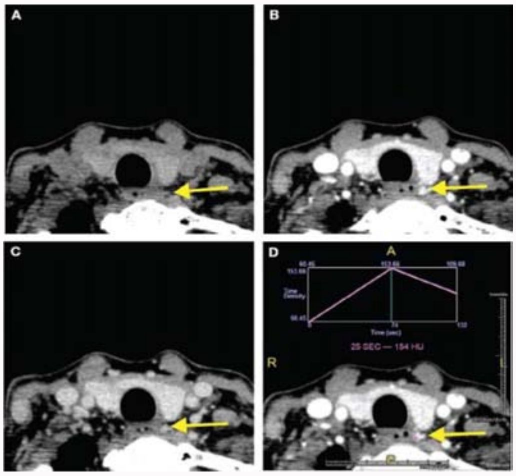

Figure 5: 4DCT. **A** is the Pre-contrast phase. The arrow shows the eventual location of the adenoma. **B** is the arterial phase demonstrating the thyroid and parathyroid enhancement. (Yellow arrow) showing the left inferior parathyroid adenoma. The peak enhancement is in the arterial phase (**B**). **C** is the delayed arterial phase as the contrast is leaving the adenoma. **D** shows the time attenuation curve of the contrast demonstrating rapid enhancement and washout from the adenomatous gland [5].

Figure 6: A sagittal 4DCT of a patient with a parathyroid adenoma localized to the Carotid Sheath (Arrow) [10,11].

Incidence and Location of Ectopic Abnormal Parathyroid Glands

Split central venous sampling of parathyroid hormone in non-localizing parathyroid tumors

Split Central Venous Sampling of Parathyroid Hormone in Non-localizing Parathyroid Tumors has become a valuable adjunct to surgical exploration [9]. For most of the 20th century, neck exploration with 4 gland identification was the treatment for primary hyperparathyroidism. Parathyroid surgery has undergone significant improvement and reliability with the development of more sophisticated and accurate Intraoperative Parathyroid Hormone Monitoring (IO-PTH) monitoring [12]. We have developed a paradigm that has been an extremely valuable adjunct in surgery for those patients that have failed to localize a parathyroid tumor with standard imaging studies (Sestamibi Scan, Ultrasound, and 4D CT) [6].

Currently, Sestamibi scans, although highly specific, will localize

Table 1: Abnormal Parathyroid Gland Locations. Ectopic Superior Location 14/231=38%.

Location	Number	Percentage
Tracheoesophageal Grove	6	43
Retroesophageal	3	22
Posterior Superior Mediastinum	2	14
Intrathyroidal	1	7
Carotid Sheath	1	7
Para esophageal	1	7
Total	14	100%

Table 2: Abnormal Parathyroid Gland Locations. Ectopic Inferior Location 23/231=62%.

Location	Number	Percentage
Intrathymic	7	30
Anterior Superior Mediastinum	5	22
Intrathyroidal	5	22
In Thyro-thymic Ligament	4	17
Submandibular	2	9
Total	23	100%

the side of an abnormal gland (single adenoma) in 71% to 79% of primary hyperparathyroid patients. When coupled with 4DCT and Neck Ultrasound, the sensitivity improves to 79% to 95%. The issue is what is the best alternative surgical plan to use when imaging studies fail to localize the abnormal gland(s)?

We have worked out the algorithm that is used when there is failure to localize the offending parathyroid gland with conventional imaging. There were 115 patients that were without definitive localization between January 2010 and May 2016. (There were no Secondary hyperparathyroid patients neither included nor were there revision surgical cases used as part of the study). A cohort of 41 individuals had bilateral internal jugular vein samples drawn low in the neck (The year 2012 was not included due to a change in the IOPTH measurements) and were analyzed with an immunochemiluminescent assay (Future Diagnostics, Wijchen, and The Netherlands). After induction of general anesthesia, a peripheral vein blood sample was obtained for comparison. Split (left and right) internal jugular vein samples were compared for gradients (Figure 8).

The algorithm above was used for all patients with complete data to direct the initial area of surgical exploration. In all cases, a suspicious gland was removed followed by an IOPTH level from a peripheral vein. The end-point was a >50% reduction of the IOPTH gradient level 10 min to 15 min after the offending gland was removed. Repeated failure of the PTH levels to drop >50% from the baseline after a careful unilateral exploration, resulted in a bilateral 4-gland exploration [13]. After applying the selection criteria, 27 patients had undergone surgery with bilateral internal jugular vein PTH samples and received a definitive pathologic diagnosis to correlate with the intraoperative findings. There was no statistically significant relationship between 4-gland hyperplasia patients and their left or right-sided IJV PTH levels. Increases in right sided IJV PTH levels correlated with right sided adenomas and an increase in left sided IJV PTH values correlated with left sided adenomas.

