



Unusual uptakes on ^{18}F -fluorocholine positron emission tomography/computed tomography (PET/CT): a retrospective study of 368 prostate cancer patients referred for a biochemical recurrence or an initial staging

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Background: ^{18}F -fluorocholine positron emission tomography/computed tomography (F-choline PET/CT) is considered a cornerstone in the staging and restaging of patients with prostate cancer (PCa). The aim of this study was to retrospectively assess unusual uptakes in patients who underwent a F-choline PET/CT for the initial staging or for the restaging of a relapsing PCa.

Methods: Three hundred and sixty-eight PCa patients were staged or restaged using F-choline PET/CT. Unusual uptakes were defined as uptakes occurring outside the usual paths of diffusion of PCa or as uptake in bone with a clear morphological evidence of nonmetastatic lesion.

Results: We found unusual uptakes in 47/368 patients (12.8%). Among them, 41/47 presented with benign F-choline uptake, usually within lymph nodes, due to inflammatory processes (22/47). Other benign processes were found in: thyroid (3/47), adrenal gland (3/47), brain (2/47), liver (1/47), bowel (3/47), frontal sinus (1/47), lungs (4/47), parotid gland (1/47) and bone (1/47). The six remaining patients presented with a second cancer, including lymphoma (1/47), non-small cell lung cancer (4/47) and neuroendocrine tumor (1/47).

Conclusions: unusual uptakes on F-choline PET/CT are quite frequent and should be explored since they may correspond to non-PCa.

Keywords: ^{18}F -fluorocholine (F-choline); positron emission tomography/computed tomography (PET/CT); incidentaloma; prostate cancer (PCa)

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Introduction

Prostate cancer (PCa) is the 2nd most common cancer in men (1), and the 5-year biochemical recurrence-free survival strongly depends on the histological grade and on the initial stage at the time of diagnosis (2,3). Approximately

15–40% of treated patients will experience local or distant recurrence during follow-up. Most of these recurrences will present as biochemical relapses, defined as an increase in serum prostate specific antigen (PSA) level (4). In patients with biochemical recurrence, functional imaging

with ^{18}F -fluorocholine (F-choline) or, more recently, ^{68}Ga -prostate-specific membrane antigen (PSMA) PET/CT, plays a key role in distinguishing a local recurrence from a systemic spread of the disease, in order to optimize the therapeutic strategy (5,6). In fact, it has been shown that the results of PET/CT could influence patient's management in more than half cases (7-9).

F-choline is a choline analogue, mimicking choline uptake and phosphorylation as a precursor in the biosynthesis of phosphatidylcholine, a membrane phospholipid (10). Physiological uptake of F-choline is noted in kidneys, liver, salivary glands, pancreas and with a weaker intensity in spleen, bone marrow and muscles. Increased uptake has been documented in benign lesions such as adrenal and parathyroid adenomas, meningiomas, sarcoidosis lesions or thymomas (10-13). Finally, increased choline kinase activity has been demonstrated in a wide variety of human malignancies (10,14) such as PCa (5,15), hepatocellular carcinoma (16) or bronchioloalveolar lung cancer (17). Currently only a few large series investigated the potential of F-choline PET/CT to detect second malignancies in patients referred for the staging of a PCa (14,18).

The aim of our study was therefore to describe and analyze unusual F-choline uptakes in a large series of PCa patients who underwent F-choline PET/CT for the initial staging of their disease, or for a restaging after a biochemical relapse.

Methods

Population

We retrospectively identified all adult patients (≥ 18 years old) who underwent F-choline PET/CT between January 2012 and March 2019 within the Nuclear Medicine Department at Besançon University Hospital. Among these patients, we included those referred for the initial staging of a PCa (because of suspicious findings on conventional imaging) or for the evaluation of a biological recurrence of a histologically proven PCa initially treated by surgery and/or radiotherapy with or without androgen deprivation therapy. Among included patients, we identified those presenting with an unusual tracer uptake, defined as a F-choline uptake outside the expected areas of PCa dissemination, i.e., the prostate and seminal vesicles, pelvic nodes, retroperitoneal nodes up to L2-L3, and bones (19-21), or as F-choline uptake in bone with a clear morphological evidence of nonmetastatic lesion.

