Opportunistic CT Assessment of Parathyroid Glands: Utility of Radiologist-Recommended Biochemical Evaluation for Diagnosing Primary Hyperparathyroidism

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Keywords

CT, opportunistic imaging, parathyroid gland, parathyroid hormone, primary hyperparathyroidism

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BACKGROUND. Existing gaps in primary hyperparathyroidism (PHPT) diagnosis and treatment have prompted calls for systemic change in the approach to this disease. One proposed change is opportunistic assessment for enlarged parathyroid glands on routine CT examinations, to target biochemical testing to individuals most likely to have undiagnosed PHPT.

OBJECTIVE. The purpose of our study was to assess the utility of a radiologist recommendation for biochemical testing in patients with a suspected enlarged parathyroid gland on routine CT for identifying previously undiagnosed PHPT.

METHODS. This retrospective study included patients without known or suspected PHPT who underwent routine CT (i.e., performed for reasons other than known or suspected parathyroid disease) between August 2019 and September 2021 in which the clinical CT report included a radiologist recommendation for biochemical testing to evaluate for possible PHPT because of a suspected enlarged parathyroid gland. Neuroradiologists at the study institution included this recommendation on the basis of individual judgment without formal criteria. The EHR was reviewed to identify patients who underwent subsequent laboratory evaluation for PHPT. An endocrine surgeon used available laboratory results and clinical data to classify patients as having PHPT, secondary hyperparathyroidism, or no parathyroid disorder independent of the CT findings.

RESULTS. The sample comprised 39 patients (median age, 68 years; 20 women, 19 men) who received the radiologist recommendation for biochemical evaluation. Of these patients, 13 (33.3%) received the recommended biochemical evaluation. Of the 13 tested patients, three (23.1%) were classified as having PHPT, four (30.8%) as having secondary hyperparathyroidism, and six (46.2%) as having no parathyroid disorder. Thus, the number of patients needing to receive a radiologist recommendation for biochemical testing per correct PHPT diagnosis was 13.0, and the number of patients needing to undergo laboratory testing per correct PHPT diagnosis was 4.3. One of the three patients classified as having PHPT underwent surgical resection of the lesion identified by CT, which was shown on histopathologic evaluation to represent hypercellular parathyroid tissue.

CONCLUSION. Radiologist recommendations for biochemical testing in patients with suspected enlarged parathyroid glands on routine CT helped to identify individuals with undiagnosed PHPT.

CLINICAL IMPACT. Opportunistic assessment for enlarged parathyroid glands on routine CT may facilitate PHPT diagnosis.

Primary hyperparathyroidism (PHPT) refers to a parathyroid glandular abnormality resulting in excess parathyroid hormone production. The incidence and prevalence of PHPT are increasing [1–3], and the disease may affect up to 1% of adults [4]. Untreated PHPT is associated not only with osteoporotic fractures, kidney stones, renal disease, depression, and cognitive impairment [5] but also with increased risk of heart attack, stroke, and death [6]. Furthermore, end-organ damage from PHPT is associated with disease duration and often precedes diagnosis. For example, at the time of PHPT diagnosis, over 40% of patients have osteopenia or osteoporosis, and over 25% have impaired renal function [5]. PHPT is diagnosed with blood tests—specifically, calcium and parathyroid hormone levels—and is cured with surgical removal of the abnormal parathyroid tissue [7].

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Existing paradigms for diagnosing and treating PHPT are unsuccessful in many patients living with this disease [8–10]. Even though PHPT represents the most common cause of hypercalcemia, only 20–30% of patients with an elevated calcium level have their parathyroid hormone level tested [10–12]. Surgery is the only possible cure and has 95% efficacy and very low morbidity [7]. However, surgery rates have declined over time, ranging from 13% to 38% in studies from 2019 to 2021 [8, 10, 13]. Furthermore, only 20–30% of patients with known PHPT are offered consultation with a parathyroid surgeon [11, 13]. These well-documented gaps have prompted calls to "change how health systems approach diagnosis and treatment of hypercalcemia and hyperparathyroidism" [11].

The conventional role of imaging in PHPT is for localization of abnormal parathyroid gland(s) in individuals with known disease to facilitate curative surgery [14, 15]. A number of imaging modalities are available for this purpose, of which parathyroid CT is particularly effective [14, 15]. Retrospective studies from 2021 and 2022 suggested a potential role for radiologists to use opportunistic parathyroid gland assessment on routine CT to reduce existing diagnosis gaps by recommending biochemical evaluation (i.e., testing of serum calcium and parathyroid hormone levels) in patients with a suspected enlarged parathyroid gland on imaging [16, 17].

In one of those earlier studies, pathologically proven parathyroid adenomas were retrospectively identified on routine contrast-enhanced CT examinations that were performed up to 10 years before the diagnosis of PHPT [17]. Based on data from another retrospective study, as few as 3.5 patients with enlarged parathyroid glands identified by routine CT would need to undergo serum calcium and parathyroid hormone level testing to yield one PHPT diagnosis [16]. Whether this approach could facilitate correct diagnoses of PHPT in clinical practice is unknown.

The purpose of this study was to assess the utility of a radiologist recommendation for biochemical testing in patients with a suspected enlarged parathyroid gland on routine CT for identifying previously undiagnosed PHPT.

