Journal of Nuclear Medicine, published on January 15, 2021 as doi:10.2967/jnumed.120.257303

Assessment and comparison of fluorocholine PET and sestamibi scans in identifying parathyroid adenomas: a meta-analysis

Julia Whitman MS,[1] Isabel E. Allen PhD,[2] Emily K. Bergsland MD,[1,3] Insoo Suh MD,[4] and Thomas A. Hope MD,[3,5,6]

1. Division of Hematology/Oncology, Department of Medicine, University of California San Francisco, San Francisco, California
2. Department of Epidemiology and Biostatistics, UCSF, San Francisco, California
3. UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, California
4. Department of Surgery, University of California San Francisco, United States
5. Department of Radiology and Biomedical Imaging, University of California San Francisco, San Francisco, California
6. Department of Radiology, San Francisco VA Medical Center, San Francisco, California

KEY POINTS:
QUESTION: Does fluorocholine (FCH) PET aid in the localization of parathyroid adenomas in patients with hyperparathyroidism?
PERTINENT FINDINGS: In this meta-analysis, FCH PET had a high sensitivity for parathyroid adenomas, and increased the sensitivity from 0.54 for sestamibi imaging to 0.96 for FCH PET.
IMPLICATIONS FOR PATIENT CARE: FCH PET is useful for localizing parathyroid adenomas, and should be used when available.

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

Keywords: Fluorocholine, hyperparathyroidism, adenoma, PET, sestamibi

Corresponding Author:
Thomas A. Hope, MD
Department of Radiology and Biomedical Imaging
University of California, San Francisco
505 Parnassus Avenue, M-391
San Francisco, CA 94143-0628, USA
Email thomas.hope@ucsf.edu

Abstract

Background: Hyperparathyroidism is an endocrine disorder caused by one or more hyperfunctioning parathyroid glands. Current imaging consisting of ultrasound and ^{99m}Tc-Sestamibi (sestamibi) is imprecise, making localization difficult. ^{18}F-Fluorocholine (FCH) Positron Emission Tomorography (PET) has recently shown promise in pre-surgical localization of parathyroid adenomas. The primary aim of this study is to summarize the sensitivities and specificities of studies using FCH PET to localize hyperparathyroidism. A secondary aim is to summarize a subset of studies in which sestamibi scans were also used, and to compare the performance of the two modalities.

Methods: We searched MEDLINE and EMBASE databases following the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) statement. Quality was assessed using the Quality Assessment of Diagnostic Accuracy Studies-2 tool. Twenty studies were included for quantitative assessment in our meta-analysis. A random effect model and a hierarchical summary receiver operating characteristic model was used to summarize the sensitivity of FCH PET in detecting abnormal parathyroid adenomas. We used the same methodology to assess sensitivity of sestamibi, as a comparison to FCH PET.

Results: FCH PET had a high sensitivity for the detection of abnormal parathyroid adenomas 0.97 (0.96-0.98). In the subpopulation where both FCH and sestamibi were reported, FCH also had a higher sensitivity of 0.96 (0.94-0.98), compared with 0.54 (0.29-0.79) for sestamibi ($p<0.001$).

Conclusions: FCH PET demonstrates high localization accuracy in patients with hyperparathyroidism. This meta-analysis supports the use of FCH in patients with hyperparathyroidism over sestamibi.

Introduction

Hyperparathyroidism is a common endocrine disorder in which one or more of the parathyroid glands becomes autonomously hyperfunctional, causing excessive secretion of parathyroid hormone into the bloodstream (*1*,*2*). It is a common endocrine disorder, with an estimated of incidence between 0.4 to 82 cases per 100,000 in the general population (*3*–*6*). The etiology is usually a benign overgrowth of parathyroid tissue in at least one of the four 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, and 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 minimally invasive parathyroidectomy, which is associated with a reduced risk of complications and disability following surgery as compared to conventional bilateral cervical exploration (*9*). Preoperative localization is complex and imaging recommendations vary considerably. Cervical ultrasonography (US) and ^{99m}Tc-sestamibi single photon emission computed tomography (sestamibi) are the most commonly employed 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 (FCH) Positron Emission Tomography (PET) and results from the literature are encouraging (*12*,*13*). For nearly 20 years, 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 FCH in localizing hyperparathyroidism remains relatively sparse and comparison of FCH PET to traditional tools is limited to single-center studies.

The primary aim of this study is to summarize studies that have used FCH PET to localize hyperparathyroidism and to assess their sensitivity and specificity following pathological confirmation. A second aim is to analyze a subset of studies in which a sestamibi scan was also used, and compare the sensitivity and specificity to that of FCH PET imaging.

Materials and Methods

Correct identification of hyperparathyroidism was defined on a per-patient level. The protocol for this meta-analysis was registered with PROSPERO.

Search Strategy

Two authors (TAH and JW) conducted independent literature reviews for article inclusion into the study. This included review of electronic databases, as well as reviewing reference lists of relevant articles. The search was applied to PubMed/MEDLINE and EMBASE databases and was last updated on August 25, 2020. The authors used a combination of the

following terms: a) choline, fluorocholine, F-choline, FCH; b) PET, positron emission tomography; and c) parathyroid, hyperparathyroidism.

Eligibility Criteria

Two reviewers (TAH and JW) 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 meta-analysis: 1) studies evaluating diagnostic accuracy of FCH PET in patients with hyperparathyroidism; 2) studies that used pathologic confirmation of hyperparathyroidism as the reference standard. No year or location restrictions were imposed on the studies. Articles were excluded for the following reasons: risk of overlap with other studies (including systematic reviews and other meta-analyses); articles unavailable in English; unpublished studies; case reports; studies with fewer than ten cases; studies in which pathology was not used as the reference standard for diagnosing hyperparathyroidism; studies in which the diagnosis of hyperparathyroidism was not available at the per-patient level. We also subsequently performed the analysis by removing manuscripts where cases of secondary and tertiary hyperparathyroidism could not be separated from primary hyperparathyroidism.

