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Incidental Findings on ^{18}F-Fluorocholine PET/CT for Parathyroid Imaging

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Abstract

Introduction ^{18}F-choline positron emission tomography/computed tomography (PET/CT) is an upcoming imaging technique for the localization of hyperfunctioning parathyroid glands. However, ^{18}F-choline is a nonspecific tracer that also accumulates in malignancies, inflammatory lesions, and several other benign abnormalities. The aim of this study was to determine the occurrence and relevance of incidental findings on ^{18}F-choline PET/CT for parathyroid localization.

Materials and Methods ^{18}F-choline PET/CTs performed in our center for parathyroid localization from 2015 to 2019 were reviewed. Abnormal uptake of ^{18}F-choline, with or without anatomical substrate on the co-registered low-dose CT and also incidental findings on CT without increased ^{18}F-choline uptake were recorded. Each finding was correlated with follow-up data from the electronic medical records.

Results A total of 388 ^{18}F-choline PET/CTs were reviewed, with 247 incidental findings detected in 226 patients (58%): 82 ^{18}F-choline positive findings with corresponding pathology on CT, 16 without CT substrate, and 149 ^{18}F-choline negative abnormalities on CT. Malignant lesions were detected in 10/388 patients (2.6%). Of all 98 detected ^{18}F-choline positive lesions, 15 were malignant (15.3%), concerning 4 metastases and 11 primary malignancies: breast carcinoma ($n = 7$), lung carcinoma ($n = 2$), thyroid carcinoma ($n = 1$), and skin melanoma ($n = 1$).

Conclusion Clinically relevant incidental findings were observed in a substantial number of patients. In 15.3% of the incidental ^{18}F-choline positive findings, the lesions were malignant. These data contribute to better knowledge of ^{18}F-choline distribution, enhance interpretation of ^{18}F-choline PET/CT, and guide follow-up of incidental findings. Attention should especially be paid to breast lesions in this particular patient group with hyperparathyroidism in which women are typically over-represented.

Keywords
- ^{18}F-fluorocholine
- PET/CT
- hyperparathyroidism
- incidental findings

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Introduction

In recent years, ^{18}F-choline positron emission tomography/computed tomography (PET/CT) has been established as a valuable imaging modality for preoperative identification of hyperfunctioning parathyroid glands in patients with hyperparathyroidism, which is a prerequisite for planning of minimally invasive parathyroidectomy.[1,2] Choline is a precursor for the biosynthesis of phosphatidylcholine, an essential component of the cell membrane. After uptake of choline by the cell, it is phosphorylated by the enzyme choline kinase and is retained in the cell. Cells with a high proliferation rate have increased demand for choline due to increased cell wall membrane synthesis that is mainly regulated by increased activity of choline kinase. After radiolabeling choline with a positron emitter such as ^{18}F, it can be used as a PET tracer to visualize tissue with high phospholipogenesis.[3] ^{18}F-choline PET/CT has been proven beneficial in detecting certain types of malignancy, especially prostate cancer, and has also been investigated in several other malignancies such as hepatocellular carcinoma, brain tumors, lung tumors, breast cancer, and genitourinary tumors.[4] However, ^{18}F-choline uptake may also be observed in benign conditions such as parathyroid adenomas, as was initially noticed in a patient scanned for prostate cancer.[5]

Knowledge about various causes of ^{18}F-choline uptake is of major importance for accurate scan interpretation and to recommend appropriate follow-up. Previously published data on ^{18}F-choline PET/CT incidental findings were retrieved from cohorts of patients with prostate cancer.[6,7] However, ^{18}F-choline PET/CT for hyperparathyroidism involves a different population in which, for example, women are over-represented. Also, the part of the body that is imaged is different. Therefore, it is expected that both the type and distribution of incidental findings on these scans are different from the above-mentioned reports. In the present study, a large cohort of patients with hyperparathyroidism who received ^{18}F-choline PET/CT was retrospectively analyzed to assess the frequency and relevance of incidental findings on ^{18}F-choline PET/CT.