F-choline PET/CT acquisition technique

All patients fasted for at least 4 hours before receiving an intravenous injection of 4 MBq/kg of F-choline. Slow hydration with normal saline was delivered to all patients between injection and acquisition. Acquisitions were performed on a GE DISCOVERY 690 PET/CT (GE Healthcare, Milwaukee, WI, USA). The acquisition protocol included a dynamic acquisition centered over the pelvis for 8 min with 1-min frames, followed by an acquisition from vertex to mid-thigh performed 45 min after injection, comprising 7-8 bed positions with an acquisition time per bed position varying between 1.5 and 2.5 min, depending on the patient's body mass index. PET images were reconstructed using a standard iterative algorithm. A "low-dose" CT (50 to 210 mA, 120 kV, 3.75 mm slice thickness) was performed for attenuation correction of the PET data for both dynamic and late acquisitions (22,23). Images were interpreted by two nuclear medicine specialists on a dedicated Advantage Workstation console (GE Healthcare, Milwaukee, WI, USA). All the relevant clinical, histological and radiological data were collected from the electronic hospital charts of the patients, analyzed and reported in this study.

This study obtained ethics approval from our Institutional Review Board, with waiver of informed consent for this retrospective study.

Results

Population

Three hundred and sixty-eight patients were included in this study. *Table 1* summarizes the main characteristics of our population. Unusual uptakes were found in 47/368 patients (12.8%). *Table 2* summarizes these unusual uptakes, as well as their associated maximum standardized uptake values (SUV_{max}).

Nodal uptake

We found unusual nodal uptake in 23 patients (6.3%). Median age was 71 years (range, 63-81 years), and the median PSA was 3 ng/mL (range, 0.2-14 ng/mL). Twenty-two cases were finally considered as benign inflammatory mediastino-hilar ($n=12$), inguinal ($n=5$), axillary ($n=4$) and cervical ($n=1$) lymph nodes. Histological evidence was available for two patients who underwent a biopsy. For the other 20 patients, diagnosis was made on the basis of

Table 1 Main characteristics of the included patients

Characteristics	Number	Percentage (%)
Initial treatment of prostate cancer		
Radical prostatectomy	84	22.8
Radical prostatectomy + lymph node dissection	17	4.6
Radical prostatectomy + adjuvant radiotherapy	53	14.4
Radical prostatectomy + salvage radiotherapy	42	11.4
Exclusive radiotherapy	25	6.8
Radiotherapy + androgen deprivation therapy	45	12.2
Brachytherapy	15	4.1
androgen deprivation therapy	35	9.5
Others	30	8.2
Missing data	22	6
Indication for F-choline PET/CT		
Biochemical relapse	314	85.3
Initial staging	54	14.7
Age at the time of PET/CT (years), median [range]	71 [51–96]	
PSA at the time of PET/CT (nanograms per milliliter), median [range]	2.4 [0.2–220.0]	

PET/CT, positron emission tomography/computed tomography; F-choline, ^{18}F -fluorocholine.

Table 2 Unusual ^{18}F -fluorocholine uptakes with their associated SUV_{max} values

Site of uptake	Number of patients (%)	SUV_{max} median (min–max)
Lymph nodes	23 (6.3)	4.2 (1.8–7.9)
Lung	8 (2.2)	3.4 (1.7–9.4)
Thyroid	3 (0.8)	4.6 (4.0–7.2)
Adrenal glands	3 (0.8)	8.4 (7.6–12.0)
Bowel	3 (0.8)	4.4 (4.4–5.6)
Brain	2 (0.5)	5.1 (4.8–5.4)
Para-oesophageal node	1 (0.3)	4.0
Frontal sinus	1 (0.3)	3.4
Parotid gland	1 (0.3)	5.9
Bone	1 (0.3)	4.5
Liver	1 (0.3)	13.7

SUV_{max} , maximum standardized uptake values.

clinical, imaging, biological and follow up data. Only one patient had a single nodal uptake. According to the D'Amico classification (2), eight patients presented with a low-risk PCa at initial diagnosis, 9 had an intermediate-risk cancer (6 with a 3+4 Gleason score and 3 with a 4+3 Gleason score) and 5 had a high-risk cancer.