Data Collection

Characteristics of eligible studies were summarized in **Table 1**. Data was extracted, where available, from each eligible article on the following variables: NCT number, prospective versus retrospective, consent performed, number of patients imaged with FCH, imaging modality (PET/CT or PET/MRI), number of patients with pathological correlate, number of

imaging readers, if readers were blinded to results of patients' pathology and/or clinical data, injected dose and range, uptake time, details of any adverse event reporting.

Quantitative data points were then extracted from eligible studies. This included number of true positive, false positive, true negative and false negative diagnoses of hyperparathyroidism based on FCH imaging as compared to pathologic correlate on a per-patient basis. If available, the same results were collected for studies in which patients were also imaged with sestamibi. One review author extracted the data points from eligible studies and the second author reviewed the extracted data for quality assurance. For each study included in the analysis, bias was assessed qualitatively by two reviewers (TAH and JW) using the QUADAS-2 tool (*15*).

Meta-analytic Methods

For this meta-analysis, 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 FCH imaging accuracy in detecting hyperparathyroidism on a per-patient level using pathologic correlate as the reference standard. We also assessed sensitivity and specificity for a subset of studies that had additionally imaged patients with sestamibi. In order to include all the studies in the meta-analysis, a small number was added to the zero cells for this subset of studies. All point estimates of sensitivity and specificity from the meta-analysis are reported as the ES and 95% confidence intervals (95% CI).

Results

Eligible Studies

An electronic search of PubMed and EMBASE libraries returned a total of 776 articles (**Figure 1**). Twenty studies were deemed eligible for the meta-analysis and are summarized in **Table 1**. Number of patients assessed ranged from 10-151 in our selected studies. All 20 papers were used to evaluate sensitivity and specificity of FCH PET in detecting hyperparathyroidism, and ten studies included data on results of sestamibi to use for comparison. Risk of bias and applicability of each study to our current research were assessed using the QUADAS-2 tool (**Supplemental Table 1**). In several cases, the risk of bias of the Index Test and Flow & Timing of the imaging protocol was unable to be determined based on 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, time of <4 weeks between imaging and surgery was considered to have a "Low" risk of bias.

Performance of FCH PET in Detecting Hyperparathyroidism

All 20 studies utilized FCH imaging (either by PET/CT, n=18 or PET/MRI, n=4) to identify hyperparathyroidism (**Table 2**). Included studies were both retrospective (n=8) and prospective (n=12), consent was obtained for research participation in the majority of cases (n=17), and one study was registered with ClinicalTrials.gov prior to conducting research procedures. Average injected FCH dose ranged from 0.1 MBq/kg to 325.1 MBq flat dose. Uptake time ranged from 0 minutes for dynamic imaging to 90 minutes for static imaging. The most common injected dose was 100 MBq and the most common uptake time was 60 minutes. Across the 20 studies, including a total of 796 patients, the results of the random effects meta-analysis of the sensitivity and specificity was 0.97 (0.96-0.98) and 0.23 (0.11-

0.35), respectively (**Figure 2**). Positive predictive value (PPV) of FCH PET compared to pathology was 0.94 (0.92-0.96). In studies that included only patients with primary hyperparathyroidism (n=16), sensitivity and specificity were 0.94 (0.92-0.97) and 0.14 (-0.08-0.36), respectively (**Supplemental Figure 1**).

Comparison of FCH PET and Sestamibi in Detecting Hyperparathyroidism

As a secondary analysis, we compared the performance of FCH PET and sestamibi in detecting cases of hyperparathyroidism prior to surgery. Ten studies, which included 301 patients, had this data available and were used in the comparison (**Table 3**, **Supplementary Figure 2**). FCH PET had a superior sensitivity of 0.96 (0.94-0.98) compared to 0.54 (0.29-0.79) for sestamibi ($p<0.001$) (**Figure 3 and 4**). In studies limited to patients with primary hyperparathyroidism, FCH PET had a superior sensitivity of 0.97 (0.94-1.00) compared to 0.55 (0.32-0.78) for sestamibi.

Discussion

A number of individual cohort studies have reported superiority of FCH PET over traditional imaging modalities such as ultrasonography and sestamibi in detecting hyperparathyroidism in patients prior to parathyroidectomy. Individual studies are difficult to interpret due to their small sample sizes and variability between studies. In this meta-analysis, we pool results of papers using FCH PET to localize abnormal parathyroid adenomas, which used 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

meta-analysis lend further evidence to support the use of FCH PET as a superior imaging technique over sestamibi in the localization of hyperparathyroidism prior to 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 or not imaging localized an overactive parathyroid gland on a per-patient basis. This approach may overestimate the accuracy of FCH PET as a pre-surgical tool in avoiding invasive open parathyroidectomies.

As with any meta-analysis, our approach is limited by the underlying data in the manuscripts included. As reported, there was a wide range in acquisition parameters employed. Most concerning was that blinding of readers to the results of parathyroidectomies prior to image interpretation was not done or unclear in the majority of cases, and most studies were retrospective in nature. This likely biased individual study results and may have skewed results in favor of 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 FCH PET or 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 technique used for sestamibi imaging in our analysis, as each approach has varying sensitivities that can lead to inconsistencies across the articles used in the comparison analysis. Of the 10 studies included for comparison with

sestamibi, six (including 41% of the analyzed patients) used dual phase, dual tracer sestamibi imaging with SPECT/CT. Three articles used SPECT, two of which used use sestamibi alone, and one article did not describe the 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 meta-analyses on this topic. The authors 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 FCH PET only, excluding studies that incorporate other choline tracers (*13*). Perhaps most notably, our study includes two important sub-analyses: 1) a comparison of FCH PET to the standard-of-care sestamibi scan, making a strong clinical case for the adoption of this more novel technique; and 2) a further study limited to cases with primary hyperparathyroidism. It is also the largest study of this kind (*12*,*16*).