Of the 20 patients that had a single adenoma, the absolute value of PTH gradient (Figure 9) was calculated as the difference between

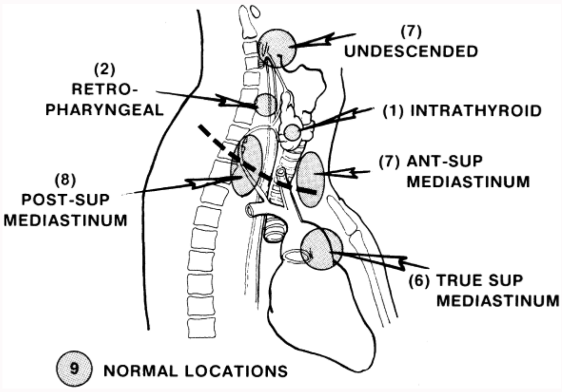

Figure 7: Normal and Ectopic Parathyroid Locations.

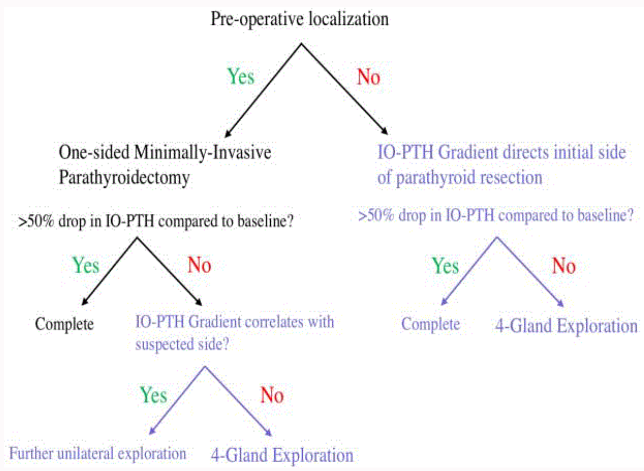

Figure 8: Internal jugular vein samples.

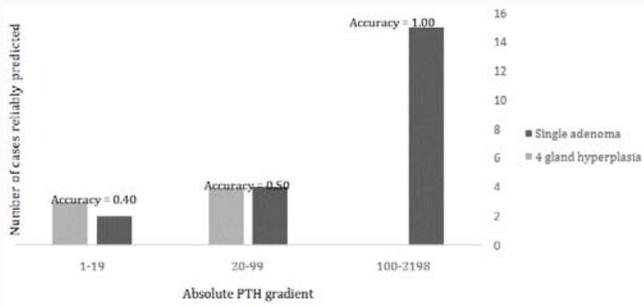

Figure 9: Predictive value of the PTH gradient.

the right and left internal jugular vein values. The value was correct in predicting the adenomas side in 19/20 cases. In cases where the Right and Left sided absolute values were equal the larger the absolute value of the gradient, the more likely the gradient correctly predicted the side of the tumor.

Cases where the Right and Left sided absolute gradient values were equal, were more likely to predict 4-gland hyperplasia. The larger the absolute value of the gradient, the more likely the gradient correctly predicted the side of the tumor (Adenoma).

Since publishing our first report in 2011, the standard for IOPTH monitoring in parathyroid surgery has remained largely unchanged. IOPTH values drawn 10 min after excision that decrease more than 50% when compared to baseline levels are widely accepted as an indicator of operative success. When inadequate localization occurs, ectopic adenomas, multiglandular disease or imaging limitations must be considered. We have demonstrated that a PTH gradient across split internal jugular vein samples positively correlates with the side of a parathyroid adenoma regardless of preoperative imaging results [14]. Furthermore, the study reinforces that unilateral adenomas exhibit a larger gradient when compared to those of multiglandular disease. Gradients above 100 pg/ml are 100% accurate in predicting a parathyroid adenoma as the root cause of the hyperparathyroidism [15].

Conclusion

A 16% incidence of ectopic parathyroid glands was reported by Phityakorn R et al. A 100% positive predictive value of sestamibi scintigraphy underscores the importance of sestamibi imaging preoperatively in patients with primary hyperparathyroidism.

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