The last case corresponded to an 81-year-old patient who underwent prostatectomy in 2012 for a localized PCa (initial PSA: 3.3 ng/mL, Gleason score 3+3, pT2cN0M0), and relapsed in 2018 (PSA level: 0.21 ng/mL). F-choline PET/CT demonstrated a local recurrence in the prostate bed as well as multiple hypermetabolic lymph nodes above and below the diaphragm, corresponding to a marginal zone B-cell lymphoma (*Figure 1*).

Lung uptake

We found unusual lung uptake in 8 patients (2.2%). Median age was 67 years (range, 58–80 years), and the



Figure 1 A case of marginal zone B-cell lymphoma. MIP of ^{18}F -fluorocholine PET/CT. MIP, maximum intensity projection; PET/CT, positron emission tomography/computed tomography.

median PSA was 1.7 ng/mL (range, 0.9–7.5 ng/mL). Four cases corresponded to non-small cell lung cancers (3 adenocarcinomas and 1 squamous cell carcinoma). *Figure 2* provides an illustrating example. For two patients, lung cancer was already diagnosed at the time of the PET/CT procedure, so these patients cannot be considered as true incidental findings. For the other two patients, lung cancer was revealed by ^{18}F -fluorocholine PET/CT.

Three patients presented with hypermetabolic isolated pulmonary nodules (median $\text{SUV}_{\text{max}} = 1.7$, range, 1.1–4.1) that did not evolve morphologically on subsequent CT scans in the absence of systemic hormonal treatment. For this reason, they were classified as benign lesions.

The last patient in this subgroup was an 80-year-old man initially treated with prostatectomy in 2002 for a localized intermediate risk PCa (initial PSA: 4.3 ng/mL, Gleason score 4+3 =7, pT2bN0M0) who underwent PET/CT because of a rising PSA up to 3.4 ng/mL. F-choline PET/CT revealed diffuse hypermetabolic ground-glass opacities of the lung ($\text{SUV}_{\text{max}} = 2.8$) with bronchial distortions and intra-lobular crosslinking without further abnormalities. This aspect was attributed to an extrinsic allergic alveolitis.

