

Assessment and Comparison of ^{18}F -Fluorocholine PET and $^{99\text{m}}\text{Tc}$ -Sestamibi Scans in Identifying Parathyroid Adenomas: A Metaanalysis

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Hyperparathyroidism is an endocrine disorder caused by one or more hyperfunctioning parathyroid glands. Current imaging consisting of ultrasound and $^{99\text{m}}\text{Tc}$ -sestamibi is imprecise, making localization difficult. ^{18}F -fluorocholine (^{18}F -FCH) PET has recently shown promise in presurgical localization of parathyroid adenomas. The primary aim of this study was to summarize the sensitivities and specificities of studies using ^{18}F -FCH PET to localize hyperparathyroidism. A secondary aim was to summarize a subset of studies in which $^{99\text{m}}\text{Tc}$ -sestamibi scans were also used and to compare the performance of the 2 modalities. **Methods:** We searched the MEDLINE and EMBASE databases following the PRISMA (Preferred Reporting Items for Systematic Review and Metaanalysis) statement. Quality was assessed using the QUADAS-2 tool (Quality Assessment of Diagnostic Accuracy Studies). Twenty studies were included for quantitative assessment in our metaanalysis. A random-effects model and a hierarchic summary receiver-operating-characteristic model was used to summarize the sensitivity of ^{18}F -FCH PET in detecting abnormal parathyroid adenomas. We used the same methodology to assess sensitivity of $^{99\text{m}}\text{Tc}$ -sestamibi, as a comparison to ^{18}F -FCH PET. **Results:** ^{18}F -FCH PET had a high sensitivity, 0.97 (range, 0.96–0.98), for the detection of abnormal parathyroid adenomas. In the subpopulation for which both ^{18}F -FCH and $^{99\text{m}}\text{Tc}$ -sestamibi were reported, ^{18}F -FCH also had a higher sensitivity, 0.96 (0.94–0.98), than the 0.54 (0.29–0.79) reported for $^{99\text{m}}\text{Tc}$ -sestamibi ($P < 0.001$). **Conclusion:** ^{18}F -FCH PET demonstrates high localization accuracy in patients with hyperparathyroidism. This metaanalysis supports the use of ^{18}F -FCH over $^{99\text{m}}\text{Tc}$ -sestamibi in patients with hyperparathyroidism.

Key Words: fluorocholine; hyperparathyroidism; adenoma; PET; $^{99\text{m}}\text{Tc}$ -sestamibi

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Hyperparathyroidism is a common endocrine disorder in which one or more of the parathyroid glands become autonomously

hyperfunctional, causing excessive secretion of parathyroid hormone into the bloodstream (1,2). It is a common endocrine disorder, with an estimated incidence of between 0.4 and 82 cases per 100,000 in the general population (3–6). The etiology is usually a benign overgrowth of parathyroid tissue in at least 1 of the 4 parathyroid glands. This occurs in a single gland in approximately 80% of cases and less frequently (15%–20% of cases) in multiple glands (7). Hyperparathyroidism is diagnosed biochemically and is associated with hypercalcemia and elevated parathyroid hormone (7); in turn, hypercalcemia, if left untreated, can cause significant morbidities ranging from skeletal complications to renal impairment, as well as complications such as nephrocalcinosis, polyuria, and polydipsia.

Surgical removal of the hyperfunctioning gland (i.e., a parathyroidectomy) remains the only curative treatment for hyperparathyroidism (8). Preoperative localization of the hyperfunctioning gland is necessary for a minimally invasive parathyroidectomy, which is associated with a reduced risk of complications and disability after surgery as compared with conventional bilateral cervical exploration (9). Preoperative localization is complex, and imaging recommendations vary considerably. Cervical ultrasonography and $^{99\text{m}}\text{Tc}$ -sestamibi SPECT are the most commonly used methods. However, their accuracy varies considerably depending on the location of the affected glands, the size of the adenoma, and the skill of individual sonographers (10,11).

