REVIEW ARTICLE

Parathyroid Miss—Does it Exist? A Critical Review

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Abstract

Primary hyperparathyroidism (PHPT) is primarily treated with surgery, achieving a 95% cure rate when performed by skilled surgeons. However, 4–5% of patients experience persistent or recurrent PHPT post-surgery due to factors such as undetected adenomas or misdiagnoses like familial hypocalciuric hypercalcemia (FHH). Despite advancements in intraoperative parathormone monitoring and preoperative imaging, some cases remain challenging due to ectopic gland locations and other factors. This underscores the need for multidisciplinary approaches and thorough preoperative planning to enhance surgical outcomes in PHPT management.

Keywords: Localization, Persistent PHPT, Primary hyperparathyroidism, Recurrent PHPT.

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Introduction

Around 95% with primary hyperparathyroidism (PHPT) are cured with surgery as the primary procedure, if performed by a skilled surgeon. Persistent and recurrent PHPT remain complex clinical entities despite this encouraging success rate. After the initial parathyroid surgery, 4–5% of patients still have issues related to PHPT. For various reasons, such as inability to identify or remove the adenoma or failing to diagnose familial hypocalciuric hypercalcemia (FHH), surgery may not provide optimal control of the disease.[1]

Inability to locate preoperatively or inability to detect parathyroid adenoma intraoperatively or eliminate all hyperplastic or suboptimal excision in cases with four-gland hyperplasia incomplete removal of a parathyroid metastasis or parathyroid cancer sometimes encountering parathyromatosis—are the major reasons for parathyroid miss.

Developments in intraoperative parathormone monitoring, preoperative imaging, and localization have dramatically reduced the persistence and recurrence rates. Unfortunately, even with these imaging modalities there are perplexing cases in which the gland cannot be localized preoperatively as well as intraoperatively. This review discusses the factors responsible for such parathyroid miss.

Rationale for Localization

Normal parathyroid glands are tiny (2–3 mm), they are usually invisible on most imaging modalities. The parathyroid glands have variable location owing to their complex embryological development. The incidence of ectopic parathyroid is up to 30% due to faulty migration during the early developmental process.[2] The ectopic glands are found usually along the path of migration of the bronchial pouches, which can vary from the level of the carotid sheath to the heart. Most frequent location is in the thyrothymic ligament and near the tracheoesophageal groove or retroesophageal region. They can be intrathyroidal when they are enclosed by thyroid parenchyma without a capsule. Perrier et al. proposed a novel classification for localization for better localization of these glands as shown in Box 1.[3] The preoperative and intraoperative factors are discussed below.

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Preoperative Localization Miss!

The ultrasound (US) outweighs other investigation as the primary investigation because there is no radiation exposure, inexpensive, availability, and opportunity to screen the thyroid gland. Currently, US and Sestamibi (MIBI) are the primary investigations

Box 1: Classification according to location of the parathyroid gland as proposed by Perrier

Type A1: The parathyroid glands are connected to the surface of the thyroid
Type A2: The parathyroid glands are completely or partially embedded in the thyroid, but located outside the capsule
Type A3: The parathyroid glands are completely within the thyroid tissue and inside the capsule, which is distinct from type A2.
Type B: There is a plane between the parathyroid and the thyroid, making it relatively easier to retain in situ
Type B1: Peripheral thyroid type, including all type B parathyroid glands excluding types B2 and B3
Type B2: Intrathymic type in which the parathyroid glands are found in the thymus
Ttype B3: Blood supply is derived from the vessels of the thymus or mediastinum

for localizing the adenoma, MIBI is particularly helpful in locating the ectopic and multiple gland (as commonly found in syndromic hyperparathyroidism). If there is an ambiguity we have other radiological and nuclear Imaging like 4D CT, Choline PET, and contrast-enhanced US. Suboptimal visualization in cases of parathyroid hyperplasia, low-lying upper or inferior glands, and high body mass index are dependent on the sonographer's experience. This poses difficulty in the interpretation of location of the adenoma. Sonography is ineffective in cases of ectopic adenomas, anterior mediastinum, or retroesophageal region.