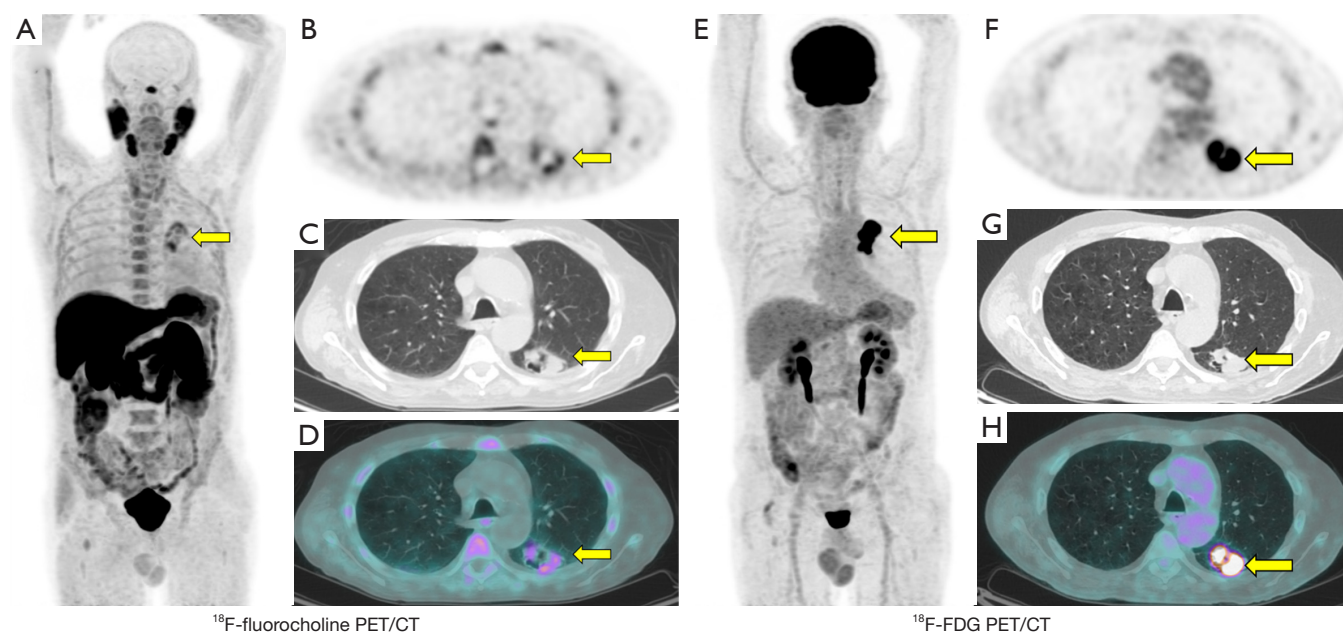


Figure 2 A case of lung squamous cell carcinoma (yellow arrows). (A,B,C,D) MIP (A), PET (B), CT (C) and fused (D) axial slices of ^{18}F -fluorocholine PET/CT. (E,F,G,H) MIP (E), PET (F), CT (G) and fused (H) axial slices of ^{18}F -FDG PET/CT. MIP, maximum intensity projection; PET/CT, positron emission tomography/computed tomography.

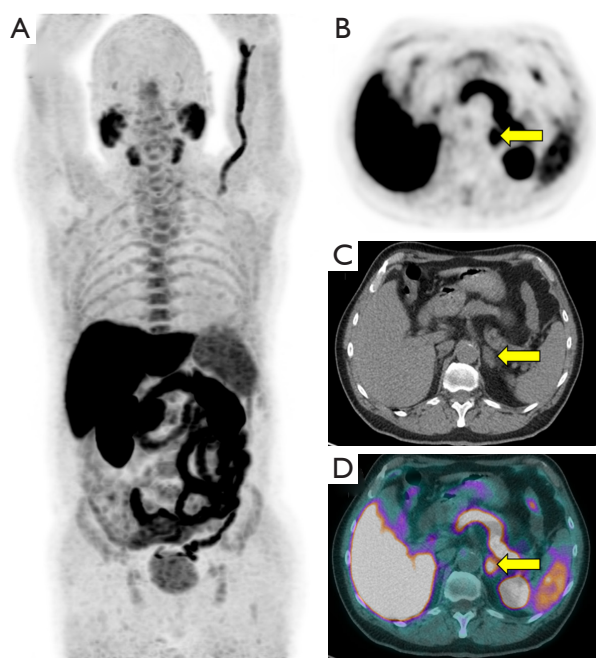


Figure 3 A case of left adrenal incidentaloma (yellow arrows). (A,B,C,D) MIP (A), PET (B), CT (C) and fused (D) axial slices. Biopsy of this lesion did not reveal any malignancy. MIP, maximum intensity projection; PET/CT, positron emission tomography/computed tomography.

known as “farmer’s lung” already recognized in the medical history of the patient. This disease is due to chronic inhalation of microorganisms living in hay, straw or moldy cereals (24).

Thyroid uptake

We found unusual thyroid uptake in 3 patients (0.8%). Median age was 69 years (range, 61–71 years), and the median PSA was 1.3 ng/mL (range, 0.2–1.7 ng/mL). Two of them displayed a diffuse uptake suggestive of thyroiditis, a diagnosis confirmed by subsequent morphological and biological data. The third patient presented with a focal uptake corresponding to a hypodense nodule in the right thyroid lobe ($\text{SUV}_{\text{max}} = 7.2$). Ultrasonography demonstrated a well-defined, hypoechoic, hyper-vascular nodular lesion of the right thyroid lobe (diameter: 30 mm). Three needle biopsies under ultrasound guidance were performed, and no signs of malignancy were found. This patient is still alive without evidence of thyroid carcinoma and presents a normal thyroid function.