Given the inconsistencies of currently approved imaging modalities, new approaches are actively being evaluated. Several studies support the utility of ^{18}F -fluorocholine (^{18}F -FCH) PET, and results from the literature are encouraging (12,13). For nearly 20 years, ^{18}F -FCH has been used to detect metastatic prostate cancer. Choline is a precursor for the synthesis of phospholipids in the cell membrane and choline kinase, which results in the elevated phosphocholine that is overexpressed in prostate cancer (14). However, data on the utility of ^{18}F -FCH in localizing hyperparathyroidism remain relatively sparse, and comparison of ^{18}F -FCH PET to traditional tools is limited to single-center studies.

The primary aim of this study was to summarize studies that have used ^{18}F -FCH PET to localize hyperparathyroidism and to assess their sensitivity and specificity after pathologic confirmation. A second aim was to analyze a subset of studies in which a $^{99\text{m}}\text{Tc}$ -sestamibi scan was also used and to compare the sensitivity and specificity with those of ^{18}F -FCH PET imaging.

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MATERIALS AND METHODS

Correct identification of hyperparathyroidism was defined on a per-patient level. The protocol for this metaanalysis was registered with PROSPERO (the International Prospective Register of Systematic Reviews).

Search Strategy

Two of us conducted independent literature reviews for article inclusion in the study. This review included electronic databases, as well as reference lists of relevant articles. The search was applied to the PubMed/MEDLINE and EMBASE databases and was last updated on August 25, 2020. We used a combination of the following terms: choline, fluorocholine, F-choline, FCH; PET, positron emission tomography; and parathyroid, hyperparathyroidism.

Eligibility Criteria

Two reviewers independently assessed article eligibility for inclusion in this study. Disagreements were resolved by consensus. Articles that met the following inclusion criteria were considered for the metaanalysis: studies evaluating the diagnostic accuracy of ^{18}F -FCH PET in patients with hyperparathyroidism, and studies that used pathologic confirmation of hyperparathyroidism as the reference standard. No year or location restrictions were imposed on the studies. Articles were excluded if they risked overlap with other studies (including systematic reviews and other metaanalyses); were not available in English; were on unpublished studies; were on case reports; had fewer than 10 cases; did not use pathology as the reference standard for diagnosing hyperparathyroidism; or did not have data on the diagnosis of hyperparathyroidism at the per-patient level. We also subsequently performed the analysis by removing articles for which cases of secondary and tertiary hyperparathyroidism could not be separated from primary hyperparathyroidism.

Data Collection

The characteristics of the eligible studies are summarized in Table 1. Data were extracted, when available, from each eligible article on the following variables: National Clinical Trial number, prospective versus retrospective, consent performed, number of patients imaged with ^{18}F -FCH, imaging modality (PET/CT or PET/MRI), number of patients with a pathologic correlate, number of imaging readers, whether the readers knew the results of patients' pathology or clinical data, injected dose and range, uptake time, and details on any adverse event reporting.

Quantitative data points were then extracted from eligible studies. These included number of true-positive, false-positive, true-negative, and false-negative diagnoses of hyperparathyroidism based on ^{18}F -FCH imaging as compared with a pathologic correlate on a per-patient basis. If available, the same results were collected for studies in which patients were also imaged with $^{99\text{m}}\text{Tc}$ -sestamibi. One reviewer extracted the data points from eligible studies, and the second reviewer reviewed the extracted data for quality assurance. For each study included in the analysis, bias was assessed qualitatively by 2 reviewers using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool (15).

Metaanalytic Methods

For this metaanalysis, we used a random-effects model and a hierarchical summary receiver-operating-characteristic model using Stata, version 12.0 (StataCorp). Sensitivity and specificity are summarized for ^{18}F -FCH imaging accuracy in detecting hyperparathyroidism on a per-patient level using the pathologic correlate as the reference standard. We also assessed sensitivity and specificity for a subset of studies that additionally imaged patients with $^{99\text{m}}\text{Tc}$ -sestamibi. To include all the studies in the metaanalysis, a small number was added to the zero cells

for this subset of studies. All point estimates of sensitivity and specificity from the metaanalysis are reported as the effect size and 95% CIs.

