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Clinical Research Article

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Use of Preoperative Imaging in Primary Hyperparathyroidism

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Abbreviations: 4D, 4-dimensional; CT, computed tomography; ICD, International, Classification of Diseases; iPTH, intact parathyroid hormone; IV, intravenous; NPV, negative predictive value; PET, positron emission tomography; PHPT, primary hyperparathyroidism; PPV, positive predictive value; SPECT, single photon emission computed tomography; US, ultrasound

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Abstract

Context: Preoperative imaging is performed routinely to guide surgical management in primary hyperparathyroidism, but the optimal imaging modalities are debated.

Objective: Our objectives were to evaluate which imaging modalities are associated with improved cure rate and higher concordance rates with intraoperative findings. A secondary aim was to determine whether additive imaging is associated with higher cure rate.

Design, Setting, and Patients: This is a retrospective cohort review of 1485 adult patients during a 14-year period (2004-2017) at an academic tertiary referral center that presented for initial parathyroidectomy for de novo primary hyperparathyroidism.

Main Outcome Measures: Surgical cure rate, concordance of imaging with operative findings, and imaging performance.

Results: The overall cure rate was 94.1% (95% confidence interval, 0.93-0.95). Cure rate was significantly improved if sestamibi/single-photon emission computed tomography (SPECT) was concordant with operative findings (95.9% vs. 92.5%, $P = 0.010$). Adding a third imaging modality did not improve cure rate (1 imaging type 91.8% vs. 2 imaging types 94.4% vs. 3 imaging types 87.2%, $P = 0.59$). Despite having a low number of cases (n = 28), 4-dimensional (4D) CT scan outperformed (higher sensitivity, specificity, positive predictive value, negative predictive value) all imaging modalities in multiglandular disease and double adenomas, and sestamibi/SPECT in single adenomas.

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Conclusions: Preoperative ultrasound combined with sestamibi/SPECT were associated with the highest cure and concordance rates. If pathology was not found on ultrasound and sestamibi/SPECT, additional imaging did not improve the cure rate or concordance. 4D CT scan outperformed all imaging modalities in multiglandular disease and double adenomas, and sestamibi/SPECT in single adenomas, but these findings were underpowered.

Key Words: preoperative, imaging, primary hyperparathyroidism, cure, concordance

Primary hyperparathyroidism (PHPT) is the most common cause of hypercalcemia in the outpatient setting and is the third most common endocrine disorder, with prevalence differing between sex and race (1-3). Despite routine serum calcium measurements, PHPT remains underrecognized (4, 5). The estimated prevalence of PHPT in 2018 was 23 cases per 10 000 women and 8.5 per 10 000 men, with an incidence of 66 cases per 100 000 person-years in women and 25 per 100 000 person-years in men (3, 6). The attributable cause in about 70% to 80% of cases is a single parathyroid adenoma with the remainder comprising multiglandular disease, which includes both double adenomas and 4-gland hyperplasia. Parathyroid malignancy is seen in 1%, typically with a more aggressive presentation (3, 7). PHPT workup uses laboratory investigation to establish the diagnosis and imaging guide surgical planning (1, 3). Pharmacologic management involves bisphosphonate or calcimimetic therapy to reduce the deleterious effects of hypercalcemia, when surgical indications are not met. However, parathyroidectomy remains the standard of care and most cost-effective option, with established criteria helping to guide surgical referral (1, 3, 6, 8).

Although preoperative imaging is not required to establish a diagnosis, it is typically performed routinely to guide surgical management. Because of the wide variability between institutional protocols and surgeon preferences, the optimal imaging modality is debated (9). Historically, ultrasound (US) and nuclear scintigraphy (sestamibi/single-photon emission computed tomography [SPECT]) are first-line imaging modalities with comparable accuracy for preoperative localization for PHPT (6, 9, 10). However, with increasing utilization of 4-dimensional (4D)-CT, the role of these traditional modalities is being questioned (11–13).

The ability to perform a focal exploration depends on reliable preoperative localization. Despite reported cure rates of ~96% with focal exploration, limited data show that preoperative localization may not be the most accurate, with nonlocalized abnormal parathyroid glands being identified at surgical exploration. Given these discrepancies, there is a need to better define the role for preoperative imaging to optimize surgical decision-making and outcomes (14–16). The aim of this study was to evaluate the primary imaging modalities associated with an improved cure rate based on intraoperative concordance with imaging in patients with PHPT. A secondary aim was to determine the effect of additive imaging modalities on remission rates.