Beyond sestamibi, there are other imaging techniques being evaluated for the localization of abnormal parathyroids, such as 4D-computed tomography (4D-CT) and 11C-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 US, has reported high but varying sensitivities in localizing adenomas (*17*,*18*). There is insufficient data at this time to compare FCH to 4D-CT to perform a meta-analysis. However, there are several theoretical advantages of FCH over 4D-CT, including the obviation of the need for intravenous iodinated contrast as well as its lower total doses of radiation (*19*). ^{11}C-choline PET, a similar radiotracer to FCH, received FDA approval in 2012 for its use in prostate cancer (*20*) and has recently been employed in preoperative localization for

hyperparathyroidism. Because ^{11}C-choline has a half-life of approximately 20 minutes, compared to 120 minutes for ^{18}F (*21*), PET acquisition must occur very shortly post-injection. The longer half-life of FCH allows for more flexible image acquisition and makes for more practical and favorable clinical use (*22*).

Conclusion

In patients with hyperparathyroidism, FCH PET demonstrates a high sensitivity (0.97) for parathyroid adenomas in patients with hyperparathyroidism. FCH PET also outperformed sestamibi with a sensitivity 0.96, compared with 0.54 for sestamibi. This meta-analysis supports the use of FCH in patients with hyperparathyroidism over sestamibi.

Tables

Table 1: Characteristics of studies included in the meta-analysis (*23–44*)

First Author	Year	Prospective/ Retrospective Study	NCT number	Consent Obtained	No. of patients with FCH Imaging	No. of patients with parathyroidectomy	Blinded Readers	No. of readers	Pathology correlation	PET/CT or PET/MRI	Injected dose (range)	Injected dose (average)	Uptake time	Primary HPT Only?
Alharbi	2018	Retrospective	No	Yes	66	52	No	2	Yes	Both	NR	150 MBq		Yes
Amadou	2019	Retrospective	No	No	41	23	No	NR	Yes	PET/CT	NR	231 MBq	60 minutes	Yes
Bossert	2019	Prospective	No	Yes	34	17	Unclear	2	Yes	PET/CT	NR	3-3.5 MBq/kg	9 & 60 mins	Yes
Broos	2019	Prospective	No	Yes	271	139	Yes	3	Yes	PET/CT	NR	150 MBq	5 & 60 mins	Yes
Christakis	2019	Prospective	No	Yes	12	12	Yes	1	Yes	PET/CT	NR	300 MBq	60 & 90 mins	Yes
Fischli	2017	Retrospective	No	Yes	39	23	No	1	Yes	PET/CT	IQR 180-149	160 MBq	45 mins	Yes
Grimaldi	2018	Prospective	No	No	27	21	Unclear	NR	Yes	PET/CT	77-230 MBq	100 MBq	30 mins	Yes
Hocevar	2016	Retrospective	No	No	151	151	No	NR	Yes	PET/CT	NR	100 MBq	5 & 60 mins	Yes
Huber	2018	Retrospective	No	Yes	26	26	Unclear	NR	Yes	Both	NR	151 MBq	45 mins	No
Khafif	2019	Prospective	No	Yes	19	19	No	2	Yes	PET/MRI	NR	93.75 MBq	16 mins	Yes
Kluijfhout	2017	Prospective	No	Yes	10	10	Yes	2	Yes	PET/MRI	188 MBq +/-26	188 MBq	0 (dynamic imaging for 40 mins)	Yes
Kluijfhout	2016	Retrospective	No	Yes	33	33	Unclear	NR	Yes	PET/CT	NR	2 MBq/kg	30 mins	No
Lezaic	2014	Prospective	No	Yes	24	24	Unclear	2		PET/CT	NR	100 MBq	5 & 60 mins	Yes
López-Mora	2020	Prospective	No	Yes	33	33	Unclear	3	Yes	PET/CT - digital vs analog	NR	0.1 MBq/kg	Unclear	Yes
Michaud	2014	Prospective	No	Yes	12	12	No	1	Yes	PET/CT	NR	3 MBq/kg	0 (dynamic imaging for 10 min followed by a static acquisition)	No
Piccardo	2019	Prospective	No	Yes	44	31	Unclear	2	Yes	PET/CT	NR	100 MBq	10 mins	Yes
Quak	2018	Prospective	NCT02432599	Yes	25	24	Yes	NR	Yes	PET/CT	NR	1.5 MBq/kg	60 mins	Yes
Thanseer	2018	Prospective	No	Yes	54	54	Unclear	NR	Yes	PET/CT	150-185 MBq	150-185 MBq	10-15 & 60 mins	Yes
Uslu-Beşli	2020	Retrospective	No		105	81	No	2	Yes	PET/CT	325.1 ±86.7	325.1	15 & 45 mins	No
Zajíčková	2019	Retrospective	No	Yes	13	13	Unclear	2	Yes	PET/CT	NR	180 MBq	30 mins	Yes

Table 2: Overview of studies comparing performance of FCH PET to pathology in 20 studies reporting a total of 796 patients. TP = true positive; FP = false positive; TN = true negative; FN = false negative.

First Author	Year	No. 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	2016	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	2018	54	52	2	NA	0
Uslu-Beşli	2020	79	76	NA	NA	3
Zajíčková	2019	13	12	0	0	1
TOTAL		**796**	**738**	**19**	**3**	**33**

Table 3: Overview of studies comparing performance of sestamibi to pathology**.**

TP = true positive; FP = false positive; TN = true negative; FN = false negative.

			Sestamibi compared to Pathology			
First Author	**Year**	**No. Patients 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	2016	33	8	0	0	21
Lezaic	2014	24	14	0	0	10
Michaud	2014	12	8	2	0	2
Thanseer	2018	54	42	1	1	10
Uslu-Beşli	2020	80	39	1	NA	NA
Zajíčková	2019	13	4	2	0	7
Total		**301**	**146**	**7**	**1**	**103**

Figure 1: PRISMA flow diagram depicting process for selecting papers included in this meta-analysis.