RESULTS

Eligible Studies

An electronic search of the PubMed and EMBASE libraries returned a total of 776 articles (Fig. 1). Twenty studies were deemed eligible for the metaanalysis and are summarized in Table 1. The number of patients assessed ranged from 10 to 151 in our selected studies. All 20 papers were used to evaluate the sensitivity and specificity of ^{18}F -FCH PET in detecting hyperparathyroidism, and 10 studies included data on the results of $^{99\text{m}}\text{Tc}$ -sestamibi to use for comparison. The risk of bias and the applicability of each study to our current research were assessed using the QUADAS-2 tool (Supplemental Table 1; supplemental materials are available at <http://jnm.snmjournals.org>). In several cases, the risk of bias of the index test and the flow and timing of the imaging protocol could not be determined from the information provided in the text. Bias concerned the retrospective nature of many studies included in this analysis, as well as the uncertain time between imaging and parathyroidectomy in several cases. For the purposes of this analysis, a time of less than 4 wk between imaging and surgery was considered to have a low risk of bias.

Performance of ^{18}F -FCH PET in Detecting Hyperparathyroidism

All 20 studies used ^{18}F -FCH imaging (either by PET/CT, $n = 18$, or by PET/MRI, $n = 4$) to identify hyperparathyroidism (Table 2). The included studies were both retrospective ($n = 8$) and prospective ($n = 12$), consent was obtained for research participation in most cases ($n = 17$), and 1 study was registered with ClinicalTrials.gov before conducting research procedures. The average injected ^{18}F -FCH dose ranged from 0.1 MBq/kg to a 325.1-MBq flat dose. The uptake time ranged from 0 min for dynamic imaging to 90 min for static imaging. The most common injected dose was 100 MBq, and the most common uptake time was 60 min. Across the 20 studies, including a total of 796 patients, the results of the random-effects metaanalysis of the sensitivity and specificity was 0.97 (range, 0.96–0.98) and 0.23 (range, 0.11–0.35), respectively (Fig. 2). The positive predictive value of ^{18}F -FCH PET, compared with pathology, was 0.94 (range, 0.92–0.96). In studies that included only patients with primary hyperparathyroidism ($n = 16$), sensitivity and specificity were 0.94 (range, 0.92–0.97) and 0.14 (range, 0–0.36), respectively (Supplemental Fig. 1).

Comparison of ^{18}F -FCH PET and $^{99\text{m}}\text{Tc}$ -Sestamibi in Detecting Hyperparathyroidism

As a secondary analysis, we compared the performance of ^{18}F -FCH PET and $^{99\text{m}}\text{Tc}$ -sestamibi in detecting cases of hyperparathyroidism before surgery. Ten studies, which included 301 patients, had these data available and were used in the comparison (Table 3; Supplemental Fig. 2). ^{18}F -FCH PET had a superior sensitivity of 0.96 (range, 0.94–0.98), compared with 0.54 (range, 0.29–0.79) for $^{99\text{m}}\text{Tc}$ -sestamibi ($P < 0.001$) (Figs. 3 and 4). In studies limited to patients with primary hyperparathyroidism, ^{18}F -FCH PET had a superior sensitivity of 0.97 (range, 0.94–1.00), compared with 0.55 (range, 0.32–0.78) for $^{99\text{m}}\text{Tc}$ -sestamibi.

TABLE 1
Characteristics of Studies Included in Metaanalysis (23–44)

