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ORIGINAL ARTICLE

18F-choline PET/CT incidental thyroid uptake in patients studied for prostate cancer

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Abstract

Purpose Thyroid incidental uptake is defined as a thyroid uptake incidentally detected by imaging examinations performed for non-thyroid disease. The aim of this study was to establish the prevalence and the pathological nature of focal thyroid incidental uptake (FTIU) among patients studied with 18F-choline-PET/CT.

Materials and methods We retrospectively evaluated 368 patients who performed 18F-choline-PET/CT between June 2016 and August 2018. The PET images were analyzed visually and semi-quantitatively by measuring the maximum standardized uptake value (SUVmax) and the mean SUV (SUVmean) of the thyroid gland and of the FTIU; every focal thyroid uptake deviating from physiological distribution and background was considered FTIU. Final diagnosis of FTIU was obtained by cytological or histological examination after surgery.

Results The average SUVmax and SUVmean of thyroid gland in population were 3 and 1.8. Among 368 patients, FTIU was identified in nine cases (2.4%) and eight underwent further investigations to determine the nature. Two FTIU were classified as malignant (thyroid carcinoma), whereas five were benign (three nodular hyperplasia, one follicular adenoma, one Hurtle cell adenoma) and one indeterminate at cytological examination. In malignant lesions, average SUVmax was 9.6 and 4.5, respectively, while average SUVmean was 5.3 and 2.9, respectively. Average SUVmax and SUVmean of benign lesions were 4.9 and 3.2 and of the indeterminate lesion 5 and 3, respectively.

Conclusions 18F-choline-PET/CT FTIU may be a relevant diagnostic reality, which requires further investigations and affects management, especially considering that, despite being mainly benign, also malignancy is possible.

Keywords Incidentaloma · PET/CT · 18F-choline · Thyroid

Introduction

Thyroid incidental uptake is defined as a thyroid uptake newly and incidentally detected by imaging techniques performed for an unrelated purpose and in particular for non-thyroid diseases [1, 2].

Focal thyroid incidental uptake (FTIU) has been previously described, especially for 18-fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT); often it causes a management dilemma for the referring clinicians, because it needs further investigations to clarify its nature [3]. Incidental thyroid uptake can be diffuse or focal: diffuse uptake is usually encountered in the presence of inflammatory conditions like thyroiditis or Grave's disease, while focal uptakes usually refer to thyroid nodules [4]. The pooled prevalence of 18F-FDG FTIU ranged from 1 to 2.46% and the pooled risk of malignancy considering histology as reference standard ranged from 33.2 to 37% [3].

On the other hand, to date, the prevalence and clinical significance of incidental radiolabelled choline uptake in the thyroid gland is not widely analysed, and only case reports were described in recent literature [5–15]. Usually thyroid has a physiological moderate diffuse uptake in choline PET/CT [16, 17] and FTIU are rare events.

Our aim was to retrospectively analyse in a consecutive cohort of patients, who underwent 18F-choline PET/CT for prostate cancer, the prevalence and the pathological nature of 18F-choline FTIU.

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Table 1 Main features of eight patients with thyroid incidentalomas

Case	Age	Site	SUVmax	SUVmean	Final diagnosis
1	56	Right lobe	4	2.5	Nodular hyperplasia (TIR2)
2	71	Left lobe	9.6	5.3	Tall cells var papillary thyroid carcinoma
3	68	Right lobe	4.2	3.1	Nodular hyperplasia (TIR2)
4	71	Left lobe	7.2	4.9	Nodular hyperplsia (TIR2)
5	74	Right lobe	4.5	2.9	Papillary thyroid carcinoma
6	63	Right lobe	5	3	Indeterminate (TIR3a)
7	78	Left lobe	4.2	3.2	Follicular adenoma
8	75	Isthmic lobe	4.8	3.1	Hurtle cell adenoma

Materials and methods

We have retrospectively evaluated 368 patients who underwent 18F-choline PET/CT for prostate cancer, both for staging or restaging purposes, from June 2016 to September 2018. Average age ± standard deviation was 69 ± 10 (range 47–89 years).