Highlights

Key Finding

- *Among 39 patients in whom the radiologist interpreting a routine CT examination recommended biochemical evaluation because of a suspected enlarged parathyroid gland, 13 underwent the recommended laboratory testing, yielding a diagnosis of primary hyperparathyroidism in three patients (23.1% of those who underwent testing and 7.7% of those recommended for testing).*

Importance

- *Radiologist assessment of the parathyroid glands on routine CT has the potential to help close existing gaps in primary hyperparathyroidism diagnosis.*

Methods

Patients

This single-institution retrospective HIPAA-compliant study was approved by the institutional review board, which waived the requirement for written informed consent. On the basis of the findings of the authors' prior work suggesting a potential role for radiologists to close existing gaps in PHPT diagnosis through opportunistic assessment for enlarged parathyroid glands on routine imaging [16, 17], some neuroradiologists at the study institution modified their reporting practices to include parathyroid adenoma in the differential diagnosis for soft-tissue nodules identified in the central compartment of the neck on cross-sectional imaging, when such nodules were not definitively lymph nodes or of thyroid gland origin (i.e., thyroid nodule or exophytic thyroid tissue). In such situations, the neuroradiologists included standardized language in the report to recommend "correlation with biochemical testing for possible primary hyperparathyroidism."

Third-party software (mPower, version 3.2.4, Nuance Healthcare) was used to search radiology reports of CT examinations performed in adult patients at the institution from August 2019 to September 2021. The search identified consecutive CT examinations performed during the study period for which the interpreting radiologist recommended "correlation with biochemical testing for possible primary hyperparathyroidism" on the basis of the presence of one or more suspected enlarged parathyroid glands. A single neuroradiologist (P.M.B. with 5 years of posttraining experience) manually reviewed the search results to exclude those performed using an examination code corresponding with a dedicated parathyroid protocol as well as those performed for a study indication relating to known or suspected parathyroid disease. The remaining examinations, after this exclusion, were considered to represent routine CT examinations for purposes of the present investigation.

For patients for whom the radiology report included the recommendation for biochemical testing, relevant demographic, clinical, and imaging data were collected from the EHR, including age, sex, care setting (outpatient, inpatient, or emergency department), serum calcium level at the time of CT (based on the most recent available measurement obtained before CT), relevant medical history (e.g., kidney stones, bone mineral density, chronic kidney disease, gastric bypass), indication for CT, CT examination type, and availability of relevant comparison CT examinations (e.g., unenhanced cervical spine CT as a relevant comparison for contrast-enhanced neck CT). The assessment for relevant comparison CT examinations included examinations performed on earlier dates as well as examinations performed concurrently with the examination that received the recommendation for biochemical testing. Patients were excluded if EHR review showed that the patient had known untreated PHPT or had been evaluated for possible PHPT in the 6 months before the date of the CT examination with the recommendation for biochemical testing. The remaining patients formed the study sample. Once the final study sample was determined, the previously noted search software was used to determine the total number of CT examinations performed in adult patients at the institution during the study period matching the various CT examination types represented in the patient sample.

CT Acquisition and Clinical Interpretation

CT examinations were acquired using parameters consistent with the institution's manual of acquisition protocols. However, heterogeneity existed in the parameters given the inclusion of

examinations performed at various sites within the health care system (e.g., main hospital campus, outpatient imaging center) and using various CT scanners.

The recommendations for biochemical testing were provided by fellowship-trained attending neuroradiologists as part of routine clinical interpretation (i.e., not as part of a prospective study of recommendations for biochemical testing). The decisions of whether the images showed a suspected enlarged parathyroid gland and whether to include a recommendation for biochemical testing were based on the individual judgment of the interpreting neuroradiologist, without formal criteria. However, the neuroradiologists generally limited the assessment for incidental enlarged parathyroid glands to contrast-enhanced CT images; considered only soft-tissue nodules with enhancement characteristics different from those of lymph nodes; and performed a comparison with noncontrast CT images, if available, to confirm the absence of intrinsic iodine [17]. The number of unique attending neuroradiologists who issued the recommendations for biochemical testing was identified.

Retrospective CT Review

Blinded to the endocrine surgeon's integrated parathyroid diagnosis (as described later in the Methods), the previously noted neuroradiologist (P.M.B.) reviewed the CT images of patients for whom the report described a suspected enlarged parathyroid gland and recommended biochemical testing. This investigator was among the neuroradiologists who included such recommendations in reports. On the basis of the CT report, the investigator identified the soft-tissue nodule suspected by the interpreting neuroradiologist to be an enlarged parathyroid gland. If the report described a single enlarged parathyroid gland, then the neuroradiologist measured the gland's length, width, and height in millimeters, and the gland's volume was estimated using the following formula: $0.52 \times length \times width \times height$ [18]. If the report described multiple enlarged parathyroid glands, then the size measurements and volume estimation were performed for the largest gland.

Retrospective Assessment of Parathyroid Disease

In December 2022 (i.e., at least 15 months after the CT examination for which biochemical testing for possible PHPT was recommended), the institution's EHR was searched to determine whether the patient had undergone the recommended biochemical evaluation. A patient was classified as tested if serum parathyroid hormone and calcium levels were evaluated after the radiologist recommendation (i.e., excluding any laboratory testing performed before CT) and as untested if these laboratory evaluations were not performed.

For tested patients, a fellowship-trained endocrine surgeon (R.W.R., with 5 years of posttraining experience in managing PHPT) evaluated the calcium and parathyroid hormone level results in the context of all other relevant information available in the EHR, including the presence or absence of vitamin D deficiency, renal dysfunction, kidney stones, osteopenia or osteoporosis, prior gastric bypass surgery, and prior kidney transplant. On the basis of the results of this evaluation, the endocrine surgeon rendered an integrated parathyroid diagnosis (PHPT, secondary hyperparathyroidism [SHPT], or no parathyroid disorder). When generating an integrated parathyroid diagnosis, the endocrine surgeon was blinded to the previously described parathyroid size measurements. Finally, the endocrine surgeon classified patients with an integrated diagnosis of PHPT in terms of whether the patient met evidence-based criteria for surgical intervention based on multidisciplinary international guidelines from 2022 [19].