Methods

Reports of all ^{18}F-choline PET/CT scans performed for hyperfunctioning parathyroid gland localization between June 2015 and September 2019 were reviewed. All incidental findings on PET or CT were recorded into a database. These findings were correlated with follow-up imaging, histopathological examinations, and clinical follow-up data, retrieved from the electronic patient records. The follow-up period was at least 6 months. Incidental findings were categorized following anatomical localization: thyroid, lung, mediastinum, lymph nodes, breast, upper abdomen, skeleton, and skin. Normal variants, vascular calcifications, and degenerative bone changes on CT were excluded from further analysis. In patients who received more than one ^{18}F-choline PET/CT, only the first scan showing additional findings was included; subsequent scans were used as follow-up data.

Scan Acquisition

PET/CT images were acquired on a Siemens Biograph-16 TruePoint PET/CT camera (Siemens Healthineers, Erlangen, Germany). Dual-time-point images were acquired at 5 and 60 minutes after intravenous injection of approximately 150 MBq ^{18}F-choline, ranging from the temporomandibular joint to the diaphragm. Images were acquired at 480 seconds per bed position with matrix size 256×256 and low-dose CT for attenuation correction using a tube current of 40 to 80 mAs at 100 to 120 kV with CARE Dose 4D dose modulation, collimation of 24×1.2 mm, and a pitch of 0.95. PET images were reconstructed with an iterative three-dimensional method using five iterations, eight subsets, and a Gaussian filter. Patient preparation consisted of hydration with 1 L water and, if applicable, discontinuation of colchicine 48 hours prior to ^{18}F-choline administration. Discontinuation of calcimimetic drugs or other medications was not required.

Statistical Analysis

Normally distributed continuous data were expressed as mean $\pm$ standard deviation and range. Noncontinuous data were expressed as numbers with percentages. The occurrences of incidental findings were calculated as percentages of the whole cohort. The analysis was performed using the Statistical Package for Social Sciences 25 (IBM SPSS Statistics, Chicago, Illinois, United States).

Results

A total of 408 ^{18}F-choline PET/CT scans were performed between June 2015 and September 2019. Twenty were excluded as these were follow-up scans of already included ^{18}F-choline PET/CT scans and were used for follow-up data. The reports of the other 388 scans were reviewed for incidental findings. Patient characteristics of this cohort are listed in ►**Table 1**. The mean follow-up period was

Table 1 Patient characteristics

Characteristic	Value
Age (mean $\pm$ SD [range]) (years)	62 $\pm$ 12 (25–86)
Sex (*n* [%])	
Male	98 (25)
Female	290 (75)
Type of hyperparathyroidism (*n* [%])	
Primary	354 (91)
Secondary	15 (4)
Tertiary	13 (3)
Unclear	6 (2)
PTH (mean $\pm$ SD [range]) (pmol/L) (normal range: 1.3–6.8 pmol/L)	20.3 $\pm$ 29.7 (1.9–339.9)
Serum calcium (mean $\pm$ SD [range]) (mmol/L) (normal range: 2.10–2.50 mmol/L)	2.64 $\pm$ 0.21 (2.01–3.86)

Abbreviations: PTH, parathyroid hormone; SD, standard deviation.

Table 2 Number of incidental findings detected on ^{18}F-choline PET/CT scans for hyperparathyroidism categorized by anatomical localization

Category	Incidental findings		Primary malignancies[a]	Metastases[a]
	^{18}F-choline avid	Non-^{18}F-choline avid		
Thyroid	18	42	1	1
Lung	26	21	2	1
Mediastinum	6	25	0	0
Lymph nodes	6	2	0	1
Breast	10	4	7	0
Upper abdomen	7	47	0	0
Skeleton	22	7	0	1
Skin	3	1	1	0
Total	98	149	11	4

Abbreviation: PET/CT, positron emission tomography/computed tomography.
[a]All detected primary malignancies and metastases were ^{18}F-choline avid.