All patients underwent a 18F-choline PET/CT using a standard activity of 3–4 MBq/kg administered intravenously, and was acquired 60 min after injection on a Discovery ST or 690 PET/CT tomograph (General Electric) with standard CT parameters (80 mA, 120 kV without contrast; 3 min per bed-PET-step of 15 cm). The reconstruction was performed in a 128 × 128 matrix and 60 cm field of view. The PET images, from the pelvis to the vertex, were analyzed visually and semi-quantitatively by measuring the maximum standardized uptake value (SUVmax) and the mean SUV (SUVmean) of the thyroid gland and focal uptake. SUV was expressed as SUV-body weight (SUVbw in g/ml) and automatically calculated by software (Volumetrix for PET/CT; Xeleris Functional imaging workstation; GE) on the basis of the following parameters: weight of the patient expressed in kilograms; height expressed in centimeters; tracer volume expressed in milliliters; radioactivity at injection time expressed in megabecquerels (MBq); post injection activity in the vial expressed in MBq; injection time; starting time acquisition; decay half-time of the radioisotope. The patients were instructed to void before imaging, no oral or intravenous contrast agents were administered or bowel preparation applied for any patient and a written consensus was obtained before studies. The readers had knowledge of the clinical history, and every focal tracer uptake deviating from physiological distribution and background was considered as suggestive of incidentaloma. No specific SUVmax cut-off value was considered to discriminate focal incidental uptake or physiological activity but only the deviation from physiological distribution, background, blood-pool or from the normal tissue activity.

The final diagnosis of FTIU was obtained by cytological examination performed after ultrasonography-guided fine-needle aspiration in four cases, or by histological examination after surgery in the four cases.

Statistical analysis

The numerical variables were described as mean, standard deviation, minimum, and maximum. The descriptive analysis of categorical variables comprised the calculation of simple and relative frequencies.

Prevalence of malignancy of FTIU was calculated (prevalence = number of patients with thyroid incidental uptake/number of male patients evaluated with PET/CT × 100).

Results

Average SUVmax and SUVmean of thyroid gland in patients without FTIU were 3 ± 1 (range 1.1–5) and 1.8 ± 0.6 (0.8–3.2), respectively. A FTIU was identified in nine (2.4%) patients. Four (44%) cases of FTIU were localized in the right lobe, four (44%) in the left and one (12%) in the isthmic region. Among the nine cases of FTIU, eight underwent further investigations to determine the nature of the focal uptake (Table 1). Five were benign, two were malignant and one was indeterminate at cytological examination (in this case a differential diagnosis between follicular adenoma and carcinoma in the absence of histological examination was impossible). Among the two cases of FTIU, which resulted in malignant at histological examination after surgery, one was a papillary thyroid carcinoma (pT2 acc. AJCC 8th edition) and the other was tall-cells variant papillary carcinoma (pT1bN0 acc. AJCC 8th edition) (Fig. 1). SUVmax values of the two malignant lesions were 9.6 and 4.5, and SUVmean 5.3 and 2.9, respectively. Among the five patients with benign FTIU, three were classified as hyperplasic nodules (Fig. 2), one as follicular adenoma, and one as Hurtle cell adenoma (Fig. 3). The average SUVmax of benign lesions was 4.9 and average SUVmean 3.2. There was only one FTIU classified as indeterminate at cytological examination (TIR3a) with a SUVmax of 5 and SUVmean of 3.

