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Preoperative parathyroid localization does not improve surgical outcomes for patients with primary hyperparathyroidism

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ABSTRACT

Background: Most patients with primary hyperparathyroidism undergo localization prior to operation with variable success. Therefore, in this study we investigated the safety of parathyroidectomy without imaging.

Methods: A prospective database of 2057 surgical patients with primary hyperparathyroidism from 2001 to 2019 was reviewed. Patients were categorized by use of preoperative imaging (ultrasound, sestamibi, CT scan), pathology, and cure.

Results: 1879 (91%) patients underwent preoperative imaging. CT scan was the most sensitive study (92%), though specificity was only 64%. Patients with imaging were older, had higher pre- and postoperative calcium, more likely to undergo unilateral exploration and have an adenoma ($p < 0.001$ −0.038). No differences were seen in nerve injury (<1%), postoperative hypocalcemia (<1%), or cure rate.

Conclusions: While localization may lead to minimally-invasive operations, we observed no differences in postoperative complications or cure rates in the hands of an experienced surgeon. Therefore, preoperative parathyroid localization does not improve outcomes for hyperparathyroidism and can be ordered sparingly.

Introduction

Both medical and surgical endocrinologists agree that primary hyperparathyroidism is a biochemical diagnosis that requires no imaging for confirmation and can only be cured surgically.[1,2] In an attempt to minimize operative extent and complications, minimally-invasive parathyroidectomy has become an attractive alternative to bilateral cervical exploration of all four glands. However, in order to accomplish this minimally-invasive approach, accurate preoperative localization with imaging studies is necessary.

While cervical ultrasound, technetium-labeled sestamibi scintigraphy, and 4D CT scan are readily available, they are imperfect studies with regional variance in accuracy, are reliant on the expertise of the reading physician, and can be costly.[3,4] Additionally, these studies are also less effective in the diagnosis of multigland disease.[5] Our group has previously reported on imageless parathyroidectomy, where 128 patients undergoing parathyroidectomy were matched (imaging v. no imaging). No differences in drop in intraoperative PTH (ioPTH) or length of operation were found.[6] Now with the recruitment of a larger cohort of parathyroidectomy patients without imaging, we further examine the safety and efficacy of imageless parathyroidectomy and to describe the evolution in practice patterns.

Materials and methods

Institutional Review Board approval was obtained at the University of Alabama at Birmingham. A prospective database of 2057 surgical patients with primary hyperparathyroidism from 2001 to 2019 was reviewed from two surgeons. The vast majority of patients were operated on by the senior author across two institutions. Early practice patterns included obtaining a cervical ultrasound or sestamibi scan for preoperative localization. If an adenoma was identified preoperatively, a minimally-invasive unilateral exploration was performed along with ioPTH levels. If no imaging studies provided concordant localization, bilateral neck exploration was performed unless an adenoma and an ipsilateral normal-appearing gland was seen, along with appropriate drop (>50% seen across 5, 10, and 15-min. samples) in ioPTH. Irrespective

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of the presence or absence of preoperative imaging, it is our practice to utilize labeled technetium injection on the day of surgery and intraoperative gamma probe to assess parathyroids ex-vivo. This is used in every patient unless there is a contraindication (ex. pregnancy, lactation). As practice patterns and surgeon experience evolved, a shift towards imageless parathyroidectomy occurred.

Outcomes measured and definitions used

Patients were categorized by the presence or absence of preoperative imaging studies including ultrasound, technetium-labeled sestamibi scintigraphy or 4D CT scan. Age, gender, body mass index, pre- and post-operative biochemical profiles, unilateral exploration, and surgical pathology were all compared. Patients were labeled as "mild disease" if they exhibited a normal calcium level in the setting of inappropriately elevated PTH levels. This is in contrast to patients with "classic" biochemical profiles, where both the calcium and PTH are overtly elevated. Outcomes included postoperative hypocalcemia as well as nerve injury as evidenced by postoperative hoarseness. Surgical cure was defined as normocalcemia at 6 months postoperatively. When imaging studies were available for review, accuracy was measured against intraoperative findings as determined by the surgeon.

Statistical analysis

Basic demographics and outcomes of patients with and without parathyroid imaging were compared using T-tests and chi-squared analysis where appropriate. IBM SPSS Statistics for Windows, version 25 was utilized (IBM Corp., Armonk, N.Y., USA). Statistical significance was defined as $p < 0.05$.

Results

Patient characteristics

Of the 2057 patients, 1879 (91%) underwent at least one preoperative imaging study. Basic patient demographics are listed in Table 1. Patients undergoing imaging were older than those without imaging [60 ± 0 v. 55 ± 1, respectively, $p < 0.001$]. The majority of patients in both cohorts were women (76 and 78%, NS) and there was no statistical difference in BMI. Patients who underwent imaging had a statistically significant higher preoperative calcium [10.9 ± 0.0 v. 10.5 ± 0.1 mg/dL, $p < 0.001$]. Those without imaging were more likely to exhibit "mild" biochemical profiles ($p < 0.001$).

Operative findings and outcomes

Patients with positive imaging studies were far more likely to undergo unilateral exploration [63 v. 13%, $p < 0.001$]. Those patients classified with "mild" biochemical profiles and no imaging were statistically more likely to exhibit multigland hyperplasia ($p < 0.001$). Between groups, no differences were seen in nerve injury (1%) or postoperative hypocalcemia (4 v. 1%). Both the imaging and no imaging groups achieved an excellent cure rate of 99%. There were no significant differences in rate of recurrent hyperparathyroidism (4 v. 3%) (Table 2).

Table 2
Operative findings and patient outcomes in the imaging versus non-imaging cohorts. Averages with standard error of the mean reported. Percentages may not add to 100% due to rounding.