Adrenal uptake

We found unusual unilateral adrenal uptake in 3 patients (0.8%) who underwent F-choline PET/CT for biological relapse after prostatectomy ($n=1$) or radiotherapy ($n=2$). Median age was 79 years (range, 66–80 years), and the median PSA was 1.3 ng/mL (range, 0.5–2.2 ng/mL). Two of them showed highly hypermetabolic supra-centimetric nodular lesions in the left adrenal gland ($\text{SUV}_{\text{max}} = 7.6$ and 12). CT-guided biopsies revealed healthy adrenal tissue without atypia in both cases. These patients are still alive with stable PCa disease 52 and 61 months after F-choline PET/CT. *Figure 3* illustrates one of these cases. The third patient also presented with a focal uptake in a nodular lesion ($\text{SUV}_{\text{max}} = 8.4$) of the left adrenal gland but no biopsy was done given the patient’s age. A CT scan performed 25 months after the PET/CT did not reveal any morphological evolution of this lesion, in the absence of androgen deprivation therapy.

Colic uptake

We found unusual colic uptake in 3 patients (0.8%). Median age was 79 years (range, 66–80 years), and the median PSA was 1.76 ng/mL (range, 0.5–2.2 ng/mL). Two of them presented with hypermetabolic foci in the recto-sigmoid, while the third patient displayed a more diffuse uptake of the left colon. Median SUV_{max} was 4.9 (range, 4.4–5.6). There was no evident morphological abnormality of the intestinal wall on CT images. Unfortunately, none of these patients underwent an endoscopy. However, they did not develop any digestive neoplasia after 3 years of follow-up for two patients (one with focal uptake, one with diffuse uptake), and after 18 months of follow-up for one patient (with focal uptake).

Cerebral uptake

In two patients, we observed an intense focal uptake within the cerebral parenchyma. First case corresponded to a meningioma (*Figure 4*). The patient has not been operated on and has been followed with annual brain magnetic resonance imaging (MRI) demonstrating a slow growth of the meningioma. The second patient displayed a focal meningeal uptake close to the *sella turcica* and unfortunately declined brain MRI because of claustrophobia. He does not complain from neurological symptoms 5 years later.

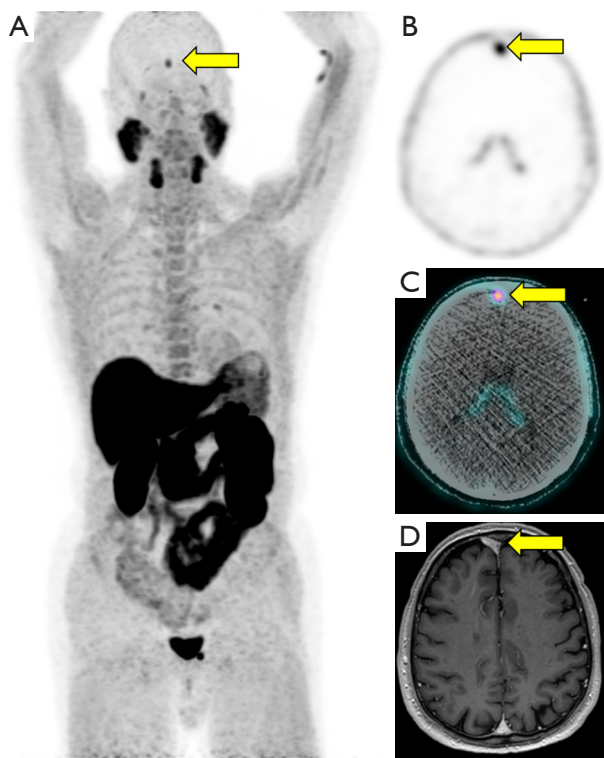


Figure 4 A case of meningioma. MIP (A), PET (B) and PET/CT (C) axial slices demonstrate a frontal parasagittal focal uptake (yellow arrows). T1-weighted MRI axial view after gadolinium injection (D) revealed an 18-mm long-axis contrast-enhanced meningeal lesion, implanted in the anterior frontal region without perilesional edema suggestive of a meningioma. MIP, maximum intensity projection; PET/CT, positron emission tomography/computed tomography.