Statistical Analysis

Data were summarized descriptively using the median, IQR, minimum, and maximum for continuous variables and the absolute and relative frequencies for categoric variables. The Fisher exact test was used to compare proportions between tested patients and untested patients, and the Pearson chi-square test was used to compare proportions among patient groups defined by integrated parathyroid diagnosis (PHPT, SHPT, or no parathyroid disorder). The Wilcoxon rank sum test was used to compare continuous variables between tested patients and untested patients, and the one-way ANOVA with the Tukey honestly significant difference was used to compare continuous variables among patient groups defined by the integrated parathyroid diagnosis; p values less than .05 indicated statistically significant differences. Analyses were performed using JMP Pro software (version 15, SAS Institute).

Results

Patients

The search identified 42 patients who received the recommendation for biochemical testing on a CT examination performed during the study period. No patient was excluded owing to the use of an examination code corresponding with a dedicated parathyroid protocol or to a study indication relating to known or suspected thyroid disease (i.e., all recommendations were performed for routine CT examinations). Of the 42 patients, three were excluded on the basis of EHR review because of known untreated PHPT (n = 2) or biochemical testing performed for possible PHPT in the 6 months preceding the CT examination with the recommendation (n = 1). Thus, the final study sample included 39 patients (median age, 68 years; 20 women, 19 men). Figure 1 shows the flow of patient selection, and Table 1 summarizes characteristics of the study sample. A total of 13 of 39 (33.3%) patients were tested (i.e., received the recommended biochemical evaluation), and 26 of 39 (66.7%) were untested. In three of the 26 (11.5%) untested patients, biochemical testing was ordered but was not performed. Tested patients and untested patients showed no significant difference with respect to sex (p = .18), age (p = .07), care setting (p = .28), or serum calcium level at the time of CT (p = .46).

CT Examinations and Clinical Interpretations

The 39 CT examinations were interpreted clinically by seven fellowship-trained attending neuroradiologists (of a total of 14 neuroradiology faculty at the institution) who had 1–26 years of posttraining experience. Examination types included contrast-enhanced neck CT (n = 23, 59.0%); contrast-enhanced CTA (n = 12, 30.8%; including five neck CTA, five head and neck CTA, and two CTA examinations performed as part of a code stroke CT examination); unenhanced cervical spine CT (n = 3, 7.7%); and contrast-enhanced thoracolumbar spine CT reformatted from a CT examination of the chest, abdomen, and pelvis in a patient

TABLE 1: Characteristics of the Study Sample, Stratified by Tested Patients Versus Untested Patients

Characteristic	All Patients (*n* = 39)	Tested Patients (*n* = 13)	Untested Patients (*n* = 26)	*p*
Sex				.18[a]
Male	19 (48.7)	4 (30.8)	15 (57.7)	
Female	20 (51.3)	9 (69.2)	11 (42.3)	
Age (y)				.07[b]
Median	68	60	72	
IQR	54–74	51–68	56–76	
Range	20–93	41–85	20–93	
Care setting				.28[c]
Outpatient	23 (59.0)	7 (53.8)	16 (61.5)	
Inpatient	3 (7.7)	0 (0.0)	3 (11.5)	
Emergency department	13 (33.3)	6 (46.2)	7 (26.9)	
Serum calcium level[d] (mg/dL)				.46[b]
Median	9.4	9.6	9.4	
IQR	9.2–9.9	9.3–9.9	9.1–9.9	
Range	8.3–11.3	9.0–11.3	8.3–10.5	

Note—Except where otherwise indicated, data are expressed as count with percentage in parentheses.
[a]Fisher exact test.
[b]Wilcoxon rank sum test.
[c]Pearson chi-square test.
[d]Most recent prior value at time of CT interpretation; available in all patients.

