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^{18}F-Fluorocholine Positron Emission Tomography/Computed Tomography Is a Highly Sensitive but Poorly Specific Tool for Identifying Malignancy in Thyroid Nodules with Indeterminate Cytology: The Chocolate Study

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Background: Refining the risk of malignancy in patients presenting with thyroid nodules with indeterminate cytology (IC) is a critical challenge. We investigated the performances of ^{18}F-fluorocholine (FCH) positron emission tomography/computed tomography (PET/CT) to predict malignancy.
Methods: Between May 2016 and March 2019, 107 patients presenting with a thyroid nodule ≥15 mm with IC and eligible for surgery were included in this prospective study. Head-and-neck PET/CT acquisitions were performed 20 and 60 minutes after injection of 1.5 MBq/kg of FCH. PET/CT acquisition was scored positive when maximal standardized uptake value in the IC nodule was higher than in the thyroid background. Pathology was the gold standard for diagnosis.
Results: At pathology, 19 (18%) nodules were malignant, 87 were benign, and one was a noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP). Sensitivity, specificity, accuracy, positive-predictive value (PPV), and negative-predictive value (NPV) of FCH PET/CT in detecting cancer or NIFTP were 90%, 50%, 55%, 29%, and 96% at 20 minutes and 85%, 49%, 67%, 28%, and 94% at 60 minutes, respectively. Higher specificity (58% vs. 33%, $p=0.01$) was observed in nononcocytic ($n=72$) than in oncocytic IC nodules ($n=35$). The pre-PET/CT probability of cancer or NIFTP in Bethesda III–IV nodules was 11% and the post-PET/CT probability was 19% in PET-positives and 0% in PET-negatives. In retrospective analysis, 42% of surgeries would have been unnecessary after PET/CT and 81% before ($p<0.001$), resulting in a hypothetical 48% reduction (95% confidence interval [32–64]).
Conclusions: FCH PET/CT offers high NPV to reliably exclude cancer in PET-negative IC nodules, but suffers from low PPV, particularly in those with oncocytic cytology. ClinicalTrials.gov identifier: NCT02784223.

Keywords: ^{18}F-choline PET/CT, fluorocholine PET/CT, PET/CT, thyroid nodules, indeterminate cytology

Introduction

Thyroid nodules are very common and two clinical questions need to be addressed. Is the nodule functional or a cancer? Regarding the latter issue, fine-needle aspiration biopsy (FNAB) is the standard procedure to help decision-making toward surgery or active surveillance according to nodule size and ultrasound features (1). Estimating the risk of malignancy remains challenging in thyroid nodules with indeterminate cytology (IC), which arises in 20–25% of

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cases. Due to implications for the patient, the health systems, and cost issues, this risk estimate is of utmost importance to better identify patients for surgery with the goal of reducing the number of unnecessary interventions in benign nodules. In the past decade, molecular testing in FNAB has been shown to improve cancer detection in IC nodules (2). A limited panel of mutations (*BRAF*, *RAS*, *RET/PTC*, *PAX8/PPARγ*) provide a fairly good positive-predictive value (PPV), but a more limited negative-predictive value (NPV) (3,4). More recently, both high PPV and NPV were reported with ThyroSeq v3 next-generation sequencing (NGS) (5). Using a recent genomic sequencing classifier, high sensitivity (91%) and NPV (96%) were reported with more limited specificity (68%) and PPV (47%) (6).

The diagnostic value of several imaging modalities has been studied previously in patients with thyroid nodules. ^{99m}Tc-methoxyisobutylisonitrile (^{99m}Tc-MIBI), first evaluated in differentiated thyroid cancer (DTC) (7,8), has been shown to have a good sensitivity but a low specificity for the preoperative assessment of thyroid nodules (9–12). For ^{18}F-fluorodeoxyglucose positron emission tomography with computed tomography (^{18}FDG PET/CT), wide ranges of sensitivity (57–100%) and specificity (32–69%) have been reported (13–21). Some authors have suggested that ^{18}FDG PET/CT has clinical utility to avoid surgery in PET-negative nodules with IC (13,15,19–21), but other investigators have not (14,16–18). As a result, ^{18}FDG PET/CT imaging is not routinely recommended by the American Thyroid Association to risk stratify a thyroid nodule (1). Recently, it was shown in a prospective study that ultrasonography (US) with shear wave elastography was not useful for discriminating benign and malignant tumors in IC nodules (22).

In Europe, ^{18}F-fluorocholine (FCH) is a PET tracer approved for imaging of prostate cancer and hepatocellular carcinoma. Also, FCH PET/CT is increasingly used in the preoperative imaging of parathyroid adenoma, due to its very high sensitivity, namely 80–90% (23,24). In the United States, PET choline is available using ^{11}C-choline (25), which was approved for prostate cancer imaging by the U.S. Food and Drug Administration in 2012 (26). Recent case reports or preliminary data have suggested that PET choline could be relevant in the assessment of thyroid nodules. In 2011, four DTC patients with ^{11}C-choline uptake in primary tumor or in persistent/recurrent disease were reported (27). Thyroid incidentalomas on FCH and ^{11}C-choline PET/CT have also been reported in patients with prostate cancer, both benign (28–32) and malignant (28,30,33–36) thyroid tumors.

We aimed to investigate the performances of FCH PET/CT for predicting malignancy in thyroid nodules with IC in a prospective study of patients who were to undergo surgery for IC thyroid nodules.