31 months (range: 6–57). A total of 247 incidental findings were observed in 226 patients (58%) (►**Table 2**). There were 82 ^{18}F-choline positive findings with accompanying abnormalities on CT in 70 patients (18%), 16 ^{18}F-choline positive findings without evidence of pathology on CT in 15 patients (4%), and 149 CT abnormalities without pathological ^{18}F-choline uptake in 130 patients (34%). Of all 98 ^{18}F-choline positive incidental findings, 15 were malignant (15.3%) concerning 11 primary malignancies and 4 metastases. These malignant lesions were detected in 10 patients (2.6%). None of the ^{18}F-choline negative CT findings were proven to be malignant during follow-up.

Thyroid

In 20 patients, a solitary thyroid nodule was detected, of which 10 nodules showed increased ^{18}F-choline uptake. Histology was acquired from six ^{18}F-choline-avid lesions, showing one papillary thyroid carcinoma **(►Fig. 1)**, one metastasis of renal cell carcinoma, and four benign etiologies (colloid cysts and hyperplastic nodules). Two of the ^{18}F-choline-avid nodules and five of the nodules without uptake were not suspicious on follow-up ultrasonography. No adequate follow-up data were available for the other nodules. Multinodular goiter with irregular ^{18}F-choline uptake was described in 35 patients and a diffusely increased uptake was seen in five patients (2 hyperthyroid patients, 2 hypothyroid patients, and 1 patient with normal thyroid function).

Lung

Increased ^{18}F-choline in the lungs was observed in 26 patients; in two of these patients no CT substrate was visible and no follow-up was available; in 18 of these patients the co-registered CT and follow-up imaging revealed infectious infiltrates and in 6 of the 26 patients this concerned uptake in nodular lesions (mean diameter of 10 mm, range: 6–19 mm). Of these, one was confirmed as primary (squamous) lung carcinoma following resection (►**Fig. 2**), one was regarded as lung carcinoma based on imaging and treated by external radiation therapy and one was regarded as pulmonary metastasis in a patient with known metastasized renal cell carcinoma. The other three patients were, according to follow-up imaging with CT or ^{18}F-fluorodesoxyglucose (FDG) PET/CT, diagnosed with inflammatory lung disease. Lung nodules without ^{18}F-choline uptake were detected in 21 patients (mean diameter of 8 mm, range: 6–13 mm). None were suspicious for malignancy on follow-up imaging with CT ($n = 13$), FDG PET/CT ($n = 2$), or chest X-ray ($n = 3$); no follow-up was available for the other three patients.

Mediastinum

Increased ^{18}F-choline uptake in lesions in the anterior mediastinum was detected in four patients. Three of those were

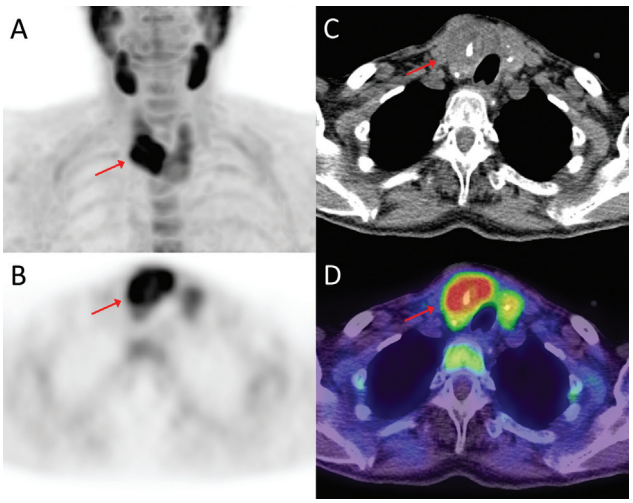

Fig. 1 Maximum-intensity projection of ^{18}F-choline positron emission tomography (PET) (**A**) and transaxial views of the thyroid gland on PET (**B**), computed tomography (CT) (**C**), and PET/CT fusion images (**D**) showing intense ^{18}F-choline uptake in the enlarged right thyroid lobe (*arrows*, maximum standardized uptake value 8.2). Histopathologic examination revealed a pT3a papillary thyroid carcinoma.