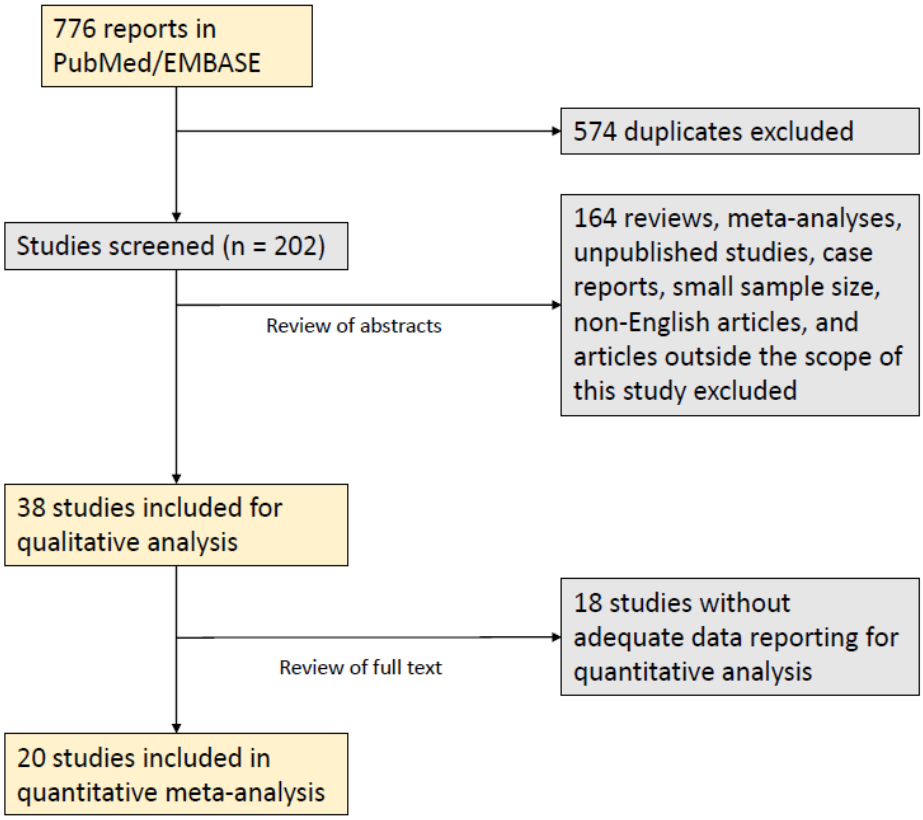


Figure 2: Summary of sensitivity, specificity, and hierarchical summary receiver-operating-characteristic (HSROC) plot of sensitivity/specificity for FCH vs. pathology overall. Effect size for sensitivity and specificity was 0.97 (95% CI, 0.96–0.98) and 0.23 (95% CI, 0.11–0.35), respectively. Size of circles represents size of individual studies.

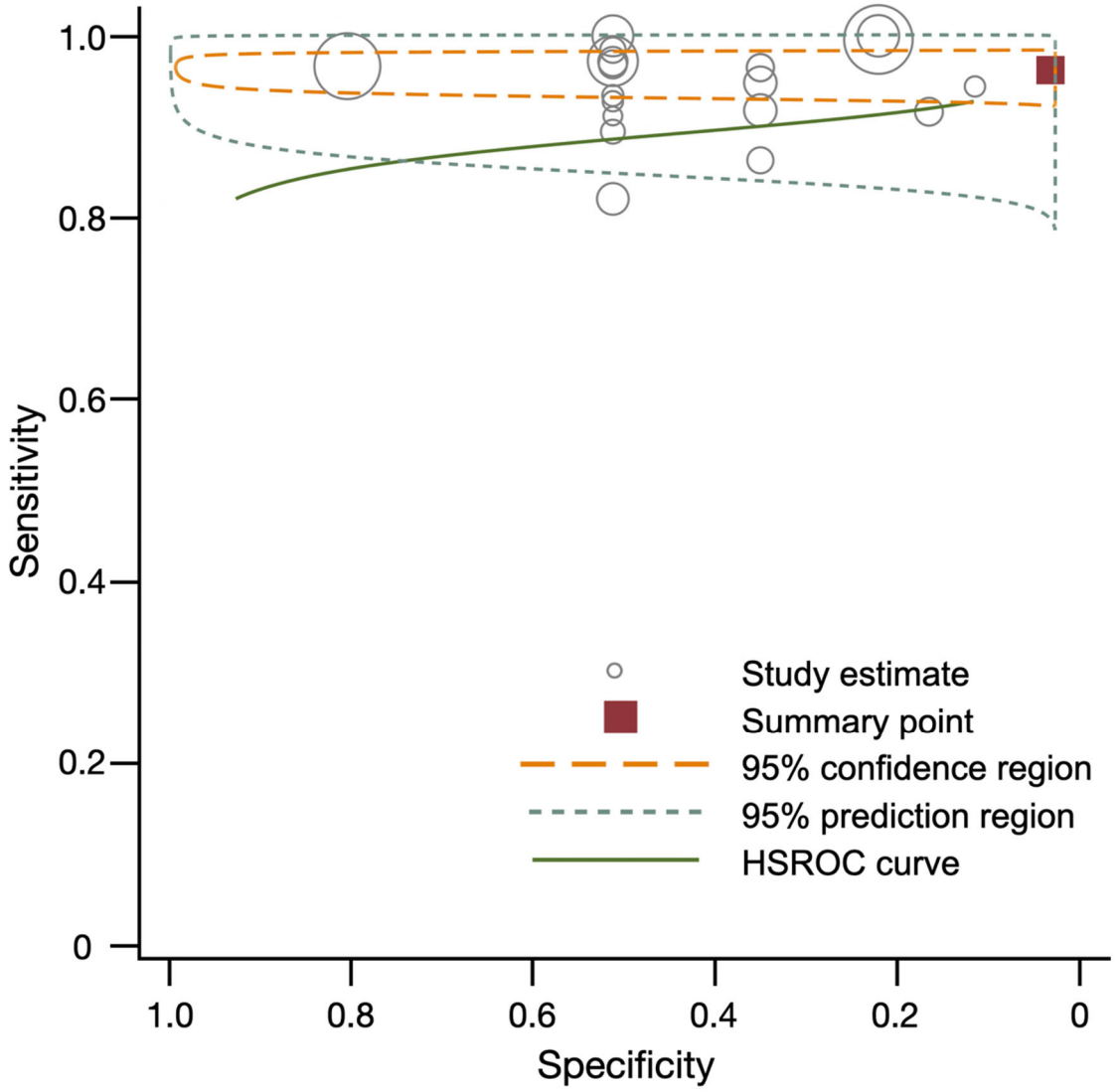


Figure 3: Summary of sensitivity, specificity, and hierarchical summary receiver-operating-characteristic (HSROC) plot of sensitivity/specificity for sestamibi vs. pathology overall. Effect size for sensitivity and specificity was of 0.54 (0.29-0.79) and 0.43 (0.30-0.57), respectively. Size of circles represents size of individual studies.