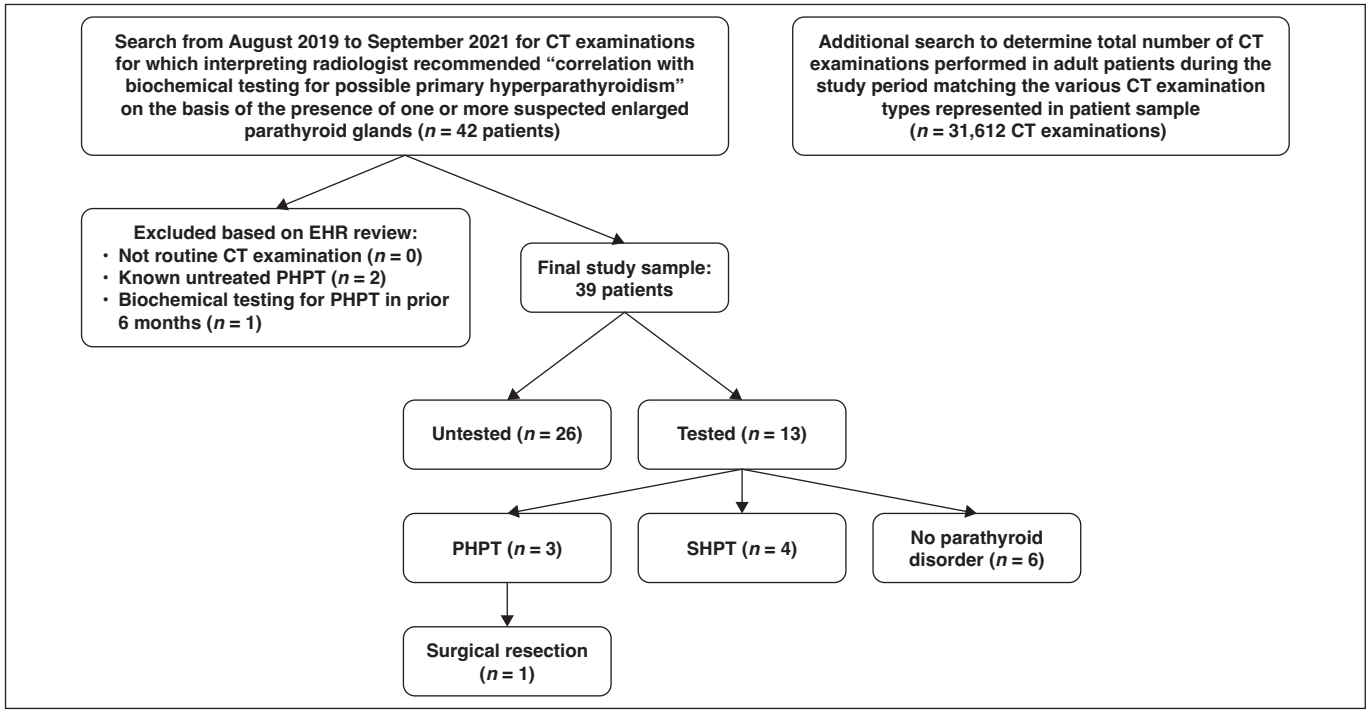

Fig. 1—Flowchart shows patient selection process. PHPT = primary hyperparathyroidism, SHPT = secondary hyperparathyroidism.

with trauma (*n* = 1, 2.6%). During the study period, 5512 contrast-enhanced neck CT examinations (23/5512 [0.4%] recommended for biochemical testing), 7156 contrast-enhanced CTA examinations (12/7156 [0.2%] recommended for testing), 15,556 unenhanced cervical spine CT examinations (3/15,556 [< 0.1%] recommended for testing), and 3388 contrast-enhanced thoracolumbar spine CT examinations reformatted from trauma chest, abdomen, and pelvis CT (1/3388 [< 0.1%] recommended

for testing) were performed in adult patients. Thus, among the CT examination types represented in the study sample, a total of 0.1% (39/31,612) of studies performed at the institution during the study period included a radiologist recommendation for biochemical testing for possible PHPT.

The clinical indications for the CT examinations were heterogeneous but included broad categories of neoplasm staging or surveillance (n = 19), trauma (n = 9), stroke workup (n = 5), neck pain (n = 4), headache (n = 1), and fever (n = 1). Of the 36 contrast-enhanced CT examinations, 23 (63.9%) had noncontrast CT images (acquired previously in 15 patients and contemporaneously in eight patients) available for comparison at the time of the contrast-enhanced CT. All three noncontrast CT examinations had a prior contrast-enhanced CT examination available for comparison. The interpreting neuroradiologist described a single suspected enlarged parathyroid gland in 27 (69.2%) patients and more than one suspected enlarged gland in 12 (30.8%) patients. The locations of the suspected enlarged parathyroid glands were unilateral right-sided in 16 (41.0%) patients, unilateral left-sided in 12 (30.8%) patients, and bilateral in 11 (28.2%) patients. The proportion of patients who were tested was not significantly different between patients with single (9/27, 33.3%) and multiple (4/12, 33.3%) suspected enlarged parathyroid glands ($p > .99$) or between patients with unilateral (9/28, 32.1%) versus bilateral (4/11, 36.4%) suspected enlarged glands ($p > .99$).

Parathyroid Gland Size Measurements

For the overall sample, the median maximum diameter of the largest suspected parathyroid gland was 11 mm (IQR, 9–11 mm; minimum, 6 mm; maximum, 29 mm), and the median estimated volume was 309 mm^3 (IQR, 131–702 mm^3; minimum, 75 mm^3; maximum, 3800 mm^3). Among the tested individuals, the median maximum diameter was 11 mm (IQR, 8–18 mm; minimum, 7 mm; maximum, 29 mm), and the median estimated volume was 204 mm^3 (IQR, 128–1858 mm; minimum, 91 mm; maximum, 3800 mm). Among the untested individuals, the median maximum diameter was 11 mm (IQR, 9–15 mm; minimum, 6 mm; maximum, 26 mm), and the median estimated volume was 320 mm^3 (IQR, 154–618 mm^3; minimum, 75 mm^3; maximum, 3245 mm^3). Tested patients and untested patients showed no significant difference in terms of maximum diameter ($p = .75$) or estimated volume ($p = .83$).

Retrospective Assessment of Parathyroid Disease

On the basis of assessment of available relevant laboratory and clinical data in the 13 tested patients, the endocrine surgeon's integrated diagnosis was PHPT in three (23.1%) patients, SPHT in four (30.8%) patients, and no parathyroid disorder in six (46.2%) patients. Figures 2–4 show representative patients in these three groups. Thus, PHPT was detected in three of 39 (7.7%) patients among those receiving a radiologist recommendation for biochemical testing; the number of patients needing to receive a radiologist recommendation for biochemical testing per correct PHPT diagnosis was 13.0 (i.e., three PHPT diagnoses after 39 recommendations), and the number of patients needing to undergo laboratory testing per correct PHPT diagnosis was 4.3 (i.e., three PHPT diagnoses after 13 biochemical evaluations).