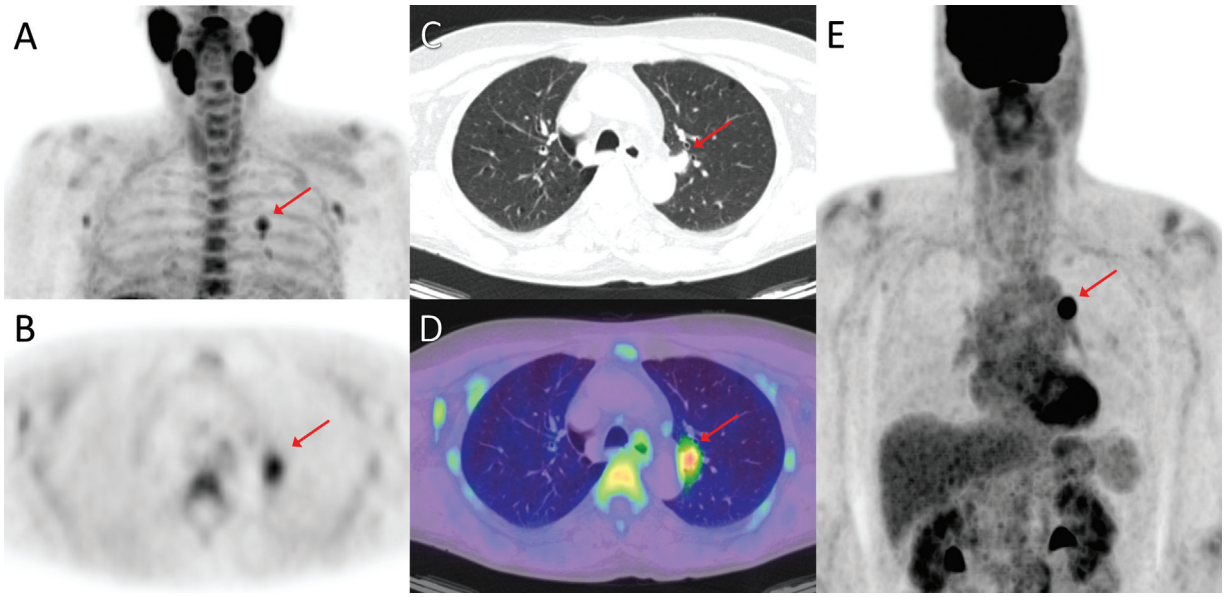

Fig. 2 Maximum intensity projection (MIP) of ^{18}F-choline positron emission tomography (PET) (**A**) and transaxial views of the lungs on PET (**B**), computed tomography (CT) (**C**), and PET/CT fusion images (**D**) showing focal ^{18}F-choline uptake in a left upper lobe lung nodule (*arrows*, diameter: 1.8 cm, maximum standardized uptake value [SUVmax]: 3.6). MIP of ^{18}F-fluorodesoxyglucose (^{18}F-FDG) PET (**E**) showing intense FDG-avidity (*arrow*, SUVmax 9.2) without evidence for metastases. Histopathologically examination after lobectomy revealed pT1b squamous cell lung carcinoma.

under 30 years of age and since follow-up imaging with CT or magnetic resonance imaging (MRI) showed involution of the lesions, the uptake was regarded as physiological uptake in residual thymus gland. In the other, 50-year-old, patient the lesion was not suspicious for malignancy on a follow-up ^{18}F-FDG PET/CT but no certain diagnosis was established.

Increased ^{18}F-choline uptake in the esophagus was seen in two patients, one due to a candida infection and one to inflammation associated with bulimia nervosa. The esophagus of one patient showed achalasia on CT and an esophageal hiatus hernia was found in 24 patients.