First author	Year	Prospective or retrospective?	NCT number	Consent obtained	Patients		Masked readers	Pathology correlation	PET/CT or PET/MRI?	Injected dose range (MBq)	Injected dose average (MBq)	Uptake time (min)	Primary HPT only?	
					Patients with ¹⁸ F-FCH imaging	Patients with parathyroidectomy								
Alharbi	2018	Retrospective	No	Yes	66	52	No	2	Yes	Both	NR	150	2 & 50	Yes
Amadou	2019	Retrospective	No	No	41	23	No	NR	Yes	PET/CT	NR	231	60	Yes
Bossert	2019	Prospective	No	Yes	34	17	Unclear	2	Yes	PET/CT	NR	3–3.5/kg	9 & 60	Yes
Broos	2019	Prospective	No	Yes	271	139	Yes	3	Yes	PET/CT	NR	150	5 & 60	Yes
Christakis	2019	Prospective	No	Yes	12	12	Yes	1	Yes	PET/CT	NR	300	60 & 90	Yes
Fischli	2017	Retrospective	No	Yes	39	23	No	1	Yes	PET/CT	IQR 180–149	160	45	Yes
Grimaldi	2018	Prospective	No	No	27	21	Unclear	NR	Yes	PET/CT	77–230	100	30	Yes
Hocevar	2017	Retrospective	No	No	151	151	No	NR	Yes	PET/CT	NR	100	5 & 60	Yes
Huber	2018	Retrospective	No	Yes	26	26	Unclear	NR	Yes	Both	NR	151	45	No
Khaff	2019	Prospective	No	Yes	19	19	No	2	Yes	PET/MRI	NR	93.75	16	Yes
Kluijfhout	2017	Prospective	No	Yes	10	10	Yes	2	Yes	PET/MRI	188 ± 26	188	0*	Yes
Kluijfhout	2016	Retrospective	No	Yes	33	33	Unclear	NR	Yes	PET/CT	NR	2/kg	30	No
Lezaic	2014	Prospective	No	Yes	24	24	Unclear	2	Yes	PET/CT	NR	100	5 & 60	Yes
López-Mora	2020	Prospective	No	Yes	33	33	Unclear	3	Yes	PET/CT: digital vs. analog	NR	0.1/kg	Unclear	Yes
Michaud	2014	Prospective	No	Yes	12	12	No	1	Yes	PET/CT	NR	3/kg	0†	No
Piccardo	2019	Prospective	No	Yes	44	31	Unclear	2	Yes	PET/CT	NR	100	10	Yes
Quak	2018	Prospective	NCT02432599	Yes	25	24	Yes	NR	Yes	PET/CT	NR	1.5/kg	60	Yes
Thanseer	2017	Prospective	No	Yes	54	54	Unclear	NR	Yes	PET/CT	150–185	150–185	10–15 & 60	Yes
Uslu-Besli	2020	Retrospective	No	Yes	105	81	No	2	Yes	PET/CT	325.1 ± 86.7	325.1	15 & 45	No
Zajčková	2018	Retrospective	No	Yes	13	13	Unclear	2	Yes	PET/CT	NR	180	30	Yes

*Dynamic imaging for 40 min.

†Dynamic imaging for 10 min followed by static acquisition.

NCT = National Clinical Trial; HPT = hyperparathyroidism; NR = not reported; IQR = interquartile range.

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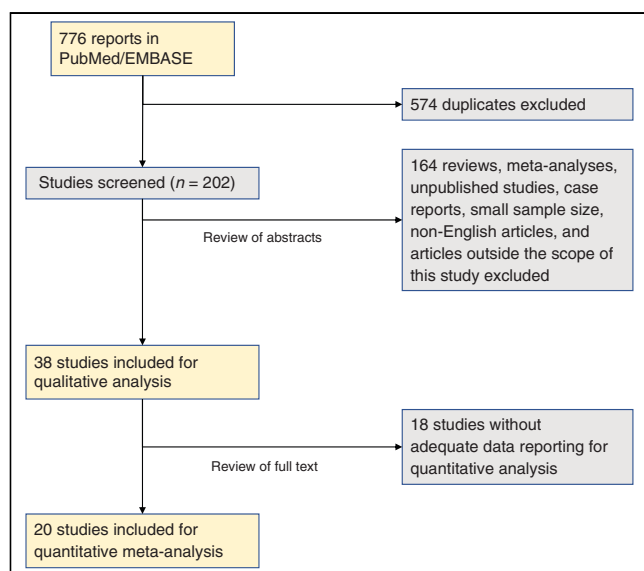


FIGURE 1. PRISMA (Preferred Reporting Items for Systematic Review and Metaanalysis) flow diagram depicting process for selecting papers included in this metaanalysis.