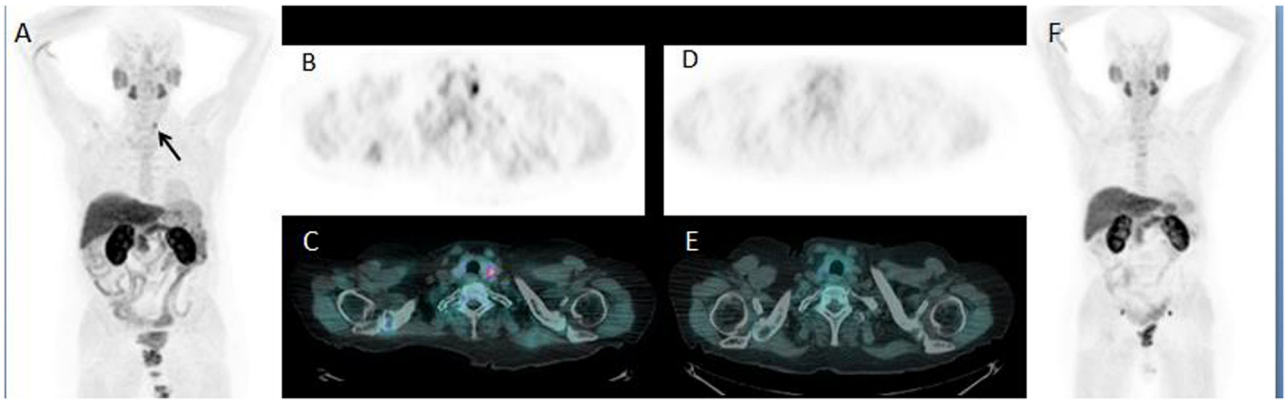

Fig. 1 A representative case of focal thyroid uptake with final diagnosis of tall cells variant papillary thyroid carcinoma (case no. 2 of Table 2). Maximum intensity projection (MIP) **a** showing the presence of an increased choline uptake in left side of the head, axial PET **b**, and PET/CT fused images **c** showing a focal thyroid uptake corresponding to a thyroid nodule in the left lobe with a SUVmax of 9.5 and SUVmean of 5.3. 18F-choline PET/CT after thyroidectomy detecting no lesions in the neck at axial PET **d**, PET/CT images **e**, and MIP **f**

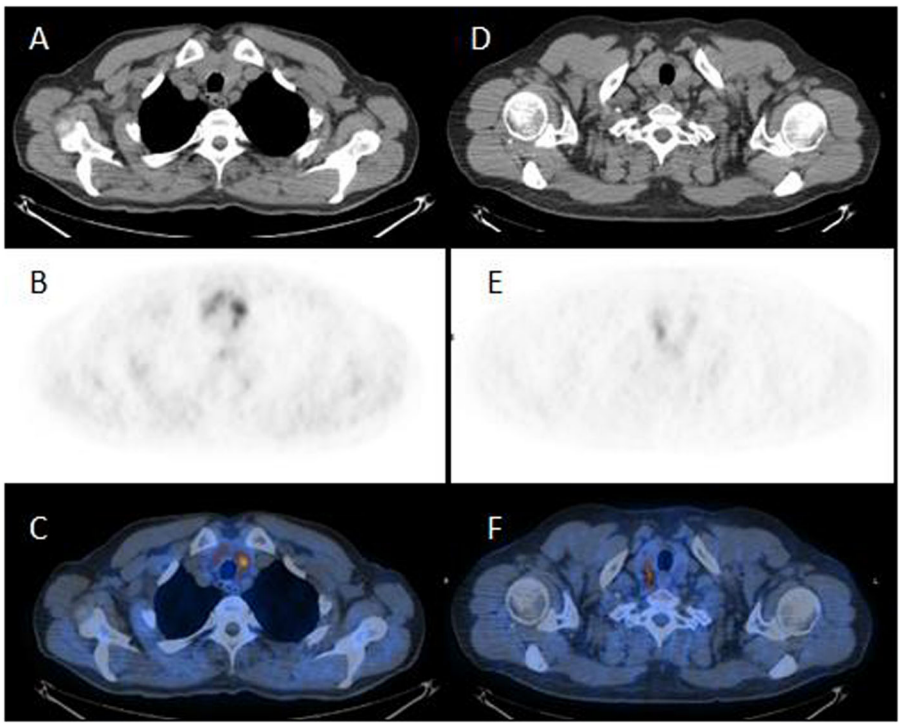

Fig. 2 Two examples of thyroid incidentalomas detected on 18F-choline PET/CT with a final diagnosis of nodular hyperplasia. A 71-year old man (case no. 4) previously treated with radiation therapy for a prostate cancer undergoing choline PET/CT for suspected disease recurrence: axial CT **a**, PET **b**, and PET/CT **c** images showing a focal area of increased 18F-choline uptake in the left thyroid lobe. A 68-year old man (case no. 3) studied for staging purpose: axial CT **d**, PET **e**, and PET/CT **f** images showing a focal area of increased 18F-choline uptake in the right thyroid lobe