Para-esophageal uptake

We found an unusual para-esophageal nodal uptake in a 68-year-old patient initially treated in 2010 with radiotherapy and 3 years of androgen deprivation therapy for a high risk PCa (initial PSA: 19 ng/mL, Gleason score: 4+5 =9, pT2cN0M0) and presenting with a biochemical relapse (PSA: 0.7 ng/mL). F-choline PET/CT demonstrated a para-esophageal hypermetabolic adenopathy ($SUV_{max}=4$), without evidence of PCa recurrence elsewhere (Figure 5). Biopsy of this lesion established the diagnosis of metastatic adenopathy of a well-differentiated grade 1 neuroendocrine tumor. Whole body CT scan and ^{111}In -octreotide scan confirmed an isolated hyper-arterialized hyper-fixing adenopathy. Biochemistry showed a normal neuron-specific enolase (NSE) blood

concentration and high levels of chromogranin A (17,277 ng/mL). This lesion was treated with exclusive radiotherapy (60 Grays in 30 fractions), as surgery was excluded because of important patient co-morbidities. The patient underwent an ^{111}In -octreotide scan in 2018 and a F-choline PET/CT in 2019, with no sign of PCa or neuroendocrine tumor relapse. The patient is still alive 45 months after the diagnosis of neuroendocrine tumor.

Frontal sinus uptake

An 82-year-old patient, treated with radiotherapy and androgen deprivation therapy in 2016 for a localized PCa (initial PSA: 13 ng/mL, Gleason score 3+4 =7, pT2cN0M0), underwent F-choline PET/CT in 2018 for a biochemical relapse (PSA: 1.9 ng/mL). This patient did not show any sign of local or systemic PCa relapse, but presented with an unusual uptake ($SUV_{max}=3.4$) in the left frontal sinus, without bone erosion. This anomaly was attributed to a banal infectious sinusitis, as it disappeared on subsequent CT scans obtained during follow-up of the patient.

Parotid uptake

A 79-year-old patient, treated with prostatectomy in 2012 for a localized intermediate risk PCa (initial PSA: 8 ng/mL, Gleason score 4+3 =7, pT2bN0M0), underwent F-choline PET/CT in 2018 for a biochemical relapse (PSA =27 ng/mL). In this patient we found a retroperitoneal nodal relapse of the PCa and a clear asymmetry of fixation between the right ($SUV_{max}=6$) and left parotid gland ($SUV_{max}=3.7$). CT scan showed a significant increase in the right parotid volume without obvious morphological lesion within the gland. There is no definite diagnosis for this anomaly. Follow-up CT scans showed a normalization of the right parotid gland size without hormone therapy. The patient was still alive 17 months later.

Bone uptake

A 79-year-old patient, treated with radiotherapy and androgen deprivation therapy in 2007 for a localized intermediate risk PCa (initial PSA: 6.8 ng/mL, Gleason score: 4+3 =7, pT2aN0M0) underwent F-choline PET/CT in 2016 for a biochemical relapse (PSA: 2.58 ng/mL). This examination showed a diffuse moderate uptake in the left hemi-pelvis ($SUV_{max}=2.7$) and in the 2nd lumbar vertebral body ($SUV_{max}=4.2$), with a typical trabecular aspect of the