Methods

The institutional review board approved this retrospective cohort study of patients undergoing initial surgery for de novo primary hyperparathyroidism from 2004–2017 at any United States-based Cleveland Clinic Health System. Consent was determined to not be necessary and was waived by the Cleveland Clinic Foundation institutional review board/independent ethics committee given the minimal risk posed to patients for this study. All patients were ≥ 18 years of age and were identified using the International Classification of Diseases 9 or 10 codes for primary hyperparathyroidism (252.0, E21.0, E21.3, E21.4, and E21.5). All charts were manually reviewed to confirm inclusion within the study.

Data collection

A manual chart review was conducted to collect variables. Demographics, including age, sex, and race, were obtained. Preoperative and postoperative laboratory values related to primary hyperparathyroidism, including calcium, intact parathyroid hormone (iPTH), and phosphorus, were reviewed. The preoperative laboratory values were the most recent in our medical record system before surgical management with a target of being within 1 month of the operative date. The postoperative laboratory values collected at 1 month postoperatively and at least 6 months after parathyroidectomy. If patients did not have preoperative laboratory values, and/or 6-month postoperative laboratory values, they were excluded from analysis. Preoperative imaging consisted of ultrasound, plain technetium sestamibi scintigraphy, sestamibi SPECT with iodine subtraction (sestamibi/SPECT), CT, or 4D CT. The CT neck images were subdivided into categories (4D CT, CT neck with and without intravenous [IV] contrast protocol), and whether the CT was performed the indication of primary hyperparathyroidism. Operative and pathology reports were reviewed to determine which parathyroid glands were removed. The operation performed was grouped according to whether a 4-gland or focal exploration was completed.

Imaging

Sestamibi scanning uses digital subtraction imaging. Patients are given iodine-123 by mouth followed by thyroid uptake measurements and scan. Tc-99m sestamibi is then given IV, with subsequent imaging. The iodine thyroid scan images are digitally subtracted from the Tc-99m sestamibi images to identify the parathyroid glands. A SPECT scan is performed with superimposed images to assist with anatomic localization. In most scenarios, our endocrine surgeons perform their own office-based neck US. Thyroid and parathyroid glands are assessed along with a complete neck evaluation to identify lymph node involvement. If a US was not performed by a surgeon, then radiologists completed the imaging test according to their protocol. As such, our study captured these as 2 different groups. Our Endocrine Surgery department uses an imaging protocol that consists of surgeon-performed US and sestamibi/SPECT. CT of the neck and 4D CT is not routinely performed for initial parathyroidectomy for patients with primary hyperparathyroidism; however, it is used at times when preoperative US and sestamibi/SPECT fail to localize an adenoma.

Because we are a major tertiary referral center, some patient did have imaging outside of our hospital system before evaluation by 1 of our providers. If no further imaging was done or repeated by 1 of our clinicians, then the outside imaging results were used. However, if repeat imaging was performed, this was used in our study because our protocols are known and standardized across our health care system.

Surgical management

This cohort included only surgeries performed by endocrine surgeons that are high-volume surgeons (≥ 50 parathyroidectomies performed per year) (16-21). The operative protocol is standardized among our endocrine surgeons. All patients undergo a 4-gland parathyroid exploration with intraoperative PTH measurements. The clinical scenario dictates whether intraoperative PTH measurements direct further exploration.

Outcomes

Primary outcomes were to determine concordance and cure rates. Concordance was defined as any preoperative imaging modality that correlated with intraoperative and surgical pathology findings. For concordance to be reached, there needed to be an exact match between the preoperative imaging and intraoperative findings and surgical pathology. The imaging modality that was concordant was captured. Cure was defined as a normal calcium value (≤ 10.5 mg/dL, or less than the upper limit of the reference range of our laboratory) and iPTH (≤ 65 pg/mL or less than the upper limit of the reference range of our laboratory at the time the laboratory was obtained) at least 6 months postoperatively (6). Serum iPTH was used in this study because iPTH is the biologically active hormone. Intraoperative PTH levels were not reported in this data set. Secondary outcomes evaluated the effect of additive imaging on cure rates.