Lymph Nodes

In six patients, increased ^{18}F-choline uptake was detected in enlarged lymph nodes (> 1 cm). Another two patients presented with enlarged lymph nodes without ^{18}F-choline uptake. In one of the patients with ^{18}F-choline-avid enlarged lymph nodes, breast cancer metastasis was histologically proven. No metastases, malignant lymphomas, or granulomatous lymphadenopathies were diagnosed in the other patients during follow-up with CT ($n = 4$), ultrasonography ($n = 2$), or histopathological evaluation ($n = 1$).

Breast

Focally increased ^{18}F-choline uptake in the breasts was detected in 10 patients (►**Fig. 3**). Breast malignancy was histologically proven in seven patients (3 patients with invasive ductal carcinoma, 2 patients with invasive lobular carcinoma, 1 patient with invasive carcinoma of no special type, and 1 patient with ductal carcinoma in situ in the left breast and mucinous carcinoma in the right breast). Follow-up imaging with mammography or ultrasonography in the other three patients did not reveal suspicious lesions and no histopathology was acquired. CT abnormalities without ^{18}F-choline uptake were detected in four patients (benign fibrosis in one patient and fibroadenomas in three patients).

Upper Abdomen

In six patients, increased uptake of ^{18}F-choline was observed in adrenal adenomas with a typical benign appearance on CT (►**Fig. 4**). Diffusely increased ^{18}F-choline uptake was observed in a cirrhotic liver in one patient. Furthermore,

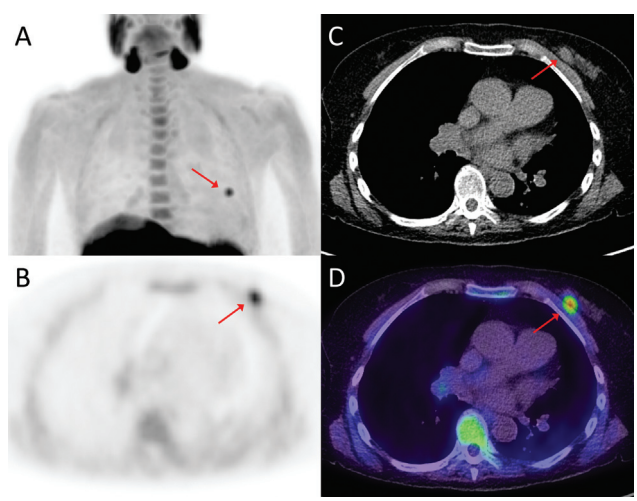

Fig. 3 Maximum intensity projection of ^{18}F-choline positron emission tomography (PET) (**A**) and transaxial views of the breasts on PET (**B**), computed tomography (CT) (**C**), and PET/CT fusion images (**D**) showing focal ^{18}F-choline uptake in a nodular mass in the left breast (*arrows*, diameter: 1.6 cm, maximum standardized uptake value: 4.5). Histopathologic examination revealed a pT1c infiltrating lobular breast carcinoma.