Materials and Methods

Patients

The Local Ethics Committee (Ref 2015–37, Comité de protection des personnes Nord-Ouest III) and the French Health Authorities (Ref 151468A-12) gave approval for this diagnostic study, and it was registered as EUDRACT 2015-005017-71. The study was approved by the Institution Review Board of Baclesse Cancer Centre (2015-11-02). It was conducted according to the provisions of the Declaration of Helsinki and the Good Clinical Practice Guidelines of the International Conference of Harmonization. Written informed consent was obtained from all patients. Inclusion criteria were patients with a thyroid nodule ≥15 mm with IC according to the Bethesda classification (37) in the six months before inclusion, for whom thyroid surgery had been recommended. IC included class III (atypia of undetermined significance/follicular lesion of undetermined significance), IV (follicular neoplasm/suspicious for follicular neoplasm [FN/SFN] or Hürthle-cell neoplasm), and V (suspicious for malignancy). Patients with coalescent nodules preventing correct individualization of the targeted nodule were not eligible for inclusion. Similarly, patients with a hot nodule on thyroid scintigraphy were not eligible for the study. Surgery was carried out within three months after FCH PET/CT imaging.

^{18}F-Fluorocholine PET/CT

FCH PET/CT imaging consisted of two head-and-neck acquisitions performed at 20 and 60 minutes after intravenous injection of 1.5 MBq/kg of FCH. For each acquisition, a low-dose CT (CAREdose ref. mAs 100, 130 kV, slice 3 mm, pitch 1.0) was performed, followed by a PET acquisition (one bed position) for 10 minutes covering the neck and upper chest in three-dimensional list-mode on a Biograph 6 TrueV PET/CT system (Siemens Medical Solutions, Erlangen, Germany) with an extended field-of-view of 21.6 cm. PET raw data were reconstructed with the point-spread function reconstruction algorithm (HD; TrueX, Siemens Medical Solutions; 3 iterations and 21 subsets) without filtering, matrix size 256 × 256 and zoom 1.0. Scatter and attenuation corrections were applied. Image analysis was performed on Leonardo workstations (Siemens Medical Solutions). The FCH PET/CT acquisition was scored positive if the maximal standardized uptake value (SUVmax) of the nodule was higher than the thyroid background (i.e., SUVmax [nodule] > SUVmax [thyroid gland background]).

Conventional thyroid US

All neck US were performed by an experienced physician using an Aixplorer SuperLinear SL15-4 high-frequency linear transducer (SuperSonic Imagine S.A., Aix-en-Provence, France). A descriptive diagram to localize the nodule was drawn and transmitted to the surgeon and pathologist. The sonographer prospectively reported the nodule characteristics. Using the US parameters, each nodule was scored according to the European Thyroid Imaging Reporting and Data System (EU-TIRADS) classification (38).

Laboratory studies

Upon inclusion, serum for thyrotropin (TSH), levothyroxine, thyroid peroxidase antibodies (TPOAb), and thyroglobulin antibodies (TgAb), calcitonin, calcium, albumin, and parathyroid hormone were collected for measurements.

Thyroid surgery and histological examination

The surgeon performed either lobectomy including the isthmus or total thyroidectomy. The pathologist used the World Health Organization criteria for diagnosis (39) and in cases of malignancy, the 2017 TNM staging classification system (40).

Statistical analysis

The planned sample size for the present study was based on the estimation of sensitivity of FCH PET/CT for detecting malignancies with a 90% confidence interval (CI) with an expected sensitivity of ~80%. Requiring a CI with a width of no more than 30%, the observation of a minimum of 18 patients with malignancy was necessary, which was reached after inclusion of 107 patients.

Quantitative variables were described with means and standard deviations, and qualitative variables were described with numbers and percentages. Patient characteristics were compared according to the pathologic diagnosis using the Wilcoxon or Kruskal–Wallis tests and chi-square or Fisher's exact tests, as appropriate. Sensitivity, specificity, accuracy, PPV, and NPV were computed with their 90% CI for each PET acquisition at 20 and 60 minutes. For all tests, a two-tailed *p*-value of 0.05 or less was considered statistically significant. The analyses were conducted using STATA version 15.0 (Stata Corp.)

Results

Patient characteristics

From May 2016 to March 2019, 107 patients, 75% women, were included. Mean age was 55 ± 14 years. The mean serum TSH level was 1.49 ± 0.97 mU/L. TPOAb and TgAb were positive in 13% and 12% of the cohort, respectively. Patient characteristics according to the pathology of the nodule are presented in Table 1. When compared with benign, patients with a malignant nodule or noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) had a higher TSH level ($p < 0.01$).

Cytological and pathological data

Thirteen (12%) patients had a thyroid nodule that was Bethesda III, 81 (76%) Bethesda IV, and 13 (12%) Bethesda V. Of the 81 Bethesda IV nodules, 46 (57%) were FN/SFN subtype and 35 (43%) were Hürthle cell neoplasm (oncocytic) subtype.

Thyroid surgery was performed 15 ± 11 days after FCH PET/CT imaging and 3 ± 2 months after the FNAB procedure. Of 107 nodules, 19 (18%) were malignant on pathological examination. There were 16 papillary thyroid cancers (PTC), including 10 classic variants of PTC, 5 follicular variants of PTC, 1 tall-cell variant of PTC, and 3 Hürthle cell carcinoma (HCC). One patient had an NIFTP. The remaining 87 patients had a benign nodule: follicular adenoma, $n = 51$; oncocytic (i.e., Hürthle cell) adenoma, $n = 20$; nodular hyperplasia, $n = 15$; thyroiditis, $n = 1$. Correlations between cytological and pathological data are presented in Figure 1.