Statistical analysis

Categorical responses were described using frequencies and percentages. Continuous variables were evaluated for normality using histograms, and measures that were normally distributed were described using means and standard deviations, whereas those that were not normally distributed were described using medians and quartiles. Comparisons of nonordered categorical variables on cure rates were assessed using Pearson χ^2 tests, whereas comparisons of ordered categorical variables on cure rates were assessed using Kruskal-Wallis or Wilcoxon rank-sum tests. Comparisons of normally distributed continuous variables on cure rates were assessed using *t* tests. Overall cure rate was presented as a 95% Agresti-Coull confidence interval. Analyses were performed using SAS software (version 9.4, Cary, NC).

Results

Patient demographics

There were 1485 patients who met inclusion criteria in this study, with a mean age of 65.6 ± 12.2 years. There were 1188 female (80.0%) and 297 male (20.0%) patients. The majority were Caucasian (82.5%) and African American (14.5%). The average preoperative calcium was 10.9 ± 0.7 mg/dL, median preoperative iPTH was 97.0 (Interquartile range 71.0-139.0), mean preoperative phosphorus was 2.8 ± 0.6 mg/dL. A majority of patients underwent preoperative neck ultrasound (99.7%) and preoperative sestamibi/SPECT (93.2%). A majority of the preoperative US scans were performed by surgeons (98.7% of all US scans performed) (Table 1). There was a minority of patients who underwent CT scan (n = 65, 4.5%), of which only 28 underwent 4D CT (Tables 1 and 2). Additionally, 100% of cases (n = 28) had 4D CT scans for an indication of primary hyperparathyroidism. Only 73.7% (n = 28) of CT neck with and without IV contrast studies were performed for an indication of primary hyperparathyroidism (Table 1).

Operative findings and outcomes

A majority of patients had single adenoma on surgical findings (57.0%), followed by 4 gland hyperplasia (20.6%) and double adenoma (19.1%). Supernumerary (0.27%) and ectopic gland disease represented the remainder of cases (3.0%), and there were no parathyroid carcinoma cases. A large majority of the cases underwent 4-gland exploration (96.4%), with the remainder of the cases undergoing focal exploration. The most commonly involved gland was the right upper gland (50.6%), followed by the left upper gland (48.6%), the right lower gland (40.2%), and left lower gland (37.6%), with 1.01% representing supernumerary or ectopic glands (Table 2). The overall cure rate was 94.1% (95% confidence interval, 0.93-0.95) (Table 1). The 2-year reoperation rate was 1.5% (95% confidence interval, 0.01-0.02) (Tables 1 and 2).

Imaging associations with cure rate

Parathyroidectomy cure rates were significantly improved if sestamibi (± SPECT) (95.9% vs. 92.5%, $P = 0.01$) was concordant with operative findings (Table 3). Whether or not the US was performed by surgeons did not make a statistically significant difference in the cure rate (94.1% vs. 100.0%, $P = 0.99$). Cure rate was not significantly affected by CT scan (or 4D CT scan) concordance with operative findings (Table 3). Last, adding a third imaging modality did not seem to improve cure rates in comparison to 2 imaging modalities (1 imaging type 91.8% vs. 2 imaging types 94.4% vs. 3 imaging types 87.2%, $P = 0.59$) (Table 3). Although there was a trend toward an improved cure rate with imaging/operative finding concordance with performing a 4-gland exploration, this result was not statistically significant (cure rate of both concordant and 4-gland exploration of 95.3% vs. cure rate of concordant imaging without 4-gland exploration of 90.4%, $P = 0.12$) (Table 3).

Imaging performance

In cases with single adenoma, US had a sensitivity of 85.4%, specificity of 45.2%, a positive predictive value (PPV) of 67.4% and negative predictive value (NPV) of 70.0%. Sestamibi/SPECT had a sensitivity of 73.3% and a specificity of 51.7%, with a PPV of 66.2% and NPV of 60.0%. CT of the neck with and without IV contrast had a sensitivity of 60.0%, specificity of 83.3%, with a PPV of 80.0% and a NPV of 65.2%. 4D CT scan had a sensitivity of 77.8%, specificity of 80.0%, PPV of 87.5%, and NPV of 66.7% (Table 4).