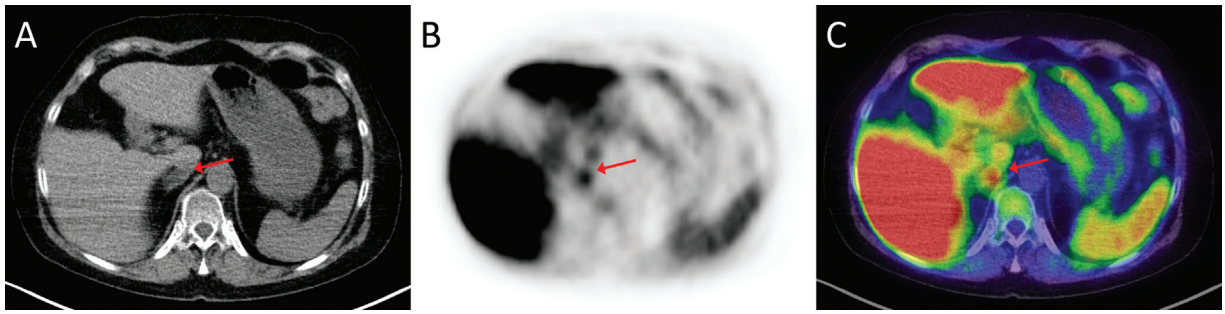

Fig. 4 Transaxial views of the upper abdomen on computed tomography (CT) (**A**), positron emission tomography (PET) (**B**) and PET/CT fusion images (**C**) showing focal ^{18}F-choline uptake in a nodular mass of the right adrenal gland (*arrows,* maximum standardized uptake value: 6.6) and a typical aspect of an adrenal adenoma on CT (radiodensity of -5 Hounsfield units).

multiple ^{18}F-choline negative findings were identified on CT, such as benign liver lesions ($n = 28$, e.g., cysts, hemangiomas), splenic cyst ($n = 1$), adrenal myelolipoma ($n = 1$), benign kidney abnormalities ($n = 6$, e.g., cysts, cortical atrophy), and gallstones ($n = 11$).

Skeleton

A physiological, diffuse uptake of ^{18}F-choline was regularly seen in the bone marrow. In 12 patients, fractures were detected of which 8 showed an increased uptake of ^{18}F-choline (mainly rib fractures and vertebral compression fractures). ^{18}F-choline-avid degenerative changes were observed in four patients, a ^{18}F-choline-avid osteoid osteoma in one patient and vertebral hemangiomas with decreased ^{18}F-choline uptake in three patients. In two patients, both diagnosed with tertiary hyperparathyroidism, a diffusely increased uptake of ^{18}F-choline was noticed in the skeleton, accompanied with diffuse sclerosis on CT.[8]

Intensely increased ^{18}F-choline uptake was detected in seven patients (average maximum standardized uptake value of 8.7, range: 4.2–18.1). Two patients did not receive follow-up. In one patient, the uptake was related to metastases of breast carcinoma. In three patients, follow-up MRI did only show degenerative changes but no signs of malignancy. In the last patient, the lesions were negative on ^{18}F-FDG PET/CT and follow-up ^{18}F-choline PET/CT showed evident decrease of uptake without any intervention (►**Fig. 5**). No certain cause for the increased ^{18}F-choline uptake could be established.

Skin

Two focally ^{18}F-choline-avid cutaneous lesions were detected. One lesion proved to be melanoma upon histopathological evaluation, published earlier in a case report.[9] No follow-up of the other lesion was available. More diffusely increased cutaneous ^{18}F-choline uptake was observed in a patient with erysipelas and multiple subcutaneous lesions without ^{18}F-choline uptake in another patient resembled sebaceous cysts.

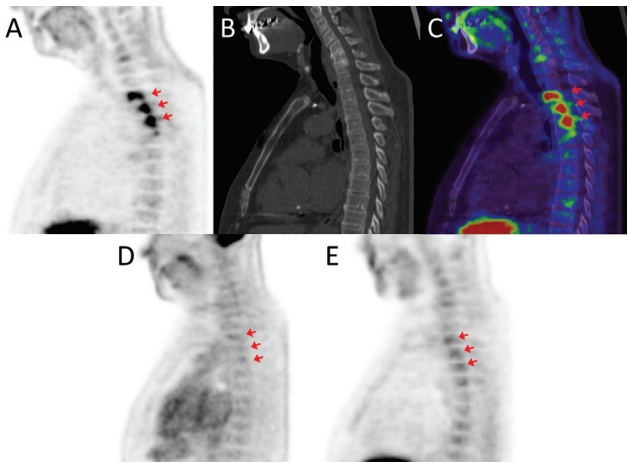

Fig. 5 Sagittal views of ^{18}F-choline positron emission tomography (PET) (**A**), computed tomography (CT) (**B**) and PET/CT fusion images (**C**) showing an example of nonspecific intense bone uptake (*arrows,* thoracic vertebrae 2–4, maximum standardized uptake value: 18.1). Additional ^{18}F-fluorodesoxyglucose (^{18}F-FDG) PET (**D**) did not show signs of malignancy and follow-up ^{18}F-choline PET (**E**) 3 months later showed a near normalization of uptake. The cause of the increased ^{18}F-choline uptake was not elucidated.