The characteristics of patients with malignant nodules or NIFTP are shown in Table 2.

US data

The median size of the 107 nodules was 29 mm (range, 15–72). Forty-six (43%) nodules were EU-TIRADS 3, 56 (52%) EU-TIRADS 4, and 5 (5%) EU-TIRADS 5. The proportion of malignant nodules or NIFTP was 4/46 (9%) in EU-TIRADS 3, 11/56 (20%) in EU-TIRADS 4, and 5/5 (100%) in EU-TIRADS 5. The EU-TIRADS scores of malignant nodules are also summarized in Table 2.

FCH PET/CT data

FCH PET/CT studies were performed 2.9 ± 2.1 months after the FNAB procedure. The interval between FNAB and PET/CT was 15–30 days in seven patients and the sonographer did not observe any bleeding in these patients during and immediately after the FNAB procedure. The time interval was >30 days in the remaining patients. The mean injected FCH activity was 109 ± 23 MBq. The PET/CT acquisitions were performed 20 ± 1 minutes and 61 ± 3 minutes postinjection (p.i.). Overall, 63 (59%) FCH PET/CT studies were scored positive. Among the 20 patients with a malignant nodule or NIFTP, 18 (90%) were scored FCH positive. Of the 87 with a benign nodule, 45 (52%) were scored FCH positive.

Sensitivity, specificity, accuracy, PPV, and NPV of FCH PET/CT in detecting cancer or NIFTP were 90% [90% CI 72–98], 49% [90% CI 40–59], 55% [90% CI 43–67], 29% [90% CI 20–40], and 96% [90% CI 87–99] at 20 minutes and 85% [90% CI 66–96], 49% [90% CI 40–59], 67% [90% CI 50–84], 28% [90% CI, 19–39], and 94% [90% CI, 84–98] at 60 minutes, respectively.

Figure 2 shows a true-positive malignant nodule with a high FCH uptake.

Regarding the two patients with false-negative results, one had no FCH uptake at all (Fig. 3), and the other had thyroid background uptake higher than in the nodule because of thyroiditis (Fig. 4).

Table 1. Patient Characteristics According to Pathology of the Thyroid Nodule

	All patients (n = *107*)	*Patients with a benign nodule* (n = *87*)	*Patients with a malignant nodule or NIFTP* (n = *20*)	p
Sex (female), *n* (%)	81 (76%)	65 (75%)	16 (80%)	0.62
Age (years), mean (SD)	55 (14)	57 (13)	52 (17)	0.16
TSH (mU/L), mean (SD)	1.49 (0.97)	1.38 (0.89)	2.03 (1.15)	<0.01
Positive TPOAb, *n* (%)	14 (13%)	10 (11%)	4 (20%)	0.30
Positive TgAb, *n* (%)	13 (13%)	11 (13%)	2 (10%)	0.90
Calcium (mmol/L), mean (SD)	2.39 (0.11)	2.38 (0.11)	2.42 (0.11)	0.10
PTH (pg/mL), mean (SD)	41.9 (18.2)	41.0 (15.2)	47.3 (28.8)	0.18
Cytology (Bethesda class), *n* (%)				
Class III	13 (12%)	12 (14%)	1 (5%)	<0.001
Class IV	81 (76%)	72 (83%)	9 (45%)	
Class V	13 (12%)	3 (3%)	10 (50%)	

NIFTP, noninvasive follicular thyroid neoplasm with papillary-like nuclear features; TSH, thyrotropin; TPOAb, thyroid peroxidase antibodies; TgAb, thyroglobulin antibodies; PTH, parathormone; SD, standard deviation.

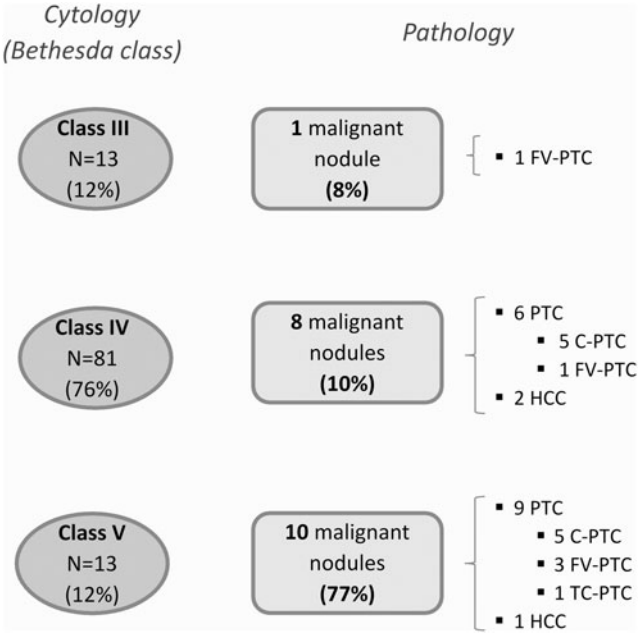

FIG. 1. Correlation between cytology and pathology in the 107 patients. C-PTC, classic variant of papillary thyroid cancer; FV-PTC, follicular variant of papillary thyroid cancer; HCC, Hürthle cell cancer; TC-PTC, tall-cell variant of papillary thyroid cancer; NIFTP, noninvasive follicular thyroid neoplasm with papillary-like nuclear features.