In cases with multigland disease, US had a sensitivity of 10.9%, a specificity of 99.3%, with a PPV of 91.4% and NPV of 63.0%. Sestamibi/SPECT has a sensitivity of 4.1%, a specificity of 98.9% with a PPV of 71.9%, and a NPV of 60.4%. CT of the neck with and without IV contrast had a sensitivity of 15.4%, a specificity of 96.0%, with a PPV of 66.7%, and a NPV of 68.6%. 4D CT scan had a sensitivity of 42.9%, a specificity of 100.0%, with a PPV of 100.0%, and a NPV of 84.0% (Table 4).

In cases with a double adenoma, US had a sensitivity of 12.9%, a specificity of 98.1%, with a PPV of 61.0% and NPV of 82.8%. Sestamibi/SPECT had a sensitivity of 4.6%, a specificity of 98.8%, with a PPV of 48.0% and a NPV of 81.5%. CT of the neck with and without IV contrast had a sensitivity of 20.0%, a specificity of 96.4%, with a PPV of 66.7%, and a NPV of 77.1%. 4D CT scan had a sensitivity of 40.0%, a specificity of 100.0%, with a PPV of 100.0%, and a NPV of 88.5% (Table 4).

In cases of supernumerary or ectopic disease, US had a sensitivity of 32.7%, a specificity of 99.9%, with a PPV of 88.9% and a NPV of 97.7%. Sestamibi/SPECT had a sensitivity of 40.0%, specificity of 99.6%, with a PPV of 75.0% and a NPV of 98.0%. CT of the neck with and without IV contrast had a sensitivity of 80.0%, a specificity of 93.9%, with a PPV of 66.7%, and a NPV of 96.9%. 4D CT scan had a sensitivity of 33.3%, a specificity of 100.0%, with a PPV of 100.0%, and a NPV of 92.6% (Table 4).

Discussion

Despite primary hyperparathyroidism being the third most common endocrine disorder, there remains a significant degree of variability in the protocol for preoperative localization between institutions, regional hospitals, and individual surgeons. This study evaluated the performance of preoperative imaging in 1485 patients who presented with de novo primary hyperparathyroidism undergoing initial parathyroidectomy by a high-volume endocrine surgeon at a tertiary referral center from 2004 through 2017. Based on the findings in this study, 2 imaging modalities should be recommended as the initial preoperative imaging modalities. If 2 imaging modalities fail to localize an abnormal parathyroid gland, then adding a third imaging modality does not improve preoperative localization or surgical cure rate. Our study supports the assertion that US and sestamibi/SPECT scan, when combined, offer the most significant association with concordance and higher cure rate.

The major strengths of this study were that a majority of patients had 2 or more imaging modalities, all surgeries were performed by high-volume endocrine surgeons (> 50 parathyroidectomies/year), and that a majority of patients underwent 4-gland exploration (96.4%). Only with

Table 1. Demographics and Laboratory Values

Factor	Total (N = 1485)	
	N	Statistics
Sex	1485	
Male		297 (20.0)
Female		1188 (80.0)
Race	1485	
White		1225 (82.5)
Black		215 (14.5)
American Indian/Alaska Native		1 (0.07)
Multiracial/multicultural		11 (0.74)
Declined/unavailable/unknown		19 (1.3)
Asian		14 (0.94)
Age, y	1485	65.6 ± 12.2
Mortality during 14-y follow-up	1485	29 (2.0)
Imaging type	1485	
US only		73 (4.9)
Sestamibi with SPECT		5 (0.34)
CT scan neck with and without IV contrast		65 (4.4%)
CT scan with and without IV contrast for indication of PHPT		28 (1.9%)
4D CT scan		28 (1.9%)
4D CT scan for indication of PHPT		28 (1.9%)
US + SPECT		1341 (90.3)
US + non-4D CT		7 (0.47)
US + 4D CT		21 (1.4)
US, SPECT, and non-4D CT		31 (2.1)
US, SPECT, and 4D CT		7 (0.47)
Preoperative laboratory values		
Preoperative calcium	1484	10.9 ± 0.69
Preoperative iPTH	1483	97.0 [71.0, 139.0]
Preoperative phosphorus	1347	2.8 ± 0.57
Postoperative laboratory values		
1-mo postoperative calcium	1451	9.6 ± 0.80
1-mo postoperative iPTH	1479	16.8 ± 18.7
1-mo postoperative phosphorus	1396	3.5 ± 1.09
≥ 6-mo postoperative calcium	1474	9.5 ± 0.55
≥ 6-mo postoperative phosphorus	1041	3.5 ± 2.5
≥ 6-mo postoperative vitamin D (25-OH vitamin D)	471	41.0 ± 16.2
Cure (calcium normal 6 mo or more postoperatively)	1485	1397 (94.1)
2-year reoperation	1485	23 (1.5)