Among the tested patients, patients with the three integrated parathyroid diagnoses (PHPT, SHPT, no parathyroid disorder) showed no significant difference in terms of the suspected enlarged parathyroid gland's maximum diameter ($p = .81$) or estimated volume ($p = .77$) (Table 2). In all three tested patients with an integrated diagnosis of PHPT, a single enlarged gland was described. Among the four tested patients with an integrated diagnosis of SPHT, a single enlarged gland was described in two patients, and multiple enlarged glands were described in two patients. Among the six tested patients with an integrated diagnosis of no parathyroid disorder, a single enlarged gland was described in four patients, and multiple enlarged glands were described in two patients. The frequency of a single suspected enlarged gland was not significantly different among the three integrated diagnosis groups ($p = .36$) (Table 2).

All three individuals with an integrated parathyroid diagnosis of PHPT satisfied the 2022 multidisciplinary international guideline criteria for parathyroidectomy [19]. One of these three patients underwent surgical resection of the suspected enlarged parathyroid gland, which was confirmed to represent hypercellular parathyroid tissue (Fig. 5). The other two patients were acknowledged to have PHPT in the EHR, but neither was referred for surgical consultation.

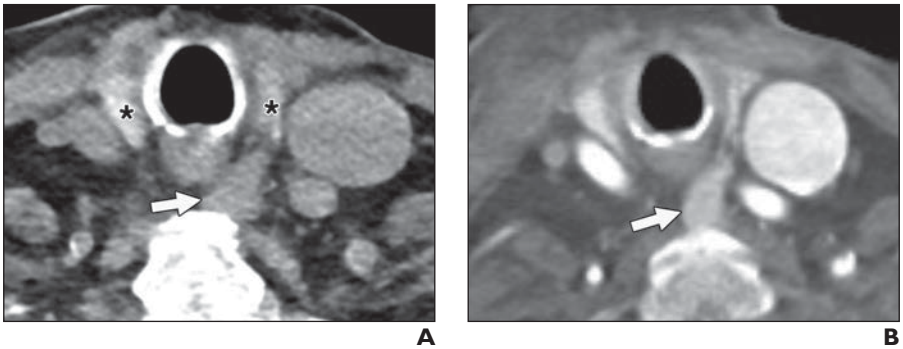

Fig. 2—85-year-old woman who underwent noncontrast cervical spine CT followed by contrast-enhanced neck CTA owing to neck pain after falling at home. **A** and **B,** Axial images from cervical spine CT (**A**) and neck CTA (**B**) show soft-tissue nodule (*arrow*) along posterior aspect of left thyroid lobe. Nodule is hypoattenuating relative to adjacent thyroid gland (*asterisks*, **A**) on cervical spine CT and exhibits hyperenhancement relative to cervical lymph nodes (not shown) on neck CTA. Interpreting neuroradiologist suspected this finding to represent opportunistically identified enlarged left superior parathyroid gland and included in clinical report recommendation for biochemical evaluation for possible primary hyperparathyroidism. Recommended laboratory testing was performed and yielded results consistent with primary hyperparathyroidism.

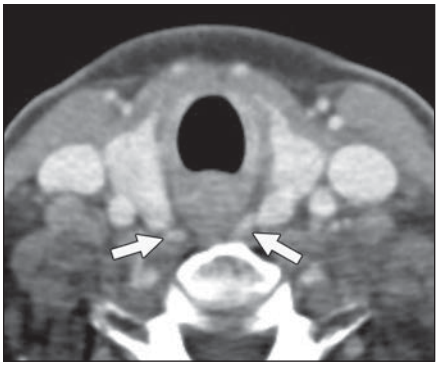

Fig. 3—52-year-old woman with history of breast cancer who underwent contrast-enhanced neck CT owing to palpable left supraclavicular abnormality. Axial image shows small bilateral central compartment nodules (*arrows*) appearing separate from adjacent thyroid gland and exhibiting enhancement different from that of lymph nodes elsewhere in neck. Interpreting neuroradiologist suspected this finding to represent opportunistically identified enlarged bilateral superior parathyroid glands and included in clinical report recommendation for biochemical evaluation for possible primary hyperparathyroidism. Recommended laboratory testing was performed and yielded results consistent with secondary hyperparathyroidism.

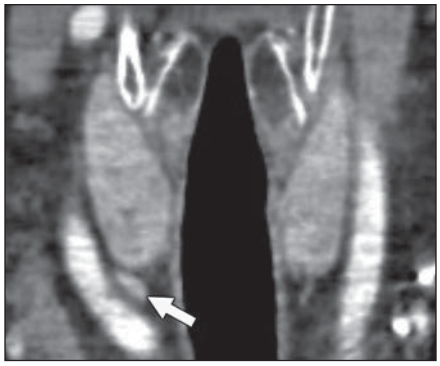

Fig. 4—64-year-old man who underwent contrast-enhanced CTA of head and neck owing to right facial numbness and right upper extremity tingling. Coronal image shows avidly enhancing nodule (*arrow*) along inferior aspect of right thyroid lobe. Interpreting neuroradiologist suspected this finding to represent opportunistically identified enlarged right inferior parathyroid gland and included in clinical report recommendation for biochemical evaluation for possible primary hyperparathyroidism. Recommended laboratory testing was performed and yielded no evidence of parathyroid disorder.