Overall, SUVmax was higher in malignant nodules and NIFTP than in benign ones, both 20 minutes p.i. (7.39 ± 2.63 vs. 5.06 ± 2.79, $p < 0.001$) and 60 minutes p.i. (6.79 ± 3.00 vs. 5.02 ± 3.05, $p < 0.01$). The SUVmax(nodule)/SUVmax(background) ratios were not statistically different between 20 and 60 minutes p.i., neither in the whole group (1.44 ± 0.82 vs. 1.43 ± 0.85, $p = 0.8$) nor in the subgroup of cancer or NIFTP (2.02 ± 0.67 vs. 1.98 ± 0.80, $p = 0.7$). However, Table 2 shows that patient 13 was FCH-positive at 20 minutes and negative at 60 minutes because of a significant FCH washout.

Figure 5 presents SUVmax measured in thyroid nodules according to pathological subtypes. Higher SUVmax was observed in HCC than in the other pathological malignant subtypes at 20 minutes (9.92 ± 0.92 vs. 6.84 ± 2.67, $p = 0.047$), but the difference did not reach statistical significance at 60 minutes (10.27 ± 1.37 vs. 6.59 ± 2.87, $p = 0.06$). SUVmax was also higher in oncocytic adenomas than in the other pathological benign subtypes, both at 20 (7.67 ± 3.86 vs. 4.46 ± 1.87, $p < 0.001$) and 60 minutes (8.03 ± 4.42 vs. 4.32 ± 1.85, $p < 0.001$). These data led us to examine the performances of FCH PET/CT in nodules with ($n = 35$) or without oncocytic features ($n = 72$) on FNAB. In nodules with cytological oncocytic features, sensitivity, specificity, PPV, and NPV of FCH PET/CT at 20 minutes in detecting cancer were 100% [90% CI 55–100], 33% [90% CI 19–50], 20% [90% CI 8–38], and 100% [90% CI 74–100], and they were 87% [90% CI 64–98], 58% [90% CI 46–69], 35% [90% CI 22–50], and

Table 2. Characteristics of the Twenty Patients with a Malignant Thyroid Nodule or Noninvasive Follicular Thyroid Neoplasm with Papillary-Like Nuclear Features

									FCH PET/CT					
							US		Early acquisition, 20 minutes p.i.			Late acquisition, 60 minutes p.i.		
Pt	Age (year)	Sex (M/F)	Cytology (Bethesda)	Pathology	TPO-Ab	Thyr.	Size (mm)	EU-TIRADS	Result	SUVmax (nodule)	Ratio	Result	SUVmax (nodule)	Ratio
1	66	M	V	FV-PTC	P	P	22	4	P	5.8	2.27	P	4.96	1.91
2	65	F	IV (o)	HCC	N	N	53	4	P	10.04	2.28	P	11.04	2.75
3	64	F	V	C-PTC	N	N	20	4	P	4.49	1.27	P	3.55	1.3
4	27	F	IV (f)	C-PTC	N	N	20	4	P	5.06	1.7	P	3.52	1.1
5	70	M	V	HCC	N	N	50	3	P	11.11	3.2	P	11.12	4.3
6	27	F	V	C-PTC	N	N	25	4	P	4.78	1.7	P	4.21	1.7
7	31	F	V	C-PTC	N	N	23	5	P	8.6	2.39	P	8.6	2.39
8	52	F	IV (f)	C-PTC	N	N	19	5	P	6.98	1.75	P	6.01	1.66
9	20	F	IV (f)	FV-PTC	N	N	29	3	P	8.55	2.87	P	6.25	2.28
10	51	F	V	FV-PTC	P	P	15	5	N	8.88	0.96	N	7.63	0.92
11	50	F	V	C-PTC	N	N	24	4	N	2.65	0.75	N	3.03	0.94
12	54	F	IV (o)	C-PTC	N	N	28	4	P	9.87	2.74	P	8.04	2.41
13	35	F	III	FV-PTC	N	N	31	3	P	4.57	1.29	N	3.47	1
14	71	M	V	C-PTC	N	N	17	5	P	5.59	1.78	P	5.8	1.55
15	69	F	V	FV-PTC	P	P	15	5	P	10.65	1.8	P	12.93	2.17
16	81	F	V	TC-PTC	P	P	29	4	P	12.13	1.94	P	11.34	2.09
17	40	F	IV (o)	HCC	N	N	19	4	P	9.53	3.2	P	8.7	2.7
18	47	F	IV (o)	C-PTC	N	N	37	3	P	5.92	1.97	P	4.61	1.91
19	65	F	IV (o)	C-PTC	N	N	19	4	P	6.03	2.36	P	5.99	2.67
20	43	M	IV (f)	NIFTP	N	N	30	4	P	6.59	2.11	P	5.08	1.75

Thyr., thyroiditis on pathological examination; FV-PTC, follicular variant of papillary thyroid cancer; IV (o), oncocytic (Hürthle) cell neoplasm; HCC, Hürthle-cell cancer; C-PTC, classic variant of papillary thyroid cancer; IV (f), follicular neoplasm/suspicious for follicular neoplasm; TC-PTC, tall-cell variant of papillary thyroid cancer; P, positive; N, negative; EU-TIRADS, European Thyroid Imaging Reporting and Data System; p.i., postinjection; US, ultrasonography.