Statistics presented as mean ± standard deviation, median [P25, P75], or N (column %).
Abbreviations: 4D, 4-dimensional; iPTH, intact parathyroid hormone; IV, intravenous; PHPT, primary hyperparathyroidism; SPECT, single photon emission computed tomography; US, ultrasound.

4-gland exploration can the accuracy of preoperative imaging on a per-gland basis be determined. An additional strength of this study is that there is a large sample size of patients with 14 years of follow-up. This gave us the benefit of being able to monitor patients for disease recurrence (with a 2-year reoperation rate of 1.5%) and reassess our current imaging protocols that were previously published in a prospective study (15).

Most experts in parathyroid surgery rely on US and sestamibi/SPECT for preoperative localization, and it has previously been identified in the literature as first-line and the most cost-effective localization strategy (6, 9, 10, 22-24). US is relatively inexpensive, does not expose the patient to radiation, and has been reported to have a sensitivity of 76.1% with a PPV of 93.2% in single adenomas (9). In our study, US had a higher sensitivity at 85.4% with a lower PPV of 67.4% and the discrepancy is likely related operator dependence. Surgeon-performed US did not have a statistically significant difference on the surgical cure rate or imaging concordance with

Table 2. Surgical Findings

Factor	Total (N = 1485)	
	N	Statistics
Operative findings	1485	
Single adenoma		847 (57.0)
Double adenoma		283 (19.1)
Supranumerary gland		4 (0.27)
Ectopic gland		45 (3.0)
Four gland hyperplasia		306 (20.6)
Gland involvement (from surgery)	1485	
Right upper gland		752 (50.6)
Right lower gland		597 (40.2)
Left upper gland		721 (48.6)
Left lower gland		559 (37.6)
Supernumerary/ectopic		15 (1.01)
Supernumerary gland/ectopic location		
Intrathyroidal		14 (0.94)
Retroesophageal		3 (0.20)
Mediastinal		10 (0.67)
Thymic		16 (1.08)
Other		6 (0.40)
Exploration of all 4 glands?	1485	1432 (96.4)
Concordance with preoperative imaging (defined as any imaging concordance with operation)?	1485	853 (57.4)
Which imaging was concordant with surgical findings?	1480	792 (53.5)
Ultrasound	1384	606 (43.8)
Sestamibi	38	15 (39.5)
Non-4D CT	38	15 (39.5)
4D CT concordance	28	17 (60.7)

Statistics presented as N (column %).
Abbreviations: 4D, 4-dimensional; CT, computed tomography.

operative findings. Although surgeon-performed US has been recommended by some as the initial and only localizing study necessary (25), our study findings are more consistent with the American Association of Endocrine Surgeons guidelines in that US should be performed by an experienced parathyroid sonographer in addition to sestamibi/SPECT (6, 22-24). Our study did not report a statistically significant difference between surgeon-performed US and radiology-performed US, and this is likely because both groups being considered experienced parathyroid sonographers. Sestamibi/SPECT had a sensitivity of 73.3% with a PPV of 66.2% in single-gland disease, which was lower than that reported in the literature of 78.9% and 90.7% for single adenomas (9), respectively. This discrepancy is likely related to patients having a significant amount of imaging performed at outside institutions before presentation, and when undergoing 4-gland exploration, are having an additional or alternate gland identified.

For the secondary aim, our study demonstrated that if the first 2 imaging modalities failed to localize the abnormal gland(s), adding a third imaging modality did not improve the localization or cure rate. It is likely that a significant number of these cases that failed to localize with 2 imaging modalities had 4-gland hyperplasia or supernumerary/ectopic glands. Although this suggests that additional imaging modalities may not be indicated for all cases of initial primary hyperparathyroidism, there remains the potential for the replacement of sestamibi/SPECT for 4D CT.