TABLE 2

Overview of Studies Comparing Performance of ^{18}F -FCH PET with Pathology in 20 Studies Reporting Total of 796 Patients

First author	Year	Patients	TP	FP	TN	FN
Alharbi	2018	52	52	0	0	0
Amadou	2019	23	21	1	0	1
Bossert	2019	17	15	0	0	2
Broos	2019	139	131	0	2	6
Christakis	2019	12	7	5	0	0
Fischli	2017	23	21	1	NA	1
Grimaldi	2018	21	17	1	NA	3
Hocevar	2017	151	144	4	1	2
Huber	2018	26	25	0	0	1
Khafif	2019	19	19	0	0	0
Kluijfhout	2017	10	9	0	NA	1
Kluijfhout	2016	33	30	1	NA	2
Lezaic	2014	24	23	0	NA	1
López-Mora	2020	33	29	1	0	3
Michaud	2014	12	11	0	NA	1
Piccardo	2019	31	25	0	0	6
Quak	2018	24	19	3	NA	2
Thanseer	2017	54	52	2	NA	0
Uslu-Bešli	2020	79	76	NA	NA	3
Zajčková	2018	13	12	0	0	1
Total		796	738	19	3	33

TP = true positive; FP = false positive; TN = true negative; FN = false negative; NA = not applicable.

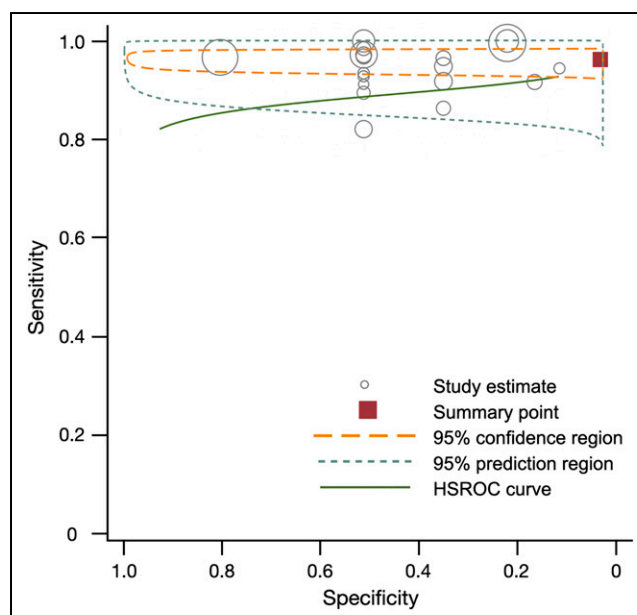


FIGURE 2. Summary of sensitivity, specificity, and hierarchic summary receiver-operating-characteristic (HSROC) plot of sensitivity and specificity for ^{18}F -FCH vs. pathology overall. Effect sizes for sensitivity and specificity were 0.97 (95% CI, 0.96–0.98) and 0.23 (95% CI, 0.11–0.35), respectively. Size of circles represents size of individual studies.

DISCUSSION

Several individual cohort studies have reported ^{18}F -FCH PET to be superior to traditional imaging modalities such as ultrasonography and $^{99\text{m}}\text{Tc}$ -sestamibi in detecting hyperparathyroidism in patients before parathyroidectomy. Individual studies are difficult to interpret because of their small sample sizes and variability between studies. In this metaanalysis, we pool the results of studies using ^{18}F -FCH PET to localize abnormal parathyroid adenomas and using pathology as a reference standard. To acknowledge individual study bias, we assessed each paper using the QUADAS-2 tool and used a random-effects model to account for between-study variability in our quantitative analysis. Overall, the results of this metaanalysis lend further evidence to support the use of ^{18}F -FCH PET as a superior imaging technique over $^{99\text{m}}\text{Tc}$ -sestamibi in the localization of hyperparathyroidism before parathyroidectomy.

To avoid loss of power and incorporate more studies into our analysis, we included studies using both PET/CT and PET/MRI. Diagnostic differences between these modalities for this indication have not been studied in previous literature, but we acknowledge that inclusion of PET/MRI may further bias this analysis. Our study did not consider results on a per-lesion basis, considering only whether imaging localized an overactive parathyroid gland on a per-patient basis. This approach may overestimate the accuracy of ^{18}F -FCH PET as a presurgical tool in avoiding invasive open parathyroidectomies.