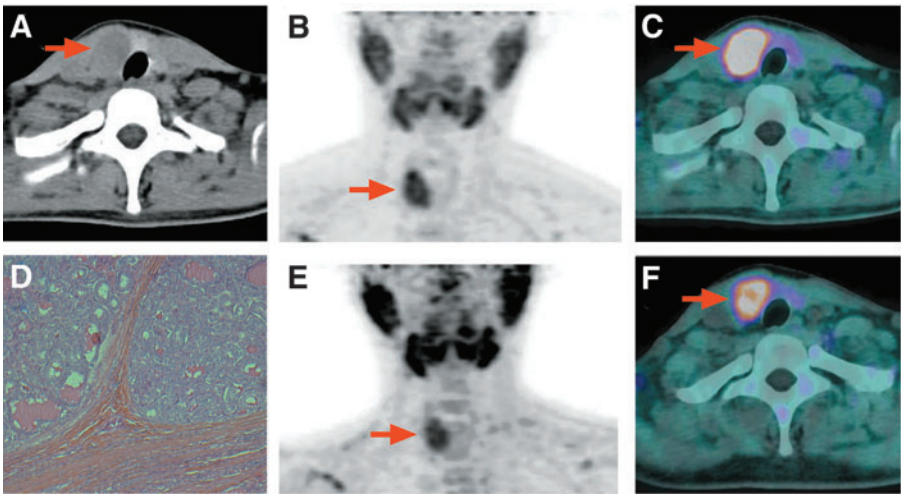

FIG. 2. Clinical example of a true-positive FCH PET/CT in a 20-year-old female patient with thyroid cancer. She was referred for a right 29 mm thyroid nodule [**(A)**, CT scan, arrow] EU-TIRADS 3, and Bethesda IV (follicular neoplasm). High FCH uptake was observed in the nodule on both PET/CT acquisitions [**(B**, **C)**, MIP and fused transaxial slice, at 20 minutes; **(E**, **F)**, MIP and fused transaxial slice, at 60 minutes] (Patient 9, see Table 2 for SUVmax). Pathology revealed a 23 mm FV-PTC (pT2NxMx) [**(D)**, HES staining, ×10]. FCH, ^{18}F-fluorocholine; PET/CT, positron emission tomography/computed tomography; EU-TIRADS, European Thyroid Imaging Reporting and Data System; MIP, maximum intensity projection image; HES, hematoxylin and eosin stain.

94% [90% CI 83–99] in nodules without oncocytic cytology, respectively. Similar results were found at 60 minutes in each subgroup of patients. At 20 minutes, specificity was lower in nodules with cytological oncocytic features than in those without this profile (33% vs. 58%, $p = 0.01$). Also, false-positive FCH PET/CT studies were more prevalent in pathology-proven oncocytic adenomas than in the other non-oncocytic benign nodules (75% vs. 45%, $p = 0.02$). Figure 6 shows positive PET/CT studies in two patients with oncocytic (Bethesda IV) cytology, including a true-positive and a false-positive one.

The pre-FCH PET/CT probability of cancer or NIFTP in patients with Bethesda III–IV nodules was 11% (10/94) and the post-FCH PET/CT probability was 19% (10/54) in PET-positive and 0% (0/40) in PET-negative patients (Fig. 7). The percentage of unnecessary surgeries in the whole population assessed by FCH PET/CT would be 42% (45/107) versus 81% (87/107) before FCH PET/CT ($p < 0.001$), resulting in a hypothetical reduction of such unnecessary surgeries by 48% (42/87) [95% CI 32–64].

Discussion

This prospective study shows that FCH PET/CT has high sensitivity (90%) and NPV (96%), but poor specificity (49%) and PPV (29%) for predicting malignancy in thyroid nodules with IC. Such a high NPV allowed to exclude malignancy with a residual cancer risk of 4% in PET-negative nodules, which is similar to that reported in cytologically benign nodules (41). By contrast, the limited specificity and PPV, especially observed in IC nodules with oncocytic cytology is a major limitation.

In the past, the clinical relevance of other nuclear imaging modalities, including ^{18}FDG PET/CT and ^{99m}Tc-MIBI scintigraphy, has been evaluated in the characterization of indeterminate nodules. Although a relatively high sensitivity (>90%) has been reported for ^{18}FDG PET/CT in some studies (13,15,19–21,42,43), two well-conducted prospective studies showed lower sensitivity and NPV, namely 77% and 81% (14) and 79% and 79%, respectively (18). Low values of specificity and PPV were also reported, namely 62% and 57%