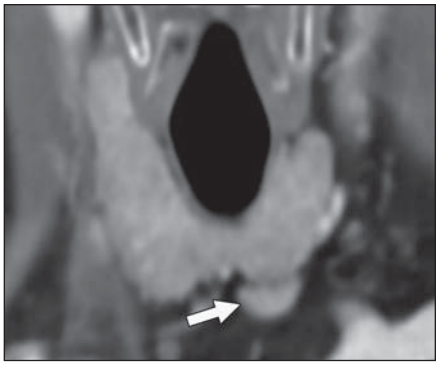

Fig. 5—65-year-old woman who underwent contrast-enhanced neck CT owing to recently diagnosed oral tongue squamous cell carcinoma. Coronal image shows avidly enhancing nodule (*arrow*) along inferior aspect of left thyroid lobe. Interpreting neuroradiologist suspected this finding to represent opportunistically identified enlarged left inferior parathyroid gland and included in clinical report recommendation for biochemical evaluation for possible primary hyperparathyroidism. Recommended laboratory testing was performed and yielded results consistent with primary hyperparathyroidism. Subsequently, lesion was surgically resected and confirmed to represent hypercellular parathyroid gland.

TABLE 2: Comparison of Characteristics of Suspected Enlarged Parathyroid Glands on CT Among Patients Who Underwent Biochemical Evaluation for Possible PHPT, Stratified by Integrated Parathyroid Diagnosis

Characteristic	Tested Patients (n = 13)	Patients With PHPT (n = 3)	Patients With SHPT (n = 4)	Patients With No Parathyroid Disorder (n = 6)	p
Maximum dimension (mm)					.81[a]
Median	11	11	12	10	
IQR	8–18	7–29	8–17	8–19	
Range	7–29	7–29	8–18	8–23	
Estimated volume (mm^3)					.77[a]
Median	204	309	394	189	
IQR	128–1858	91–3800	115–1401	161–2305	
Range	91–3800	91–3800	112–1647	131–3014	
Single suspected enlarged gland, no. (%) of patients	9 (69.2)	3 (100.0)	2 (50.0)	4 (66.7)	.36[b]

Note—PHPT = primary hyperparathyroidism, SHPT = secondary hyperparathyroidism.
[a]One-way ANOVA with Tukey honestly significant difference.
[b]Pearson chi-square test.

Tested patients and untested patients had kidney stones in six of 13 (46.2%) versus six of 26 (23.1%) (p = .16), a history of fragility fracture in one of 13 (7.7%) versus five of 26 (19.2%) (p = .64), and decreased bone mineral density (i.e., osteopenia or osteoporosis) in two of 13 (15.4%) versus six of 26 (23.1%) (p = .69).

Discussion

In this study, biochemical evaluation of patients with suspected enlarged parathyroid glands on routine CT, based on real-world clinical interpretations, yielded a new diagnosis of PHPT in 7.7% of patients who received a radiologist recommendation for such testing and in 23.1% of patients who underwent such testing. Well-documented gaps in the diagnosis and treatment of PHPT have led to calls for new approaches in hypercalcemia and hyperparathyroidism workup [11]. One systemic change would be to leverage the millions of CT examinations performed each year for reasons unrelated to known or suspected PHPT to opportunistically assess for enlarged parathy-

roid glands. The current study provides supporting evidence for such an approach.

Among patients with known PHPT undergoing parathyroid CT, size criteria have been proposed for differentiating abnormal parathyroid glands from normal glands [18, 20]. In a study of patients with single parathyroid adenomas (i.e., only one abnormal parathyroid gland causing PHPT), an estimated weight of greater than 60 mg had sensitivity of 97% and specificity of 96% for identifying the single abnormal gland [20]. A diameter in any dimension of greater than 6.5 mm performed similarly (i.e., 95% sensitivity, 96% specificity) and entailed fewer measurements for the radiologist [20]. In a different study of patients who underwent successful surgical treatment of PHPT with either single-gland or multigland disease, an estimated volume equal to or greater than 55 mm^3 had sensitivity of 93% and specificity of 87% for individual glands requiring surgical removal, and a diameter equal to or greater than 7 mm achieved sensitivity of 93% and specificity of 84% [18]. In the current study, the interpreting neuroradiologists used personal judgment (rather than application of specific size criteria) in determining the presence of a suspected enlarged gland; however, on the basis of retrospectively performed measurements of the largest described gland in each patient, all glands exhibited an estimated volume of at least 75 mm^3 and a maximum diameter of at least 6 mm.

In a retrospective study of 336 patients with trauma with no known parathyroid disorder, a neuroradiologist assessed for enlarged (defined as estimated weight > 60 mg) parathyroid glands on contemporaneously performed noncontrast cervical spine CT and contrast-enhanced neck CTA examinations (analogous to noncontrast and arterial phases, respectively, of parathyroid CT examinations) [16]. A parathyroid surgeon reviewed the EHR of patients with suspected enlarged parathyroid glands to determine the likelihood of undiagnosed PHPT. Enlarged glands were identified in 3% of patients, of whom 36% were classified as highly likely or likely to have undiagnosed PHPT [16]. The likelihood of PHPT increased in patients with larger glands. On the basis of those findings and assuming a prevalence of PHPT of 0.86% [4], the authors estimated that as few as 3.5 patients with enlarged parathyroid glands identified by CT would need to undergo biochemical testing to yield one PHPT diagnosis [16]. However, that study was limited by absence of biochemical confirmation of PHPT and of pathologic confirmation of any abnormal parathyroid glands.