Discussion

In the past decades, ^{18}F-choline has been extensively used in PET/CT imaging for prostate cancer as a valuable alternative to ^{18}F-FDG, due to its capability to accumulate in lesions with a low rate of glucose metabolism. However, choline is also known to accumulate in various other malignancies and has been investigated for several tumors, with variable results.[4] The reported variety of secondary malignancies detected on choline PET/CT for prostate cancer imaging is extensive and comprises malignancies of the thyroid, lung, esophagus, colon, kidney and bladder, as well as melanoma, lymphoma, glioma, multiple myeloma, pleural mesothelioma, and invasive thymoma.[7,10–12] In larger prostate cancer patient cohorts, secondary malignancies were discovered on choline PET/CT in 10/1000 (1%) patients by Calabria et al, in 7/454 (1.5%) patients by García et al, and in 2/77 (2.6%) by How Kit et al[7,10,13] A study specifically focused on incidental ^{18}F-choline uptake in the thyroid gland found two malignant thyroid lesions in a cohort of 368 patients (0.5%).[14]

In the present study, ^{18}F-choline PET/CT scans were analyzed that were performed for the localization of hyperfunctioning parathyroid glands in patients with hyperparathyroidism. Of all 98 ^{18}F-choline positive incidental findings,

15 were malignant (15.3%), newly detected in 10/388 patients (2.6%). The most frequently found malignancy was breast cancer, which was detected in 7 patients. In two of those breast cancer patients, a coincidental second primary tumor was detected (one thyroid carcinoma and one skin melanoma) and in another breast cancer patient metastases to the bone and lymph nodes were detected. Lung cancer was diagnosed in two patients and renal cell carcinoma metastases to the lung and thyroid gland in another patient. Several case reports of incidental findings on ^{18}F-choline PET/CT for hyperparathyroidism are available; however, to our knowledge, no comparable patient cohort has been studied. The population scanned for hyperparathyroidism often consists of younger patients and relatively more women are represented, as a result of a female-to-male prevalence ratio of approximately 2.5 to 1.[15] In the current study, this ratio was 3 to 1, which explains the relatively high number of incidentally found breast malignancies. Distribution and pitfalls of ^{18}F-choline in female patients were studied in a small cohort of 21 breast cancer patients, but besides uptake in breast cancer and metastases, only benign incidental findings were found.[16] Another difference with earlier studied prostate cancer cohorts is the scan range, which for parathyroid PET/CT typically is limited to the level of the diaphragm. One research group purposely scanned to the level of the pelvis in men and the liver in women, in order not to miss prostate, breast, or hepatocellular carcinoma, but in their small cohort, none of these were detected.[17,18] Furthermore, the risk of a second primary malignancy in cancer patients is higher than the risk of cancer among the general population.[19] In contrast, the present study concerns PET/CT performed for benign pathology.

Apart from choline uptake in malignancies and physiologic uptake in liver, spleen, pancreas, kidney, bone marrow, and salivary glands, ^{18}F-choline uptake can also be observed in several benign conditions.[6] In the aforementioned study by Calabria et al, ^{18}F-choline uptake was detected in inflammation-related findings in 80/1000 patients (e.g., lymph nodes, skin, thyroid, lungs), benign tumor uptake in 26/1000 patients (e.g., meningiomas, colon adenomas, thymomas), uptake associated with hypermetabolism in 7/1000 patients (e.g., hyperthyroidism, adrenal adenomas), and nonspecific uptake in 46/1000 patients (abnormal uptake without clinical evidence, laboratory tests, or correlative imaging).[7] In a retrospective study on choline PET/CT in 2,933 men with prostate cancer, parathyroid adenoma was diagnosed in 13 patients.[20] In the present study, incidental ^{18}F-choline uptake with a high likelihood of benign etiology was seen in 78/388 patients (20%) and the most common cause of increased ^{18}F-choline uptake was inflammation. In inflammatory tissue, ^{18}F-choline is mainly accumulated in macrophages, as was demonstrated in mice by Wyss et al,[21] to increase phosphatidylcholine biosynthesis that primes the macrophages to respond appropriately to immune stimuli.[22]