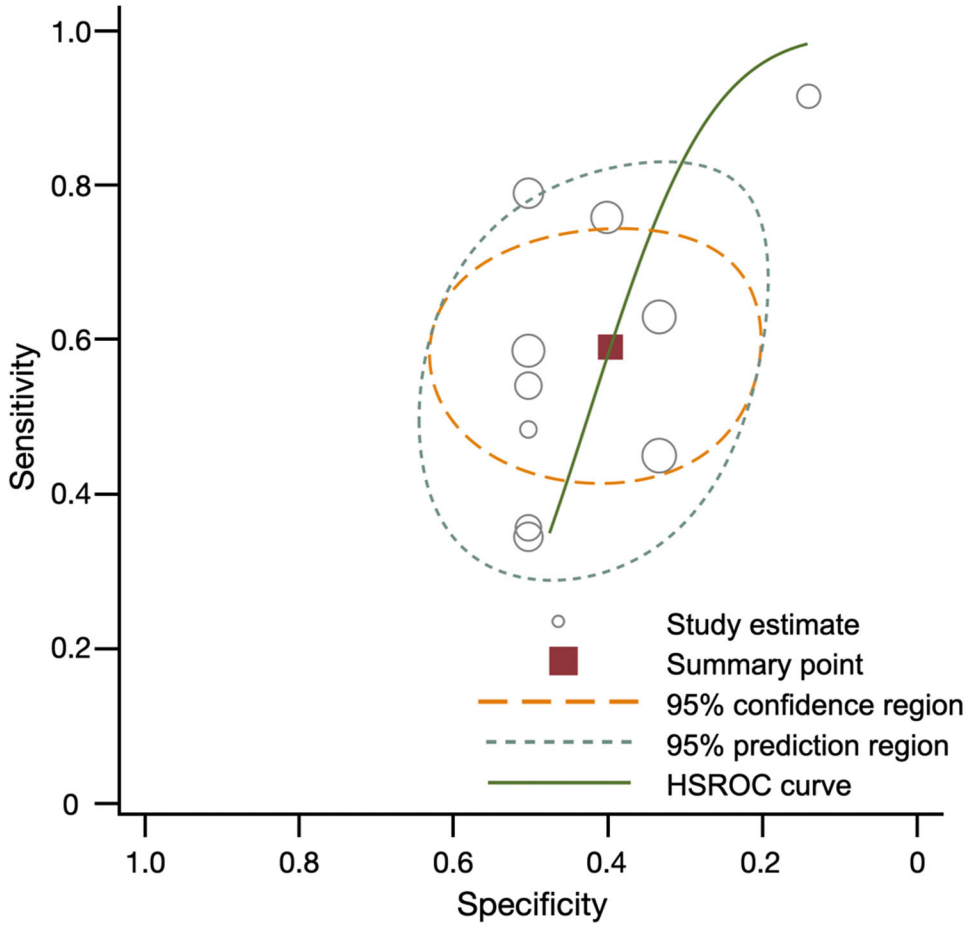
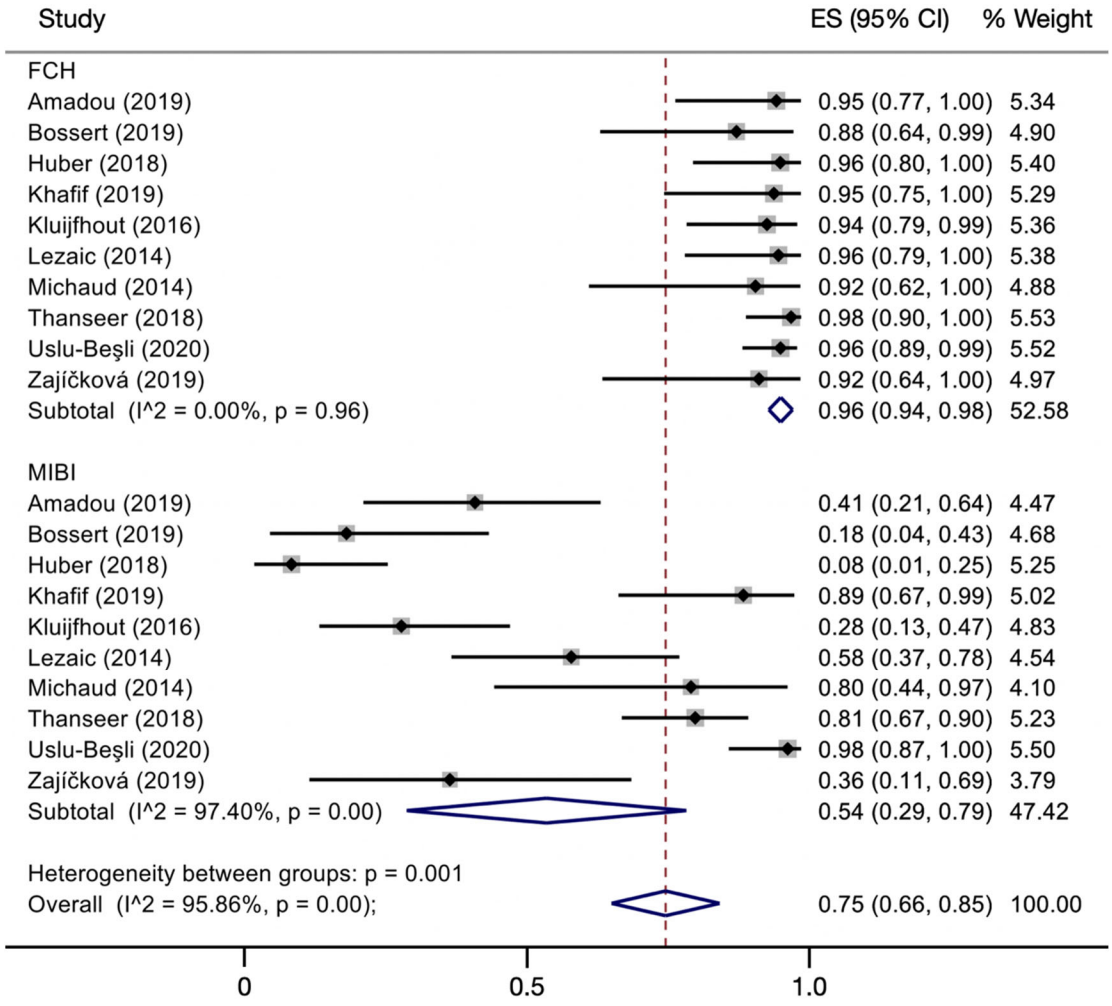