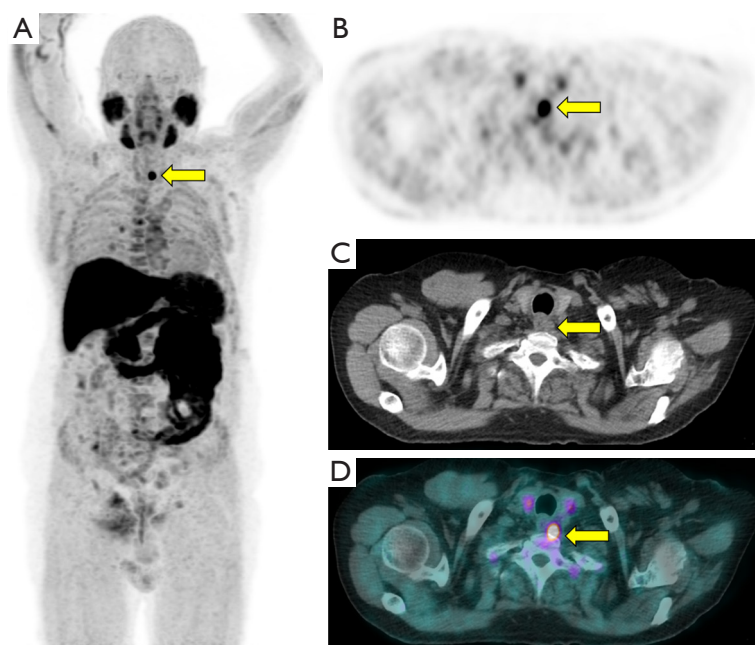


Figure 5 A case of neuroendocrine tumor. MIP (A), PET (B), CT (C) and fused (D) axial slices of ^{18}F -choline PET/CT show a hypermetabolic adenopathy on the left side of the esophagus (yellow arrows). MIP, maximum intensity projection; PET/CT, positron emission tomography/computed tomography.

bone on CT images. These lesions were related to a Paget's disease, already known in the patient's history. There was no sign of PCa relapse. Because of a persistent PSA elevation, this patient underwent a ^{68}Ga -PSMA PET/CT in 2017, which demonstrated a nodal pelvic and lombo-aortic relapse, without any sign of bone metastases.

Liver uptake

A 58-year-old patient, treated with radical prostatectomy in 2018 for a localized PCa (initial PSA: 6.4 ng/mL, Gleason score: 4+4 =8, pT2cN0M0), underwent F-choline PET/CT in 2018 for a persistent high PSA level after surgery (PSA: 2.1 ng/mL). This examination showed a focal uptake in a peri-rectal nodular lesion suspected to correspond to a seminal vesicle remnant. There was also a focal uptake ($\text{SUV}_{\text{max}} = 13.7$) in a hypodense lesion of the liver. This anomaly was explored with MRI and contrast-enhanced ultrasonography, both in favor of a hepatic angioma, but the ultrasonography data were ambiguous and the patient eventually underwent biopsy: the results were in favor of a cavernous hemangioma, with absence of any malignant structure.

Discussion

In our population of 368 patients who underwent F-choline PET/CT, we found atypical, non-PCa related uptake in 47 patients (12.8%). Our results are comparable to those published by Calabria *et al.* (14), who described abnormal F-choline uptake in a population of 300 patients referred for a relapsing PCa and found 48 cases (16.0%) of tracer uptake not related to PCa.

Lymph nodes are, in our study, the most common site of unusual tracer accumulation, accounting for almost 50% of cases in our population. They largely predominated in the mediastinal, inguinal and axillary areas. Our results support data available in the literature (14,15,18). Most cases of nodal uptake have been considered to be of inflammatory origin, and increased F-choline uptake during inflammation could be related to the activation of macrophages (25). In fact, it has been reported that in inflammatory conditions extracellular signals can activate the transcription of the gene coding for CTL1 (choline transporter-like protein 1), a membrane transporter of choline, in macrophages. Increased CTL1 expression is associated to an increase in phosphatidylcholine synthesis (25). Phosphatidylcholine is

involved in many biochemical pathways in macrophages, including the production of pro-inflammatory cytokines such as TNF- α or IL-6 (25,26). These data could also explain the likely inflammatory uptake that we observed in the frontal sinus of one patient. Finally, alveolar macrophages activation plays a key role in the development of “farmer’s lung” allergic alveolitis, promoting the recruitment of T lymphocytes in the lung parenchyma (27).