As with any metaanalysis, our approach is limited by the underlying data in the articles included. As reported, there was a wide range in acquisition parameters used. Most concerning was that masking of readers to the results of parathyroidectomies before image interpretation was not done or was unclear in most cases,

TABLE 3
Overview of Studies Comparing Performance of ^{99m}Tc -Sestamibi with Pathology

First author	Year	Patients with pathology	^{99m}Tc -sestamibi compared with pathology			
			TP	FP	TN	FN
Amadou	2019	23	9	1	0	13
Bossert	2019	17	3	0	0	14
Huber	2018	26	2	0	0	24
Khafif	2019	19	17	0	0	2
Kluijfhout	2017	33	8	0	0	21
Lezaic	2014	24	14	0	0	10
Michaud	2014	12	8	2	0	2
Thanseer	2017	54	42	1	1	10
Uslu-Bešli	2020	80	39	1	NA	NA
Zajčková	2018	13	4	2	0	7
Total		301	146	7	1	103

TP = true positive; FP = false positive; TN = true negative; FN = false negative; NA = not applicable.

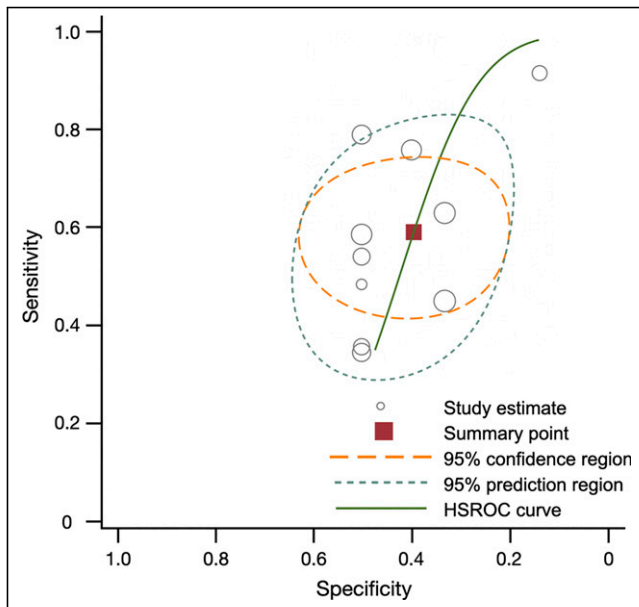


FIGURE 3. Summary of sensitivity, specificity, and hierarchic summary receiver-operating-characteristic (HSROC) plot of sensitivity and specificity for ^{99m}Tc -sestamibi vs. pathology overall. Effect sizes for sensitivity and specificity were 0.54 (0.29–0.79) and 0.43 (0.30–0.57), respectively. Size of circles represents size of individual studies.

and most studies were retrospective. This likely biased individual study results and may have skewed results in favor of ^{18}F -FCH PET. Furthermore, several studies included patients with a history of thyroid or parathyroid surgery; it is unclear what effect this may have had on the accuracy of either ^{18}F -FCH PET or ^{99m}Tc -sestamibi in detecting the affected parathyroid glands and may limit the applicability of these results to patients being imaged at baseline.

One other issue is the heterogeneity of the technique used for ^{99m}Tc -sestamibi imaging in our analysis, as each approach has

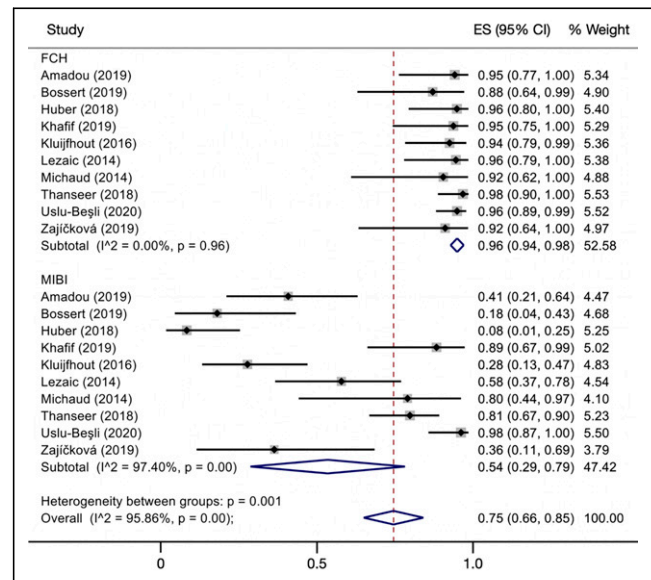


FIGURE 4. Comparison of diagnostic sensitivities of ^{18}F -FCH and ^{99m}Tc -sestamibi. Overall effect sizes (ES) were 0.96 (95% CI, 0.94–0.98) for ^{18}F -FCH PET and 0.54 (95% CI, 0.29–0.79) for ^{99m}Tc -sestamibi. Size of squares represents size of individual studies. Reference numbers are in Supplemental Table 2.