Outcomes	Imaging n = 1879	No Imaging n = 178	P value
	No. (%)	No. (%)	
Pathology	1312 (70)	67 (38)	<0.001
Adenoma	208 (11)	21 (12)	
Double Adenoma	353 (19)	90 (50)	
Hyperplasia	6 (<1)	0 (0)	
Carcinoma			
Nerve Injury	18 (1)	0 (0)	
Hypocalcemia	75 (4)	2(1)	
Unilateral Exploration	1184 (63)	23 (13)	<0.001
Cure	1861 (99)	177 (99)	
Recurrence	76 (4)	5 (3)	

Imaging

Of the patients undergoing parathyroidectomy with preoperative localization, a total of 2390 studies were ordered, for an average of 1.27 studies per patient. For those patients undergoing imaging preoperatively, 92% underwent technetium-labeled sestamibi scintigraphy, followed by ultrasound (28%) and 4D CT scan (7%). For patients undergoing imaging, CT scan was the most sensitive (92%), though its specificity was only 64%.

Practice patterns changed significantly over the 19-year period over which these cases were performed. For the first 13 years, 97% of patients were either referred to the endocrine surgery service with imaging or localization studies were ordered by the operating surgeon. For the final 6 years in the included time period, 25% of patients were taken to surgery without imaging (Table 3).

Discussion

As surgical intervention is the only cure for primary hyperparathyroidism, the desire of the referring physician and surgeon should always be timely and cost-effective care, while simultaneously achieving excellent patient-centered outcomes. The surgeon's desire to minimize operative time and avoid complications while performing minimally invasive parathyroidectomy (MIP) certainly adheres to these overarching principles. However, the MIP

Table 1
Patient Demographics of patients with and without imaging. Averages with standard error of the mean reported.

Patient Characteristics	Imaging n = 1879	No Imaging n = 178	P value
	No. (%)	No. (%)	
Age	60 ± 0	55 ± 1	<0.001
Female Gender	1466 (78)	135 (76)	
BMI	31 ± 0	31 ± 1	
Preoperative Calcium (mg/dL)	10.9 ± 0	10.5 ± 0.1	<0.001
Preoperative PTH (pg/mL)	128 ± 0	123 ± 10	
Postoperative Calcium (mg/dL)	9.4 ± 0	9.3 ± 0.1	0.038
Postoperative PTH (pg/mL)	51 ± 1	48 ± 5	
Mild Disease	376 (20)	84 (47)	<0.001

Table 3
Distribution of imaging by year of surgical practice.

	2001–2007 n = 661	2008–2013 n = 879	2014–2019 n = 517	P value
	No. (%)	No. (%)	No (%)	
Imaging	639 (97)	852 (97)	388 (75)	<0.001
No Imaging	22 (3)	27 (3)	129 (25)	

approach requires localization studies that are often inaccurate, expensive and discordant with one another.[7] Moreover, patients undergoing minimally invasive parathyroidectomy appear to have a higher long-term recurrence rate.[8]

In our study, localization techniques exhibited a wide-range of sensitivities (71–92%). It has previously been shown that regional variation in imaging accuracy leads to non-diagnostic studies. While this is improved at high volume centers, 4D CT scan was again shown to be most sensitive at 92%.[3] Additionally, with increased understanding of mild biochemical profiles of PHPT, prior studies have shown these patients to more often exhibit 4-gland disease.[9,10] Our cohort confirms this knowledge. Thus these patients would benefit more from a thorough bilateral exploration than preoperative localization in order to achieve surgical cure.

Value-based care, defined as therapy that is cost-effective, patient-centered, and curative, should always be pursued. Wang et al. performed a cost-analysis to determine the most effective combination of localization studies for PHPT. They concluded that sestamibi-SPECT and US (±4D CT scan) was the most cost-effective strategy for PHPT. However, each of these studies range from $119 (US) to $765 (sestamibi-SPECT).[7] In another study, Madorin et al. highlighted the fact that both sestamibi and CT expose patients to radiation. Additionally, while 4D CT scans can be performed quickly (<5 min), sestamibi scans can take on average 306 min to complete.[11] These patient-centered factors should be taken into consideration when utilizing localization studies.

One concern with bilateral parathyroid exploration is that it results in increased operative time. However, we have previously shown that patients undergoing parathyroidectomy without imaging had similar operative times as patients with pre-operative imaging studies. The authors reasoned this was likely due to the fact that if an adenoma is identified and removed, they would most often be able to perform a contralateral exploration in the same time it would take the lab to result the ioPTH.[6]

Proponents of routine imaging prior to parathyroidectomy appropriately point to the fact that without at least an ultrasound, thyroid pathology can be missed and potentially change surgical planning. We have previously investigated this in a study of 222 patients, where only 1 patient (0.4%) was ultimately diagnosed with a thyroid malignancy over the average follow-up time of 14.9 years.[12] With regard to supernumerary or ectopic glands, in a 2012 study of 1562 patients, ectopic glands were seen in up to 22% of patients. Upon retrospective review of preoperative imaging of these cases, sestamibi and ultrasonography had a sensitivity of 89 and 59%, respectively. Yet the accuracy of detection was variable with regard to the location of the ectopic glands.[13] Our belief is that the surgeon's intimate knowledge of the likely location of ectopic glands, in the presence of an inappropriate drop in ioPTH during parathyroidectomy, is more effective than any localizing study.

Conclusion

While parathyroid imaging may lead to a more limited operation, we have found no differences in postoperative complications or rates of cure in imageless parathyroidectomy in the hands of an experienced endocrine surgeon. We conclude that preoperative parathyroid localization does not improve surgical outcomes and that parathyroid localization can be utilized sparingly.

Declaration of competing interest

No conflict of interest.

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