Figure 4. Comparison of diagnostic sensitivities of FCH and sestamibi. Overall effect size (ES) for FCH PET was 0.96 (95% CI, 0.94–0.98) and 0.54 (95% CI, 0.29-0.79) for sestamibi. Size of squares represents size of individual studies. Reference numbers are in Supplemental Table 2.



References

1. Khan AA, Hanley DA, Rizzoli R, Bollerslev J, Young JEM. Primary hyperparathyroidism : review and recommendations on evaluation , diagnosis , and management . A Canadian and international consensus. *Osteoporos Int*. 2017:1-19.
2. Fuleihan, Ghada El-Hajj; Silverberg S. Patient education: Primary hyperparathyroidism (Beyond the Basics). Up to Date. https://www.uptodate.com/contents/primary-hyperparathyroidism-beyond-the-basics.
3. Yeh MW, Ituarte PHG, Zhou HC, et al. Incidence and prevalence of primary hyperparathyroidism in a racially mixed population. *J Clin Endocrinol Metab*. 2013;98:1122-1129.
4. Wermers RA, Khosla S, Atkinson EJ, et al. Incidence of primary hyperparathyroidism in Rochester, Minnesota, 1993-2001: an update on the changing epidemiology of the disease. *J Bone Miner Res*. 2006;21:171-177.
5. Press DM, Siperstein AE, Berber E, et al. The prevalence of undiagnosed and unrecognized primary hyperparathyroidism: a population-based analysis from the electronic medical record. *Surgery*. 2013;154:1232-1238.
6. Walker MD, Silverberg SJ. Primary hyperparathyroidism. *Nat Rev Endocrinol*. 2019;14:115-125.
7. Bilezikian JP, Bandeira L, Khan A, Cusano NE. Hyperparathyroidism. 2018;391.
8. Imperiale A, Taieb D, Hindie E. (18)F-Fluorocholine PET/CT as a second line nuclear imaging technique before surgery for primary hyperparathyroidism. *Eur J Nucl Med Mol Imaging*. 2018;45:654-657.
9. Udelsman R, Lin Z, Donovan P. The superiority of minimally invasive parathyroidectomy based on 1650 consecutive patients with primary hyperparathyroidism. *Ann Surg*. 2011;253:585-591.
10. Ruda JM, Hollenbeak CS, Stack BCJ. A systematic review of the diagnosis and

treatment of primary hyperparathyroidism from 1995 to 2003. *Otolaryngol Head Neck Surg*. 2005;132:359-372.

11. Kobylecka M, Plazinska MT, Chudzinski W, et al. Comparison of scintigraphy and ultrasound imaging in patients with primary, secondary and tertiary hyperparathyroidism - own experience. *J Ultrason*. 2017;17:17-22.
12. Kim S-JJ, Lee S-WW, Jeong SY, et al. Diagnostic Performance of F-18 Fluorocholine PET/CT for Parathyroid Localization in Hyperparathyroidism: a Systematic Review and Meta-Analysis. *Horm Cancer*. 2018;9:440-447.
13. Treglia G, Piccardo A, Imperiale A, et al. Diagnostic performance of choline PET for detection of hyperfunctioning parathyroid glands in hyperparathyroidism: a systematic review and meta-analysis. *Eur J Nucl Med Mol Imaging*. 2019;46:751-765.
14. Vali R, Loidl W, Pirich C, Langesteger W, Beheshti M. Imaging of prostate cancer with PET/CT using (18)F-Fluorocholine. *Am J Nucl Med Mol Imaging*. 2015;5:96-108.
15. Penny F. Whiting, PhD; Anne W.S. Rutjes, PhD; Marie E. Westwood, PhD; Susan Mallett, PhD; Jonathan J. Deeks, PhD;Johannes B. Reitsma, MD, PhD; Mariska M.G. Leeflang, PhD; Jonathan A.C. Sterne, PhD; Patrick M.M. Bossuyt P the Q-2 G. QUADAS-2: A Revised Tool for the Quality Assessment of Diagnostic Accuracy Studies. *Ann Intern Med*. 2011;154:253-260.
16. Pardal-Refoyo JL, Tamayo-Alonso P, Ferreira-Cendon S, Martin-Gomez E. Pathological uptake with 18-Fluorocholine versus 99mTc-MIBI in the location of the parathyroid glands in hyperparathyroidism. Systematic review and meta-analysis. *medRxiv*. January 2020:2020.07.25.20161927.
17. Yeh R, Tay Y-KD, Tabacco G, et al. Diagnostic Performance of 4D CT and Sestamibi SPECT/CT in Localizing Parathyroid Adenomas in Primary Hyperparathyroidism. *Radiology*. 2019;291:469-476.
18. Bann D V, Zacharia T, Goldenberg D, Goyal N. Parathyroid localization using 4D-computed tomography. *Ear Nose Throat J*. 2015;94:E55-E57.
19. Mahajan A, Starker LF, Ghita M, Udelsman R, Brink JA, Carling T. Parathyroid four-dimensional computed tomography: evaluation of radiation dose

exposure during preoperative localization of parathyroid tumors in primary hyperparathyroidism. *World J Surg*. 2012;36:1335-1339.