In a series of 87 patients, Starker et al have previously suggested that 4D CT provides significantly greater sensitivity and specificity than US or sestamibi/SPECT, and further recommended that 4D-CT be used as the initial localization study for patients with de novo primary hyperparathyroidism (13). Further, a cost-analysis study demonstrated that US is the most cost-effective imaging modality, followed by 4D CT (14). Our study investigated the performance of imaging, and 4D CT scan was found to outperform (higher sensitivity, specificity, PPV, NPV) US, sestamibi/SPECT, and CT neck with and without IV contrast in patients with multiglandular disease and double adenomas. Additionally, 4D CT scan outperformed sestamibi/SPECT in single adenomas with a higher sensitivity, specificity, PPV, and NPV. These data

Table 3. Cure Rate Association With Imaging Concordance

Factor	Overall (N = 1485)		Not Cured (N = 88)		Cured (N = 1397)		*P* Value
	N	Statistics	N	Statistics	N	Statistics	
Ultrasound performed by the surgeon?	1473		86		1387		0.99[a]
No		4 (0.27)		0 (0.0)		4 (100.0)	
Yes		1469 (99.7)		86 (5.9)		1383 (94.1)	
Ultrasound concordance	1480		86		1394		0.074[a]
Not concordant		688 (46.5)		48 (7.0)		640 (93.0)	
Concordant		792 (53.5)		38 (4.8)		754 (95.2)	
Sestamibi concordance (with and without SPECT)	1384		83		1301		0.010[b]
Not concordant		778 (56.2)		58 (7.5)		720 (92.5)	
Concordant		606 (43.8)		25 (4.1)		581 (95.9)	
Non-4D CT scan concordance	38		4		34		0.14[a]
Not concordant		23 (60.5)		4 (17.4)		19 (82.6)	
Concordant		15 (39.5)		0 (0.0)		15 (100.0)	
4D CT scan concordance	28		3		25		0.54[a]
Not concordant		11 (39.3)		2 (18.2)		9 (81.8)	
Concordant		17 (60.7)		1 (5.9)		16 (94.1)	
Number of imaging types	1485		88		1397		0.59[c]
1		61 (4.1)		5 (8.2)		56 (91.8)	
2		1385 (93.3)		78 (5.6)		1307 (94.4)	
All 3		39 (2.6)		5 (12.8)		34 (87.2)	
Exploration of all 4 glands?	1485		88		1397		0.24[a]
No		53 (3.6)		5 (9.4)		48 (90.6)	
Yes		1432 (96.4)		83 (5.8)		1349 (94.2)	
Concordance/4-gland exploration	1485		88		1397		0.12[a]
Not concordant/no 4-gland exploration		1 (0.07)		0 (0.00)		1 (100.0)	
Concordance only		52 (3.5)		5 (9.6)		47 (90.4)	
4-gland exploration only		631 (42.5)		45 (7.1)		586 (92.9)	
Both concordant and 4-gland exploration		801 (53.9)		38 (4.7)		763 (95.3)	

Statistics presented as N (row %).
[a]Fisher exact test.
[b]Pearson χ^2 test.
[c]Wilcoxcon Rank Sum test.
Abbreviations: 4D, 4-dimensional; CT, computed tomography; SPECT, single photon emission computed tomography.

should be interpreted with caution given that there was a low number of cases with CT of the neck with and without IV contrast (n = 38) and 4D CT scans (n = 28) in our cohort in comparison to the higher number of US (n = 1480) and sestamibi/SPECT (n = 1384) imaging modalities. Last, the combination of US and 4D CT scan concordance did not demonstrate a statistically significant increase in cure rate that was observed with US and sestamibi/SPECT. Therefore, until we have a more adequately powered comparison between US with sestamibi/SPECT and US with 4D CT, it is difficult to compare these imaging modalities at this time.

There are several limitations to our study. One limitation is that our endocrine surgery department has a protocol that enlists that all patients who present for an initial operation of de novo (nonrecurrent) primary hyperparathyroidism undergo US and sestamibi/SPECT with 4-gland exploration. Before this retrospective cohort review, a prospective trial was performed between November 1999 and August 2003 that investigated the utility of focal versus 4-gland exploration. In that trial, it was found that even in patients with concordant sestamibi and US scans with an appropriate PTH drop during surgery, additional abnormal parathyroid glands were found on 4-gland exploration in 15% of cases (15). After that study, most patients received a 4-gland exploration as part of their operation at our institution as part of a standard protocol.