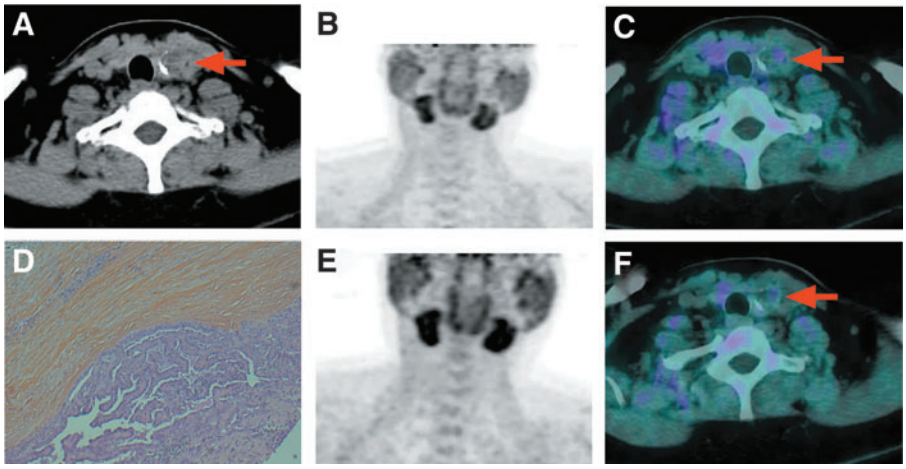

FIG. 3. Clinical example of a false-negative FCH PET/CT result. A 50-year-old female patient with a 24 mm nodule in the left thyroid lobe [**(A)**, CT scan, arrow] EU-TIRADS 4, and Bethesda V. PET/CT did not show any FCH uptake in the thyroid nodule neither at 20 minutes [**(B)**, MIP; **(C)**, fused transaxial slice] nor at 60 minutes [**(E)**, MIP; **(F)**, fused transaxial slice] (Patient 11, see Table 2 for SUVmax). An 18 mm C-PTC (pT1bN0Mx) was found on pathology [**(D)**, HES staining, ×10].

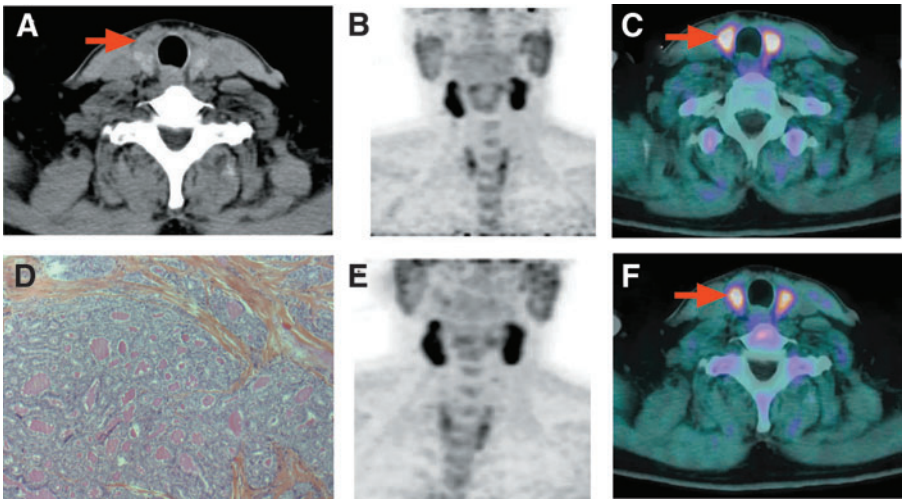

FIG. 4. Clinical example of false-negative FCH PET/CT result. A 51-year-old female patient was referred for a 15 mm nodule of the right thyroid lobe [**(A)**, CT scan, arrow] EU-TIRADS 5, and Bethesda V. FCH PET/CT showed diffuse thyroid uptake on both acquisitions [**(B, C)**, MIP and fused transaxial slice, at 20 minutes] (SUVmax = 9.29); **(E, F)** MIP and fused transaxial slice, at 60 minutes (SUVmax = 8.25), which was higher than in the nodule (Patient 10, see Table 2 for SUVmax). A 12-mm FV-PTC (pT1bN0Mx) was found on pathology [**(D)**, HES staining, × 10).

(14) and 32% and 31%, respectively (18). Of note, one study did not find any difference between SUVmax of malignant and benign nodules (17). In a meta-analysis of 267 patients with a cancer prevalence of 26%, Wang *et al.* reported a pooled sensitivity of 89% and a specificity of 55% (44).

Studies focusing on ^{99m}Tc-MIBI uptake in thyroid nodules are difficult to compare since the methods and assessment of uptake (visual analysis or washout index) differed among the studies. Nevertheless, there are concordant data showing that ^{99m}Tc-MIBI has high NPV (10,11,45), suggesting that malignancy might be safely ruled out in nodules without ^{99m}Tc-MIBI uptake. Data also show low specificity and PPV (10,11,45). Our results suggest that FCH also has a high NPV, but unlike MIBI scintigraphy, PET/CT allows quantitative measurements and easier interpretation.

^{18}FDG, ^{99m}Tc-MIBI, and FCH explore different metabolic pathways. While ^{18}FDG is a tracer of glucose metabolism, ^{99m}Tc-MIBI tumor uptake reflects the activity of mitochondria and FCH uptake, the phospholipid synthesis in cell membranes. High uptake has been reported in oncocytic tumors with ^{99m}Tc-MIBI and ^{18}FDG (9,11,14,42), as we observed with FCH. Also, although high and diffuse thyroid ^{18}FDG uptake is a typical feature of Hashimoto's thyroiditis, FCH uptake has not been clearly described so far in these patients. Out of four patients with cancer/NIFTP and thyroiditis, only one patient had high FCH thyroid uptake leading to misinterpretation. Thus, we believe that FCH PET scanning is evaluable in patients with thyroiditis.