20. FDA Approves 11C-Choline for PET in Prostate Cancer. *J Nucl Med* . 2012;53:11N-11N.
21. Grassi I, Nanni C, Allegri V, et al. The clinical use of PET with (11)C-acetate. *Am J Nucl Med Mol Imaging*. 2012;2:33-47.
22. Massaro A, Ferretti A, Secchiero C, et al. Optimising (18)F-Choline PET/CT Acquisition Protocol in Prostate Cancer Patients. *N Am J Med Sci*. 2012;4:416-420.
23. A.A. A, F.M. A, A.A. A, et al. [18F]Fluorocholine Uptake of Parathyroid Adenoma Is Correlated with Parathyroid Hormone Level. *Mol Imaging Biol*. 2018;20:857-867.
24. C. A, G. B, M. E, et al. 18F-Fluorocholine PET/CT and Parathyroid 4D Computed Tomography for Primary Hyperparathyroidism: The Challenge of Reoperative Patients. *World J Surg*. 2019;43:1232-1242.
25. Kluijfhout WP, Pasternak JD, Gosnell JE, et al. 18F fluorocholine PET/MR imaging in patients with primary hyperparathyroidism and inconclusive conventional imaging: A prospective pilot study. *Radiology*. 2017;284:460-467.
26. Lezaic L, Rep S, Sever MJ, Kocjan T, Hocevar M, Fettich J. 18F-Fluorocholine PET/CT for localization of hyperfunctioning parathyroid tissue in primary hyperparathyroidism: a pilot study. *Eur J Nucl Med Mol Imaging*. 2014;41:2083-2089.
27. Michaud L, Burgess A, Huchet V, et al. Is 18F-fluorocholine-positron emission tomography/ computerized tomography a new imaging tool for detecting hyperfunctioning parathyroid glands in primary or secondary hyperparathyroidism? *J Clin Endocrinol Metab*. 2014;99:4531-4536.
28. A. P, P. T, M. R, et al. Additional value of integrated 18 F-choline PET/4D contrast-enhanced CT in the localization of hyperfunctioning parathyroid glands and correlation with molecular profile. *Eur J Nucl Med Mol Imaging*. 2019;46:766-775.

29. N. T, S.K. B, A. S, et al. Comparative Effectiveness of Ultrasonography, 99mTc-Sestamibi, and 18F-Fluorocholine PET/CT in Detecting Parathyroid Adenomas in Patients With Primary Hyperparathyroidism. *Clin Nucl Med*. 2017;42:e491-e497.
30. Zajíčková K, Zogala D, Kubinyi J, et al. Parathyroid imaging by 18F-fluorocholine PET/CT in patients with primary hyperparathyroidism and inconclusive conventional methods: Clinico-pathological correlations. *Physiol Res*. 2018;67:S551-S557.
31. Quak E, Blanchard D, Houdu B, et al. F18-choline PET/CT guided surgery in primary hyperparathyroidism when ultrasound and MIBI SPECT/CT are negative or inconclusive: the APACH1 study. *Eur J Nucl Med Mol Imaging*. 2018;45:658-666.
32. Khafif A, Masalha M, Landsberg R, et al. The role of F18-fluorocholine positron emission tomography/magnetic resonance imaging in localizing parathyroid adenomas. *Eur Arch Otorhinolaryngol*. 2019;276:1509-1516.
33. López-Mora DA, Sizova M, Estorch M, et al. Superior performance of 18F-fluorocholine digital PET/CT in the detection of parathyroid adenomas. *Eur J Nucl Med Mol Imaging*. 2020:572-578.
34. Romano R, Manzo N, Montefusco I, Romano A, Santini A. Liquid Carbon Dioxide Use in the Extraction of Extra Virgin Olive Oil From Olive Paste. *J Food Res*. 2014;3:119-128.
35. Beheshti M, Hehenwarter L, Paymani Z, et al. 18F-Fluorocholine PET/CT in the assessment of primary hyperparathyroidism compared with 99mTc-MIBI or 99mTc-tetrofosmin SPECT/CT: a prospective dual-centre study in 100 patients. *Eur J Nucl Med Mol Imaging*. 2018;45:1762-1771.
36. Huber GF, Hüllner M, Schmid C, et al. Benefit of18F-fluorocholine PET imaging in parathyroid surgery. *Eur Radiol*. 2018;28:2700-2707.
37. Uslu-Beşli L, Sonmezoglu K, Teksoz S, et al. Performance of F-18 Fluorocholine PET/CT for Detection of Hyperfunctioning Parathyroid Tissue in Patients with Elevated Parathyroid Hormone Levels and Negative or Discrepant Results in conventional Imaging. *Korean J Radiol*. 2020;21:236-

247.