As per a recent meta-analysis, the sensitivity of US can reach 79% however, it can go down to 30% in cases of parathyroid hyperplasia. Nonetheless, better results can be if the US is combined with Sestamibi or 4D-CT. When Sestamibi and US are used together, the sensitivity for detecting an adenoma is much higher than when either technique is used alone.[4]

MIBI targets the tissues with high mitochondrial density, which absorb the radiotracer's and retain it in high concentration. The advantages of this technique include decreased radiation exposure, the ability to assess parathyroid tissue auto grafts, and the capability to study parathyroid glands found in ectopic or deeper areas, including the mediastinum. The limitations of this method include a less precise assessment of the thyroid gland, the possibility of false-positive results for thyroid nodules, and reduced effectiveness in detecting parathyroid hyperplasia.[5] Sestamibi is utilized with other nuclear Imaging modalities techniques like dual-phase, I131 subtraction, SPECT, and 4-D SPECT-CT imaging, each with distinct benefits and drawbacks. The sensitivity for large solitary glands is 88.4% as reported in a meta-analysis of 96 trials, whereas the sensitivity dropped to 44.2% for cases with multiglandular disease.[6] Whereas 4D CT has a sensitivity of 79% (range 45–92%) helps identify superior parathyroid adenomas that are posteriorly situated and typically obscured by thyroid absorption. Sensitivity decreases in the presence of parathyroid hyperplasia and double adenomas. A meta-analysis concludes that in situations of double adenomas (33%) or parathyroid hyperplasia (44%), its sensitivity is dramatically decreased. Moreover, the weight of the gland also has an implication on 4D CT and MIBI sensitivity. The sensitivity drops down to 51% if the weight is less than 500 mg, but it will reach 93% if it is more than 500 mg.[7] An adenoma is characterized by rapid absorption and gradual elimination of contrast. The precise anatomical location, regardless of its ectopic or normal position, the fact that 4D-CT is the only modality capable of identifying normal parathyroids, and its higher sensitivity for parathyroid hyperplasia in comparison to other techniques (62.5–85.7%) are just a few of its benefits. Cost, increased radiation exposure, restricted availability and accessibility, and the need for trained radiologists are its drawbacks. Another meta-analysis indicates that its sensitivity is 89%.[8] When compared directly, 4D-CT has a higher sensitivity than that of MIBI (65%) or US (57%).[9]

The causes of recurrent/persistent PHPT are adenoma (68%), parathyroid hyperplasia (28%), parathyroid carcinoma (3%), and other causes (1%, parathyromatosis, autograft recurrence). It is more common in cases with double adenomas or four-gland hyperplasia.[10] The hypoglossal nerve, the posterior triangle of the neck, the axilla, the mediastinum, the pericardium, the thymus gland, and the thyroid gland are among the ectopic locations of PA (about 0.3–8%).[11]

Apart from the ectopic location hyperplasia, the concealed second adenoma is one of the common frequent reasons for parathyroid miss. A second adenoma that is usually dormant, only to become active after the removal of the more active gland leading to persistence or recurrence after some time.

Surgeons Miss!

Then, during surgery, the adenoma may be missed because of misinterpretation by the nuclear physician or the radiologist, or even by the surgeon. This can be resolved by an intraoperative US either by the same radiologist or the surgeon. Even then in around 5% of the cases, the adenoma is failed to be identified and a lymph node or thyroid nodule is mistaken for a parathyroid. This obviously will result in persistent hypercalcemia with elevated PTH. Intraoperatively, adenoma is identified by the fleshy appearance of the gland after bisecting it, and it does not float unlike fat globule. The coming-of-age modalities for intraoperative identification include the use of ICG and autofluorescence but these techniques are of help when there is a tissue that is suspicious of being an adenoma, which is not the case always.

Conclusion

In the era of technology where we have various imaging modalities for preoperative localization of parathyroid glands, we have some cases of non-localization. We ought to have at least two concordant modalities for localization. In cases of ambiguity, we should always discuss it in multidisciplinary team meetings. Despite a heavy armamentarium, there will be a certain percentage of cases with a missed culprit gland, and it is the burden of the endocrine surgeon to live with.

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