Several patients in the studied cohort showed intense osseous uptake of ^{18}F-choline without a clear explanation despite thorough follow-up. Since literature also provides no clues regarding the etiology of those lesions, these are considered nonspecific. Degenerative changes have been shown to accumulate ^{18}F-choline, probably due to inflammation.[23] Moreover, we hypothesize that occult (micro) fractures could lead to increased ^{18}F-choline uptake. Also, some benign bone lesions have been shown to demonstrate uptake, such as fibrous dysplasia.[24] Besides known uptake in bone metastases from prostate carcinoma and other malignancies, uptake of ^{18}F-choline has also been described in multiple myeloma and various primary bone tumors.[4,25,26]

A total of 154 findings without increased ^{18}F-choline uptake were detected on the co-registered low-dose CT in 134 patients (35%). In the literature, a variable frequency of incidental findings on low-dose CT has been reported for PET/CT with other radiopharmaceuticals, such as ^{18}F-FDG, ^{18}F-sodium fluoride, and ^{13}N-ammonia, ranging from 51 to 93%, and with potentially clinical significance in 8 to 23% of patients.[27–29] In case of incidentally detected abnormalities on the co-registered low-dose CT, it is advised to follow radiological guidelines such as recommendations of the Fleischner Society or the American College of Radiology incidental findings committee.[30,31]

Limitations of this study are its retrospective design and the relatively short follow-up period for some patients. Also, in several patients with additional findings no follow-up imaging or histopathological examination was available; therefore, the number of detected malignancies may be underestimated. One lung carcinoma and one pulmonary metastasis were not biopsied but treatment was initiated based on the convincing imaging results only; all other reported malignancies were histopathologically proven.

To summarize, increased ^{18}F-choline uptake during PET/CT parathyroid imaging resulted in a variety of incidental findings in 58% of the patients and malignancies were detected in 2.6%. The chance of an incidental ^{18}F-choline positive finding to be malignant was 15.3%. In general, we advise additional imaging or biopsy for all focal ^{18}F-choline uptake in the breasts or thyroid gland. Also, focal pulmonary uptake should warrant biopsy or follow-up imaging. Cutaneous uptake should be correlated with at least visual examination of the skin. Moderate ^{18}F-choline uptake in lymph nodes is frequently benign or physiological; however, no maximum uptake value can be given to discriminate pathological lymph nodes based on the results of this study. In any case, patients with enlarged lymph nodes or nodes with a typical pathologic distribution pattern should be further analyzed. Focal uptake in the skeleton can be nonspecific and, in the absence of a corresponding benign lesion on CT, further analysis is advised to exclude malignancy. Noncholine-avid CT abnormalities should be classified according to radiological guidelines.

Conclusion

In this study, a substantial number of incidental findings were observed in ^{18}F-choline PET/CT scans performed for parathyroid adenoma localization, including malignancies in 2.6% of the patients. Since a large number of patients scanned for hyperparathyroidism are women, relatively high

numbers of breast cancer were incidentally detected. These data contribute to better knowledge of both physiological and pathological ^{18}F-choline uptake in the human body and therefore enhance interpretation of ^{18}F-choline PET/CT and guide follow-up of incidental findings.

Informed Consent

All patients gave written informed consent for the use of their anonymized data for scientific purposes. Besides the standard imaging protocol and clinical management, no additional measurements or actions affecting the patient were performed. The study was approved by the institutional research department and performed in accordance with the Declaration of Helsinki. Approval of the local ethical committee for the present study was not necessary since the study does not fall within the scope of the Dutch Medical Research Involving Human Subjects Act (section 1.b WMO, 26th February 1998).

Conflicts of Interest

None declared.

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