In the current study, biochemical evidence of PHPT was confirmed in multiple tested patients, and pathologic confirmation of hypercellular parathyroid tissue was obtained for the one patient with PHPT who underwent surgery. Based on the present data, the number of patients with enlarged parathyroid glands who would need to undergo biochemical testing per PHPT diagnosis was 4.3, similar to the earlier study's estimate of 3.5 [16]. During the study period, a very small proportion (0.1%) of CT interpretations included the recommendation for biochemical testing, markedly less than a prior report of an enlarged parathyroid gland identified in 3% of patients with trauma [16]. However, the two studies have important methodologic differences. Unlike the previous study in which a single neuroradiologist performed a targeted review of all examinations for research purposes, the current study captures only those glands deemed by one of multiple neuroradiologists to warrant reporting in the context of clinical practice. The neuroradiologists who issued the recommendations for biochemical testing did not interpret all instances of the represented CT examination types performed during the study period, and the neuroradiologists did not necessarily perform a systematic assessment for enlarged parathyroid glands on all CT examinations that they interpreted during the study period. In fact, the findings may allay concerns that real-world implementation of opportunistic parathyroid gland assessment would result in widespread misidentification of central compartment lymph nodes as enlarged parathyroid glands with recommendation for biochemical evaluation. Although more data are needed to inform a true cost-effectiveness assessment of the radiologist recommendation for biochemical evaluation, such testing has an estimated cost of USD99.35 per patient [12], and in patients with untreated PHPT, the estimated risk of developing a composite endpoint of osteoporosis, nephrolithiasis, impaired renal function, or hypercalciuria over 5 years is 27–42% [5].

This study raises additional questions warranting further investigation. One question is whether the size criteria proposed for differentiating abnormal parathyroid glands from normal glands [18, 20] in the setting of known PHPT (i.e., 100% pretest probability of disease) are appropriate for opportunistic parathyroid gland assessment in patients with no known or suspected parathyroid disorder (i.e., < 1% pretest probability of disease). A higher size threshold may increase specificity for the true biochemical diagnosis of PHPT while maintaining reasonable sensitivity. An additional possibility is that integration of clinical information available to the interpreting radiologist at the time of imaging interpretation could improve targeting of biochemical testing to individual patients most likely to have undiagnosed PHPT. Data from much larger patient samples would be needed to evaluate these possibilities. A further question relates to the 46.2% of tested patients with a suspected enlarged parathyroid gland on CT who had no parathyroid disorder based on the endocrine surgeon's integrated diagnosis. In these patients, the CT findings may have represented an entity other than enlarged parathyroid glands (i.e., lymph node or thyroid nodule). Alternatively, the CT findings may have represented nonfunctioning parathyroid adenomas, a reported but exceedingly rare entity [21–23]. A third possibility is that the findings indeed represented hyperfunctioning parathyroid tissue, but associated laboratory abnormalities had not yet manifested. In this scenario, clinical follow-up or repeat laboratory testing could be appropriate; however, data to support such a recommendation are currently lacking.

Although the proportion of patients with undiagnosed PHPT who stand to benefit from opportunistic imaging-based parathyroid gland assessment is unknown, we suspect that such assessment alone would be insufficient to substantially reduce existing diagnosis and treatment gaps. However, the current study shows that biochemical testing of patients with opportunistically detected enlarged parathyroid glands can identify some individuals with undiagnosed PHPT, suggesting that this approach could be a helpful component of a larger multilevel strategy to improve PHPT diagnosis and treatment. A study from 2022 evaluated an EHR-based clinical decision support tool designed to improve parathyroid hormone testing among patients with chronic hypercalcemia [24]. At baseline, only 7% of patients with chronic hypercalcemia had undergone parathyroid hormone testing

[24]. After implementation of an EHR-based alert, the parathyroid hormone testing rate increased to 45% [24]. A total of 99% of patients receiving parathyroid hormone testing met the criteria for PHPT [24]. A practitioner notification system combining information regarding imaging findings and serum calcium levels could potentially achieve higher rates of parathyroid hormone testing than those achieved by notification based on hypercalcemia alone (45%) or imaging findings alone (33%). Integrating additional imaging findings (e.g., presence of kidney stones, evidence of osteopenia or osteoporosis) and clinical data (e.g., history of fragility fracture) into practitioner notifications might also enable more informed decision-making regarding the choice to test, with possible increased testing rates among patients most likely to have undiagnosed PHPT. For example, in the current study, rates of decreased bone mineral density and prior fragility fracture were higher (albeit not statistically significant differences) in untested individuals than in tested individuals, potentially indicating that some untested patients were at risk of having undiagnosed PHPT. If such clinical information had been included, when appropriate, with the recommendation for biochemical testing, ordering practitioners may have been more likely to act on the radiologist's recommendation.

In 2022, an international expert panel published updated evidence-based clinical management guidelines describing three clinical phenotypes of PHPT: symptomatic, asymptomatic, and normocalcemic [19]. Patients with symptomatic PHPT exhibit overt skeletal or renal complications, which may include fractures, chronic kidney disease, and nephrolithiasis. Patients with asymptomatic PHPT lack overt skeletal or renal complications but may exhibit a variety of neurobehavioral (e.g., depression, anxiety, impaired cognition), gastrointestinal (e.g., nausea, emesis), cardiovascular (e.g., hypertension), and muscular (e.g., weakness) effects associated with, but not specific to, PHPT. Patients with normocalcemic PHPT exhibit persistently normal calcium levels in the setting of at least two elevated parathyroid hormone levels measured over a 3- to 6-month period. These guidelines recommend parathyroidectomy for all patients with symptomatic PHPT unless medically contraindicated and for asymptomatic patients with any of the following: serum calcium value greater than 1 mg/dL above the upper limit of normal, evidence of skeletal involvement (e.g., fracture or decreased bone mineral density detected by imaging), evidence of renal involvement (e.g., estimated glomerular filtration rate < 60 mL/min, nephrocalcinosis, or nephrolithiasis detected by imaging), or age younger than 50 years. Thus, radiologists can increase the relevance and immediacy of a recommendation for biochemical testing by also commenting on the presence of any of these features, along with the suspected enlarged parathyroid gland. No recommendations are made for managing normocalcemic PHPT because of limited data. For patients who do not undergo parathyroidectomy, a monitoring plan is recommended. This plan includes annual laboratory testing (i.e., calcium level, 25-hydroxyvitamin D level, renal function tests); dual-energy x-ray absorptiometry every 1–2 years; and imaging assessment, when clinically indicated, for the development of fractures or kidney stones [19].