The present data suggest using PET acquisition at 20 rather than at 60 minutes. This would shorten the imaging time of patients in the PET unit improving their comfort. From a dosimetric point of view, low activities of FCH were administered (i.e., 1.5 MBq/kg; mean, 109 MBq per patient) with low-dose CT scan focusing on the neck and upper mediastinum resulting in low body irradiation. Other important issues are the availability and cost of FCH PET/CT for which significant differences are observed worldwide. While FCH is widely available in Europe, only PET/CT with ^{11}C-choline is available in the United States. Regarding the cost of FCH PET/CT, it is necessary to take into account both the price of the tracer and the rate of reimbursement of the PET scan. In France, given the activity of FCH injected in comparison with ^{18}FDG (1.5 vs. 3.5 MBq/kg), the price of FCH (211 Euros for a patient of 70 kg) is similar to that of ^{18}FDG (230 Euros). The reimbursement rate being the same for PET/CT regardless of the radioisotope used, the costs of FCH or ^{18}FDG

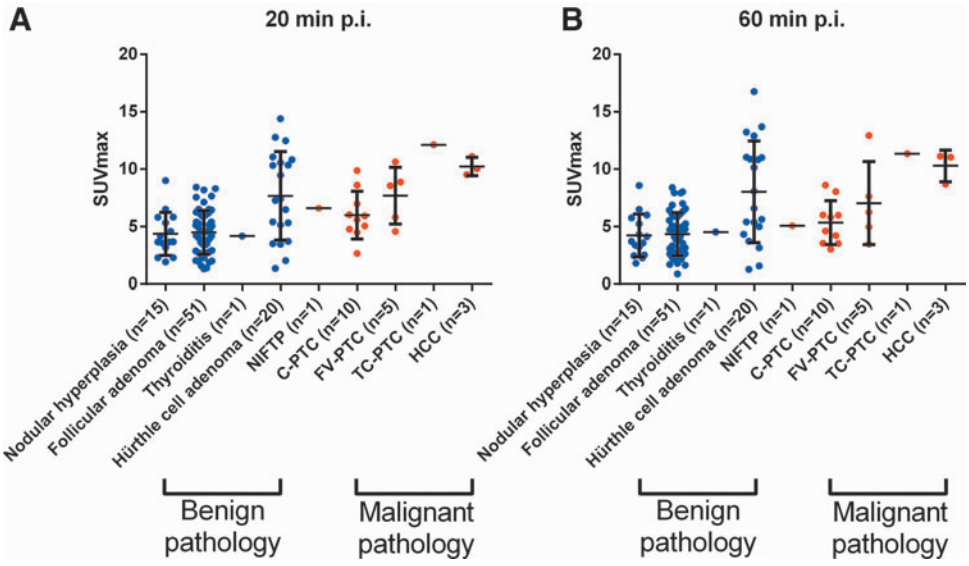

FIG. 5. Quantitative assessment of FCH uptake in benign, NIFTP, and malignant nodules scanned with PET/CT according to the pathological subtype and the acquisition time [**(A)**, at 20 minutes; **(B)**, at 60 minutes].