A second limitation is that all of the imaging and surgeries represent multiple hospitals as part of a single health system and may not reflect the practices of other institutions (or the associated accuracy of imaging associated within those institutions). It is important to note that sensitivity, specificity, PPV, and NPV may have operator and institutional variability. An attempt was made

Table 4. Imaging Performance

Factor	Modality (n)	Pathology Positive (n)	Modality Positive (n)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Imaging modality							
Single adenoma							
US	1480	845	1070	85.4	45.2	67.5	70.0
Sestamibi/SPECT	1384	780	864	73.3	51.7	66.2	60.0
CT with/without IV contrast	38	20	15	60.0	83.3	80.0	65.2
4D CT	28	18	16	77.8	80.0	87.5	66.7
Multigland disease							
US	1480	586	70	10.9	99.3	91.4	63.0
Sestamibi/SPECT	1384	559	32	4.1	98.9	71.9	60.4
CT with/without IV contrast	38	13	3	15.4	96.0	66.7	68.6
4D CT	28	7	3	42.9	100.0	100.0	84.0
Double adenoma							
US	1480	280	59	12.9	98.1	61.0	82.8
Sestamibi/SPECT	1384	263	25	4.6	98.8	48.0	81.5
CT with/without IV contrast	38	10	3	20.0	96.4	66.7	77.1
4D CT	28	5	2	40.0	100.0	100.0	88.5
Supernumerary/ectopic							
US	1480	49	18	32.7	99.9	88.9	97.7
Sestamibi/SPECT	1384	45	24	40.0	99.6	75.0	98.0
CT with/without IV contrast	38	5	6	80.0	93.9	66.7	96.9
4D CT	28	3	1	33.3	100.0	100.0	92.6

Abbreviations: 4D, 4-dimensional; CT, computed tomography; IV, intravenous; NPV, negative predictive value; PPV, positive predictive value; SPECT, single photon emission computed tomography; US, ultrasound

to control for this variable by looking at the entire health system across high-volume surgeons within the same department to obtain a more homogeneous population, although there is still variability. A third limitation is that our institution did not have data available to investigate magnetic resonance imaging, 11C-methionine positron emission tomography (PET), and CT, or 18-flourocholine-PET-CT in this study because of its retrospective design, timeframe (this study's data collection period was 2004-2017), and regulatory issues for use in the United States (18-flourocholine-PET-CT). The 11C-methionine PET and CT have demonstrated promise for localizing a single adenoma previously in a prospective study with a PPV of 93% (26), and additionally has been described as a useful option for reoperative surgery in patients who had initial negative imaging (27). In a systematic review, 18-fluorocholine-PET-CT previously demonstrated sensitivity between 80% and 100%, and a specificity of 95% and 100%, and is an interesting area of future research (28). Last, our definition for cure is limiting. We used the definition supported by the American Association of Endocrine Surgeons, in which cure was defined as eucalcemia at more than 6 months after surgery (6), and we refined this definition to include a normal PTH at 6 months after surgery. Although this definition has been used, a recent study suggests that longer follow-up may be needed to better define cure rates (29). We further explored this and found that the 2-year reoperation rate of those who did not achieve cure was 1.5% of cases. Additionally, there was no notable difference in imaging performance when comparing 2-year reoperation to the 6-month time point as the definition of cure (data not shown).

Conclusion

In this retrospective review of de novo primary hyperparathyroidism undergoing initial parathyroidectomy by high-volume endocrine surgeons, preoperative US combined with sestamibi/SPECT were associated with the highest cure and concordance rates. Additionally, if pathology was not found on US and sestamibi/SPECT, additional imaging did not improve the cure rate or concordance. Our data suggest that 4D CT scan outperforms US, sestamibi/SPECT, and CT of the neck with/without IV contrast in multiglandular disease and double adenomas. Additionally, 4D CT scan outperformed sestamibi/SPECT in single gland disease, but did not have a significant association with concordance and cure rate, but was underpowered.

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Additional Information

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