F-choline PET/CT revealed diffuse hypermetabolic adenopathies in a patient suffering from an indolent marginal zone B-cell lymphoma. F-choline uptake in different lymphoma subtypes has already been reported (28,29), in connection with tumor cell overexpression of choline kinase alpha (30). Overexpression of choline kinase and phosphorylcholine-cytidyl transferase has also been documented in different subtypes of lung cancer (18,31). In our population, two cases of lung cancer were unknown before F-choline PET/CT and this examination clearly influenced the therapeutic approach for these patients. Based on these results, we believe that it is necessary to establish a definite diagnosis for any hypermetabolic pulmonary lesion on F-choline PET/CT.

We found 3 patients presenting with diffuse or focal F-choline uptake in the thyroid, and all were finally considered as benign diseases. These results are similar to those of Calabria *et al.* (11) who found 2 out of 300 patients with diffuse uptake due to thyroiditis. However, a retrospective study of 368 patients focusing exclusively on abnormal F-choline uptake in the thyroid gland at PET/CT found two cases of thyroid carcinoma out of nine cases of atypical thyroid uptake (32). Case reports also demonstrated that focal uptake of F-choline in the thyroid should raise suspicion for malignancy (33–35). Thus, in agreement with the conclusion of a recent literature review evaluating the prevalence and clinical significance of focal incidental radiolabeled choline uptake in the thyroid gland (36), any abnormal thyroid uptake at F-choline PET/CT should be explored with at least a TSH and calcitonin assay and an ultrasonography.

Three patients presented with atypical adrenal uptake in our cohort, none of them related to a malignant tumor. These data are consistent with the literature (14,15,18). Adrenal uptake may be stimulated by acute stress such as cold exposure prior to examination, which has been shown to increase choline acetyltransferase activity in a rat model (37). Adrenal adenomas can appear hypermetabolic on F-choline PET/CT (38). Of note, one case report has

been published concerning an adrenal metastasis of PCa diagnosed at F-choline PET/CT (39).

Overexpression of choline kinase has been documented in colon cancers (40,41) as well as in colic adenomas (14). As a consequence, a colonoscopy should have been performed in patients demonstrating atypical colic uptake. Unfortunately, none of our patients underwent an endoscopy, but none of them developed a colorectal cancer during follow-up.

Asymmetrical F-choline uptake in salivary glands can be due to asymmetric development of the glands, as frequently observed for the submandibular glands. It may also be due to intraglandular lithiasis which can cause a lack of tracer uptake in the affected gland (42). However, in our case the affected parotid demonstrated a transient enlargement with hypermetabolism, and we speculate that it could have resulted from an acute episode of sialadenitis (43).

Concerning unusual brain uptakes, F-choline uptake has already been reported in meningiomas as well as in glioblastomas or brain metastases (14,44,45). Of note, F-choline uptake was faint in grade II and III gliomas (44). Pathophysiology of increased choline uptake in these tumors is poorly documented and may involve an increase in cell membrane synthesis.

Finally, F-choline uptake in well-differentiated neuroendocrine tumors has been described in various contexts including isolated pulmonary nodule (46) and metastatic mediastinal and cervical lymph nodes from gastro-entero-pancreatic neuroendocrine tumor (47).

Some limitations should be acknowledged in our study. First, this is a retrospective study and not all atypical uptakes can be considered as true incidentalomas. Then, we do not have a pathological proof in most cases, but a definite diagnosis could be established for 17 patients based on biological, imaging and/or pathological data (there is no need for a biopsy when diagnosing a thyroiditis, for example). Among these 17 patients we found a malignant lesion in 6 patients. For the remaining 30 patients, a diagnosis of benign anomaly was reasonably assumed based on clinical and/or imaging follow-up.

Conclusions

Atypical F-choline uptake on PET/CT occurred in 12.8% of our patients (47/368), with only 6 cases of malignant lesion. Despite the fact that most unusual F-choline uptakes are benign, they should be explored in order to not miss a non-PCa.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/qims-19-981>). Dr. AC serves as an unpaid editorial board member of *Quantitative Imaging in Medicine and Surgery*. The other authors have no conflicts of interest to declare.

Ethical Statement: The study was conducted in accordance with the Declaration of Helsinki. This study obtained ethics approval from our Institutional Review Board, with waiver of informed consent for this retrospective study.

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