This study had limitations including its small sample size and retrospective nature. Although all recommendations for biochemical evaluation were issued as a component of clinical care, the exact reasons why individual patients did or did not undergo subsequent testing are unknown, and we have not shown the ability to prospectively improve outcomes in patients with PHPT. In addition, the included CT examinations were of a heterogeneous range of examination types. Given the focus on clinical reports documenting the original clinical interpretations of seven faculty neuroradiologists, interreader reliability was not evaluated. This retrospective review of clinical interpretations relied on individual radiologist judgment rather than on formal criteria for determining the presence of an enlarged parathyroid gland. Also, the study lacked a mechanism for detecting or quantifying possible missed parathyroid adenomas on CT examinations performed during the study period. Moreover, the radiologists at the institution who issued recommendations for biochemical evaluation were all neuroradiologists, and accordingly all CT examinations with the recommendation were examinations of the neck or spine. Such recommendations could also be issued by thoracic or general radiologists as well as for CT examinations of the chest. Finally, only 33.3% of patients received the recommended biochemical testing, which is at the lower end of reported adherence rates for radiology report recommendations [25–30].

In conclusion, recommendations for biochemical evaluation in patients with suspected enlarged parathyroid glands opportunistically detected by routine CT examinations, which were issued as part of real-world clinical practice, identified undiagnosed PHPT in 23.1% of patients who underwent such testing. The potential for systematic implementation of this approach to substantially impact existing gaps in PHPT diagnosis remains unknown.

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Editorial Comment: Value-Added Assessment for Parathyroid Adenomas on Routine CT Examinations

Radiologists should seek avenues to apply imaging tests to provide value for patients and health care systems. This mission can be achieved through a focus on the triple aim of improving patient outcomes, enhancing patient experience, and decreasing the cost of care [1].

Primary hyperparathyroidism (PHPT) is a common endocrine disease that, since its discovery in the early 1900s, has increased in incidence due to the advent of serum evaluation for the condition. Specifically, PHPT is diagnosed in the presence of the combination of hypercalcemia and an elevated or inappropriately normal parathyroid hormone level [2]. The authors of this retrospective study focus on the existing gap in diagnosing PHPT. The authors' key proposal is that a radiologist recommendation for biochemical testing in patients with a suspected enlarged parathyroid gland on a routine CT examination (i.e., an examination performed for reasons other than known or suspected parathyroid disease) can help identify individuals with undiagnosed PHPT.

Using real-world clinical data, the authors identified a sample of 39 patients at their institution who received a radiologist recommendation to undergo biochemical evaluation based on a suspected enlarged parathyroid gland on routine CT. Thirteen of those patients underwent the recommended testing. Of those 13 patients, three were diagnosed with PHPT, four were diagnosed with secondary hyperparathyroidism, and six were found to be without parathyroid disorder. The authors also comment on the potential cost-effectiveness of detecting an enlarged parathyroid gland on CT in otherwise undiagnosed patients, considering for example the cost of the recommended biochemical testing as well as the risks of untreated PHPT, including osteoporosis, nephrolithiasis, and impaired renal function. The study overall presents a representative example of the opportunity to apply imaging to add value to patient care.

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Opportunistic CT Assessment of Parathyroid Glands: Utility of Radiologist-Recommended Biochemical Evaluation for Diagnosing Primary Hyperparathyroidism

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Introduction

1. What are the different types of hyperparathyroidism? What are the risks associated with primary hyperparathyroidism (PHPT)? How is PHPT treated?
2. What is the stated purpose of this study?

Methods

3. What study design was used? What were the inclusion criteria? What were the exclusion criteria?
4. For patients selected in this study, what data were collected from the medical record? What primary outcome and secondary outcomes were evaluated in this study?
5. What factors did the endocrine surgeon include in their integrated parathyroid diagnosis?

Results

6. How often was biochemical testing for possible PHPT recommended?
7. How often were single versus multiple enlarged parathyroid glands suspected in the studies evaluated? What were the median maximum diameters and estimated volumes of these enlarged parathyroid glands?

Discussion

8. What are the limitations of this study? Are these adequately discussed?
9. Do you specifically include evaluation for parathyroid gland presence and enlargement when interpreting CT examinations that include their location?
10. What diameter is presented as a potential threshold for a single abnormal parathyroid gland correlating with a subsequent diagnosis of PHPT?
11. How might you design a follow-up study?

Suggested Reading

1. Bunch PM, Goyal A, Valenzuela CD, Randle RW. Parathyroid 4D CT in primary hyperparathyroidism: exploration of size measurements for identifying multigland disease and guiding biochemically successful parathyroidectomy. *AJR* 2022; 218:888–897
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*Please note that the authors of the Study Guide are distinct from those of the companion article.