
The Truth about Double Adenomas: Incidence, Localization, and Intraoperative Parathyroid Hormone



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- BACKGROUND:** Double adenoma is reported in 3% to 12% of patients with primary hyperparathyroidism. The aim of this study was to determine the true incidence of double adenoma and analyze the use of localization studies and intraoperative parathyroid hormone (IOPH) assay in these cases.
- STUDY DESIGN:** We conducted a retrospective review of a series of consecutive parathyroid surgical operations from 2010 to 2013. According to the surgical findings, the series was divided into single-gland disease (SGD), double-gland disease (DGD), and multi-gland disease (MGD, more than 2 glands). The sensitivity of ultrasound, technetium 99m-sestamibi, and 4-dimensional CT to correctly lateralize each gland in the DGD group was calculated. Results of the IOPH assay and how they impacted the extent of surgery were analyzed.
- RESULTS:** Three hundred and forty-seven patients had SGD (69%), 68 patients had DGD (13.5%), and 86 had MGD (17%). In the DGD group, sensitivity of ultrasound, technetium 99m-sestamibi, and 4-dimensional CT to lateralize each adenoma was 42%, 34.5%, and 64%, respectively. Initially, 27 patients (40%) with DGD had been planned for a focal exploration. The conversion to bilateral neck exploration was due to the IOPH assay in 18 cases (two-thirds of the initially planned focal explorations). At 6-month follow-up, all DGD patients were normocalcemic.
- CONCLUSIONS:** Localization studies in DGD can be misleading by reporting SGD. Four-dimensional CT seems to have the highest sensitivity. In focal explorations, the excision of all hyperfunctioning parathyroid tissue should be verified by IOPH measurement. (J Am Coll Surg 2016;222:1044–1052. © 2016 Published by Elsevier Inc. on behalf of the American College of Surgeons.)
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The incidence of primary hyperparathyroidism (pHPT) is approximately 100,000 new cases per year.¹ Surgery is the only curative treatment for pHPT.² The reported incidence of multi-gland disease (MGD) varies widely in the literature,^{3–7} and the existence of double adenomas

has been questioned.^{8,9} However, there is substantial published evidence that some patients with pHPT have 2 abnormal glands removed at surgery and on long-term follow-up do not experience persistent or recurrent disease.^{3,4,6,10–16}

Multi-gland disease and double adenoma represent a challenge in the management of pHPT, from the interpretation of the preoperative localization studies to deciding the extent of exploration and excision. Currently, there is no clinical or biochemical feature that can consistently predict the existence of MGD in patients with sporadic pHPT. Preoperative localization studies are notoriously unreliable at accurately predicting multi-gland parathyroid enlargement, leaving surgeons to rely on intraoperative findings and clinical judgment in treating patients with pHPT and more than one abnormal gland.

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Abbreviations and Acronyms

4D	= 4-dimensional
BNE	= bilateral neck exploration
DGD	= double-gland disease
HPT	= hyperparathyroidism
IOPTH	= intraoperative parathyroid hormone assay
IQR	= interquartile range
MGD	= multi-gland disease
MIBI	= technetium 99m-sestamibi single-photon emission CT
pHPT	= primary hyperparathyroidism
PTH	= parathyroid hormone
SGD	= single-gland disease
US	= ultrasound

In this study, we aimed to analyze the incidence and outcomes of patients with 2 abnormal glands resected during surgery at our institution, as well as to evaluate the performance of preoperative imaging studies and the intraoperative parathyroid hormone (IOPTH) assay in this setting.

METHODS**Patient selection**

We used a prospectively maintained endocrine surgical database and reviewed 1,076 consecutive parathyroid surgical cases, corresponding to 1,064 patients, from January 2010 through December 2013. All data were obtained with Institutional Internal Review Board approval at the Massachusetts General Hospital.

Patients included in the study had a preoperative diagnosis of pHPT undergoing a first-time operation with a postoperative follow-up of at least 6 months. Patients known to have MEN syndrome were excluded. Patients who had a first-degree family member with HPT not related to MEN syndrome were not excluded from our study. Demographic data, BMI, preoperative and postoperative levels of serum calcium, ionized calcium, intact PTH, phosphorus, 25-hydroxy vitamin D3, creatinine, and preoperative 24-hour urinary calcium were registered.

Five hundred and four cases that met inclusion criteria were reviewed. Patients were classified into 3 groups: patients that had only 1 pathologic gland excised (single-gland disease [SGD] group), patients that had 2 enlarged glands excised (double-gland disease [DGD] group), and patients that had 3 or more abnormal glands excised (MGD group). Patients with an adenoma and a normal-appearing gland removed or biopsied were considered part of the SGD group. Demographic and preoperative biochemical parameters from the DGD group were compared with those in the SGD and MGD groups.

Imaging

The remaining information focuses on the DGD group. Patients were preoperatively studied by ultrasound (US), technetium 99m-sestamibi single-photon emission CT (MIBI), and/or 4-dimensional (4D) CT. The preoperative imaging reports were classified as “positive” when at least 1 abnormal gland was detected or “negative” when no abnormal gland was identified. When the localization study was positive, it could be indicative of SGD or DGD. In cases in which the imaging reported DGD, it could indicate unilateral or bilateral parathyroid enlargement. These results were compared with the operative findings, and the sensitivity of the tests was calculated. An abnormal gland intraoperatively that was correctly lateralized by the imaging study was considered a true positive. An abnormal gland intraoperatively identified but not detected by the localization study was considered a false negative. When an imaging study identified a gland as abnormal but the gland was found to be normal intraoperatively, it was considered a false positive. Because not all patients had a bilateral neck exploration with 4-gland assessment, true negative glands on imaging studies could not be calculated. Whenever 2 tests were positive, we assessed whether the studies’ findings agreed in lateralizing the same abnormal glands.

Operative and pathology reports

From the operative reports, we recorded the preoperative intended approach, which was reported in the first paragraph of each operative note. When 2 imaging studies were positive and concordant for SGD, a focal surgical approach was attempted unless the patient had a thyroid condition that obliged a bilateral neck exploration. If the IOPTH levels did not drop appropriately after a focal exploration, the exploration was extended. On the other hand, patients with inconclusive imaging results or imaging that was suspicious for MGD were planned for a bilateral exploration.

The protocol for IOPTH monitoring consisted of a baseline determination of serum PTH before induction of anesthesia. Parathyroid hormone was again measured 10 to 15 minutes post excision of the suspicious parathyroid gland or glands. The determination of intraoperative intact PTH was done by immunoassay analyzer Roche Cobas e601 (Roche Diagnostics). An exploration was considered successful if the PTH dropped by $\geq 50\%$ and into the normal reference range after the excision of the abnormal gland or glands.

In all DGD patients, the weight (mg) and greatest diameter (mm) measured by the pathologist were recorded. The largest by weight of the 2 glands was labeled as “adenoma 1” and the smallest but still enlarged gland as “adenoma 2.”

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