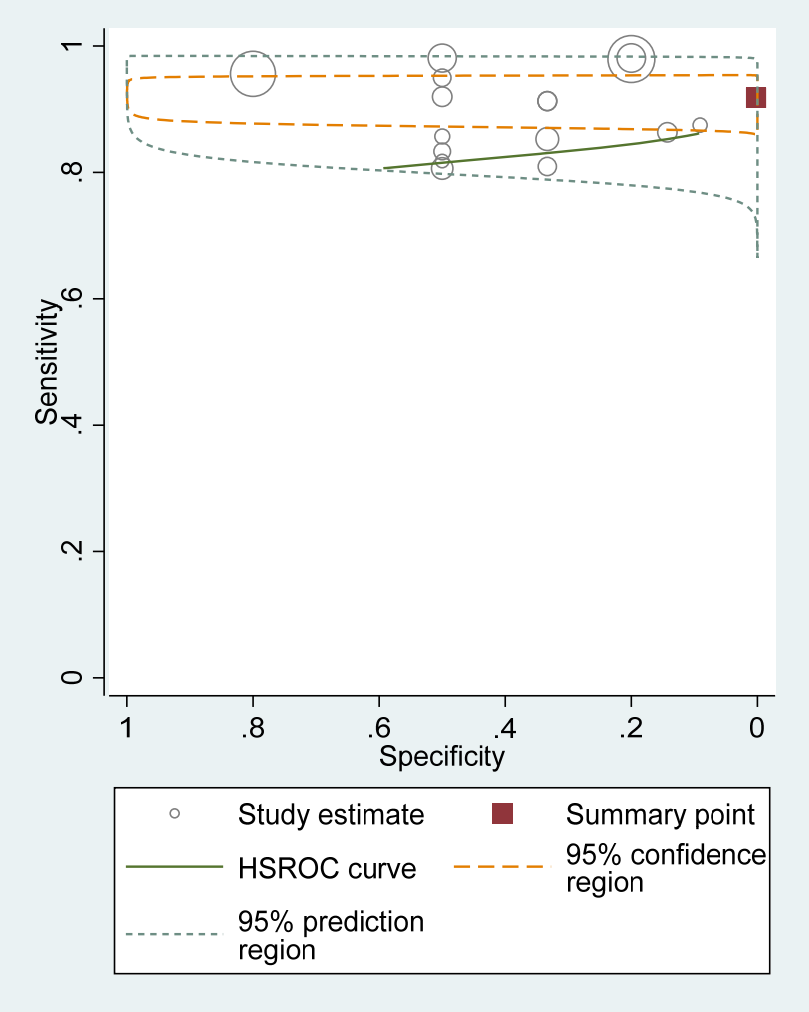
38. Bossert I, Chytiris S, Hodolic M, et al. PETC/CT with 18 F-Choline localizes hyperfunctioning parathyroid adenomas equally well in normocalcemic hyperparathyroidism as in overt hyperparathyroidism. *J Endocrinol Invest*. 2019;42:419-426.
39. Broos WAMM, Wondergem M, Knol RJJJ, et al. Parathyroid imaging with 18F-fluorocholine PET/CT as a first-line imaging modality in primary hyperparathyroidism: a retrospective cohort study. *EJNMMI Res*. 2019;9:72.
40. I. C, S. K, G.P. S, et al. (18)Fluorocholine PET/CT scanning with arterial phase-enhanced CT is useful for persistent/recurrent primary hyperparathyroidism: first UK case series results. *Ann R Coll Surg Engl*. 2019;101:501-507.
41. Fischli S, Suter-Widmer I, Nguyen BT, et al. The significance of 18F-fluorocholine-PET/CT as localizing imaging technique in patients with primary hyperparathyroidism and negative conventional imaging. *Front Endocrinol (Lausanne)*. 2018;8:1-7.
42. Grimaldi S, Young J, Kamenicky P, et al. Challenging pre-surgical localization of hyperfunctioning parathyroid glands in primary hyperparathyroidism: the added value of 18F-Fluorocholine PET/CT. *Eur J Nucl Med Mol Imaging*. 2018;45:1772-1780.
43. Hocevar M, Lezaic L, Rep S, et al. Focused parathyroidectomy without intraoperative parathormone testing is safe after pre-operative localization with 18F-Fluorocholine PET/CT. *Eur J Surg Oncol*. 2017;43:133-137.
44. Kluijfhout WP, Vorselaars WMCM, van den Berk SAM, et al. Fluorine-18 fluorocholine PET-CT localizes hyperparathyroidism in patients with inconclusive conventional imaging: a multicenter study from the Netherlands. *Nucl Med Commun*. 2016;37:1246-1252.

Supplemental Materials

Supplemental Table 1: Bias assessment using QUADAS-2

		Risk of Bias				Applicability		
First Author	**Year**	**Patient Selection**	**Index Test**	**Reference Standard**	**Flow and Timing**	**Patient Selection**	**Index Test**	**Reference Standard**
Alharbi	2018	High	Low	Low	Low	Low	Low	Low
Amadou	2019	High	Low	Low	Low	Low	Low	Low
Bossert	2019	Low	Low	Low	Unclear	Low	Low	Low
Broos	2019	Low	Low	Low	Unclear	Low	Low	Low
Christakis	2019	Low	Low	Low	Unclear	Unclear	Low	Low
Fischli	2017	Unclear	Unclear	Low	High	Low	Low	Low
Grimaldi	2018	Unclear	Low	Low	High	Low	Low	Low
Hocevar	2016	Low	Unclear	Low	Low	Low	Low	Low
Huber	2018	Unclear	Unclear	Low	Low	Low	Low	Low
Khafif	2019	Low	Low	Low	Unclear	Low	Low	Low
Kluijfhout	2017	Unclear	Low	Low	Low	Low	Low	Low
Kluijfhout	2016	Unclear	Unclear	Low	Low	Low	Low	High
Lezaic	2014	Low	Low	Low	Low	Low	Low	Low
López-Mora	2020	Low	High	Low	Unclear	Low	High	Low
Michaud	2014	Unclear	Low	Low	Low	Low	Low	Low
Piccardo	2019	Low	Low	Low	Unclear	Low	High	Low
Quak	2018	Unclear	Low	Low	Low	Low	Low	Low
Thanseer	2018	Low	Low	Low	Low	Low	Low	Low
Uslu-Beşli	2020	Unclear	Low	Low	Low	Low	Low	Low
Zajíčková	2019	Unclear	Low	Low	Unclear	Low	Low	Low

Supplemental Figure 1: Summary of sensitivity, specificity, and hierarchical summary receiver-operating-characteristic (HSROC) plot of sensitivity/specificity for FCH vs. pathology in studies reporting primary hyperparathyroidism only. Effect size for sensitivity and specificity was 0.94 (95% CI, 0.92–0.97) and 0.14 (95% CI, -0.08–0.36), respectively. Size of circles represents size of individual studies.



Supplemental Figure 2: Effect Size for FCH vs Pathology Sensitivity