varying sensitivities that can lead to inconsistencies across the articles used in the comparison analysis. Of the 10 studies included for comparison with ^{99m}Tc -sestamibi, 6 (including 41% of the analyzed patients) used dual-phase, dual-tracer ^{99m}Tc -sestamibi imaging with SPECT/CT. Three articles used SPECT, 2 of which used ^{99m}Tc -sestamibi alone, and 1 article did not describe the ^{99m}Tc -sestamibi imaging.

Despite these weaknesses, we believe this study is important in a setting that has seen little change in practice over many years. Furthermore, there are features of this study that we feel distinguish it from prior metaanalyses on this topic. We have taken care

to define strict study eligibility criteria, including a minimum cohort size to limit patient selection bias, the requirement of a histopathologic correlate for all cases in the analysis, and a focus on ^{18}F -FCH PET only, excluding studies that incorporate other choline tracers (13). Perhaps most notably, our study included 2 important subanalyses: a comparison of ^{18}F -FCH PET to the standard-of-care $^{99\text{m}}\text{Tc}$ -sestamibi scan, making a strong clinical case for the adoption of this more novel technique; and a further study limited to cases with primary hyperparathyroidism. To our knowledge, it is also the largest study of this kind (12,16).

Beyond $^{99\text{m}}\text{Tc}$ -sestamibi, there are other imaging techniques being evaluated for the localization of abnormal parathyroids, such as 4-dimensional (4D) CT and ^{11}C -choline PET. Both have also demonstrated utility in preoperative localization of parathyroid glands in patients with hyperparathyroidism. Literature on the use of 4D CT, with or without ultrasonography, has reported high but varying sensitivities in localizing adenomas (17,18). There are insufficient data at this time to compare ^{18}F -FCH with 4D CT to perform a metaanalysis. However, there are several theoretic advantages of ^{18}F -FCH over 4D CT, including obviation of intravenous iodinated contrast, as well as the lower total doses of radiation (19). ^{11}C -choline PET, a similar radiotracer to ^{18}F -FCH, received Food and Drug Administration approval in 2012 for use in prostate cancer (20) and has recently been used in preoperative localization for hyperparathyroidism. Because ^{11}C -choline has a half-life of approximately 20 min, compared with 120 min for ^{18}F (21), PET acquisition must occur very shortly after injection. The longer half-life of ^{18}F -FCH allows for more flexible image acquisition and makes for more practical and favorable clinical use (22).

CONCLUSION

In patients with hyperparathyroidism, ^{18}F -FCH PET demonstrates a high sensitivity (0.97) for parathyroid adenomas in patients with hyperparathyroidism. ^{18}F -FCH PET also outperformed $^{99\text{m}}\text{Tc}$ -sestamibi, with a sensitivity of 0.96 for the former compared with 0.54 for the latter. This metaanalysis supports the use of ^{18}F -FCH over $^{99\text{m}}\text{Tc}$ -sestamibi in patients with hyperparathyroidism.

DISCLOSURE

Thomas Hope receives grant support from the National Institutes of Health (R01CA212148). Isabel Allen is supported by the National Institute on Aging (R43AG066230). No other potential conflict of interest relevant to this article was reported.

KEY POINTS

QUESTION: Does ^{18}F -FCH PET aid in the localization of parathyroid adenomas in patients with hyperparathyroidism?

PERTINENT FINDINGS: In this metaanalysis, ^{18}F -FCH PET had a high sensitivity for parathyroid adenomas and increased the sensitivity from 0.54 for $^{99\text{m}}\text{Tc}$ -sestamibi imaging to 0.96 for ^{18}F -FCH PET.

IMPLICATIONS FOR PATIENT CARE: ^{18}F -FCH PET is useful for localizing parathyroid adenomas and should be used when available.

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