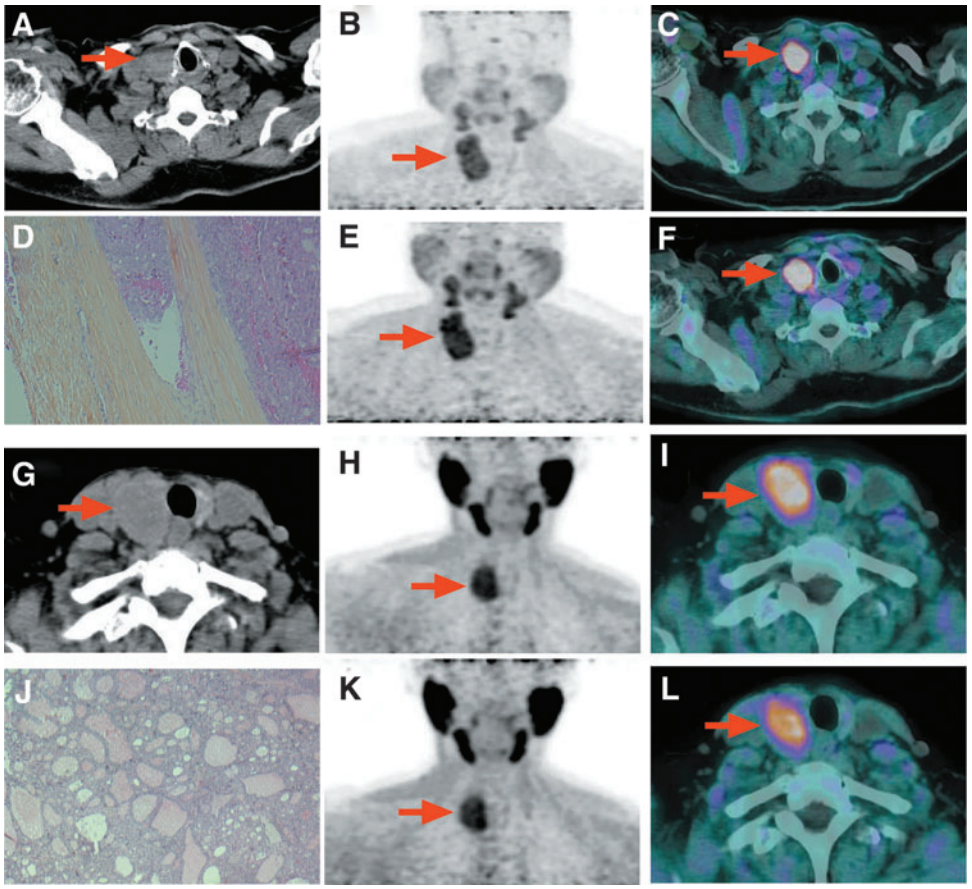

FIG. 6. FCH PET/CT results in two patients with a cytology consistent with oncocytic (Hürthle) cell neoplasm (Bethesda IV). **(A–F)** True-positive FCH PET/CT in a 65-year-old female patient with a right 53 mm thyroid nodule [**(A)**, CT scan, arrow] and EU-TIRADS 3. High FCH tumor uptake was present on both acquisitions [**(B, C)**, MIP and fused transaxial slice, at 20 minutes; **(E, F)**, MIP and fused transaxial slice, at 60 minutes] (Patient 2, see Table 2 for SUVmax). Pathology showed a 55 mm HCC (pT3aNxMx) [**(D)**, HES staining, ×10). **(G–L)** False-positive FCH PET/CT in a 71-year-old female patient referred for a 38 mm right thyroid nodule [**(G)**, CT scan, arrow] and EU-TIRADS 4. PET/CT showed high FCH uptake in the nodule on both acquisitions [**(H, I)**, MIP and fused transaxial slice, at 20 minutes (SUVmax = 6.47); **(K, L)**, MIP and fused transaxial slice, at 60 minutes (SUVmax = 6.59)]. A 40-mm oncocytic adenoma was found on pathology [**(J)**, HES staining, ×5].

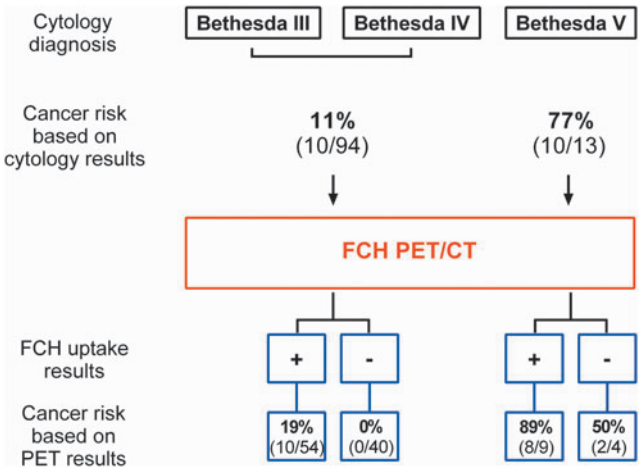

FIG. 7. Cancer risk in indeterminate cytology thyroid nodules based on cytology and FCH PET/CT results.

PET/CT are similar for the hospital. Another point is the cost-effectiveness of the strategies used for the characterization of indeterminate nodules. Although CHOCOLATE is not a cost-effectiveness study, the immediate cost savings of an FCH PET/CT-based decision-making strategy have been estimated (Supplementary Fig. S1). In comparison with surgery in all indeterminate nodules, the immediate costs would be reduced by 14% if FCH PET/CT imaging was used for decision-making.

The major drawback of FCH PET/CT is its poor specificity and PPV, especially in nodules with oncocytic cytology. This limitation has been previously highlighted with ^{18}FDG (14,42) and ^{99m}Tc-MIBI (9,11). Giovanella *et al.* (9) reported that performances of ^{99m}Tc-MIBI scintigraphy were worse in oncocytic nodules compared with nononcocytic ones, similar to our findings for FCH PET/CT. These data strongly suggest not performing FCH PET/CT in patients with oncocytic cytology to limit the number of false-positives, and to improve specificity and PPV. Another limitation of this study is the low prevalence of cancers in Bethesda III–IV nodules, which may lead to overestimation of the NPV. This highlights the

need to include cytopathology expert consensus review in future studies. However, as shown in a recent review (46), a sensitivity of 90% as observed in the present study enables keeping NPV above 94%, the accepted limit for rule-out tests, in disease prevalence below 35%.

In the future, it would be of interest to further identify patients who are most likely to benefit from FCH PET/CT based on some combination of US-derived risk, cytology, and genomic test results in the framework of prospective, multicenter, and cost-effectiveness studies. Such studies could include patients with Bethesda III/IV, EU-TIRADS 3 or 4 nodules, without oncocytic features, and exclude those with Bethesda V or EU-TIRADS 5 nodules given the high risk of cancer. As NGS multigene panel testing has been shown to be a specific diagnostic method, a prospective cost-effectiveness study could be designed to assess FCH PET/CT at 20 minutes p.i in combination with such molecular testing in patients with an FCH-positive PET/CT.

In summary, this prospective study shows that FCH PET/CT has high NPV (96%) and could reliably exclude cancer in PET-negative IC nodules, but has poor PPV, particularly in nodules with oncocytic cytology.

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Authors' Contributions

R.C. conceived the study and its design. R.C. and S.B. performed data analysis and drafted the article. J.-M.G. and B.C. helped for the design. R.C., A.L.-C., E.B., D.d.R., D.B., V.B., V.S.-R., and D.P. performed or contributed to data acquisition. I.L. and J.L. performed the statistical analysis. I.L., A.L.-C., E.B., D.d.R., D.B., V.B., V.S.-R., J.L., D.P., J.-M.G., and B.C. revised the article.

Author Disclosure Statement

No competing financial interests exist.

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Supplementary Material

Supplementary Figure S1

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