Discussion

Choline is a precursor in the biosynthesis of phosphatidylcholine and has been demonstrated to be very useful for the evaluation of patients affected by prostate cancer. An increased cell membrane choline metabolism is not specific for prostate cancer; in fact it has been demonstrated that it can also increase in other pathological conditions, both oncological and non-oncological [18–22]. For example, the use of choline PET/CT has been demonstrated to be useful in patients with primary hyperparathyroidism [21], and considering the near anatomical localization between thyroid gland and parathyroid glandes, an in-depth analysis of thyroid bed seems to be essential. Thus, a proper interpretation of choline thyroid uptake is fundamental; in our analysis, we have defined FTIU every focal tracer uptake deviating from physiological distribution and background.

The consolidation of 11C- and 18F-choline PET/CT as useful tools to evaluate prostate cancer patients in the presence of biochemical recurrence has raised the level of experience on this functional imaging modality and has led to a higher rate of detection of incidental malignant lesions

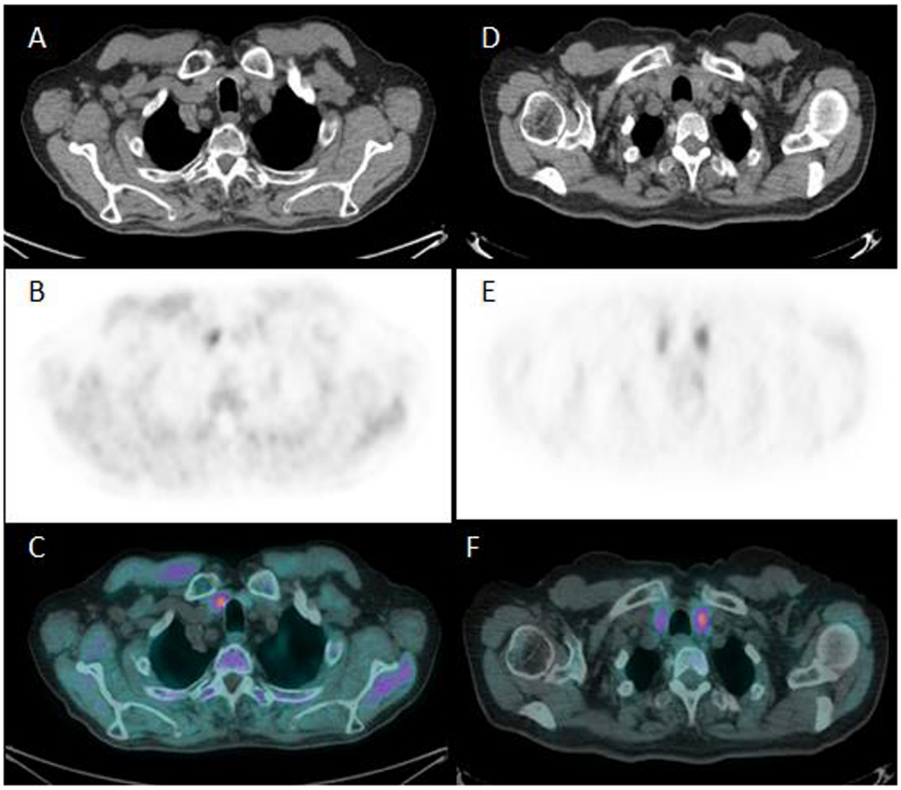

Fig. 3 A 63-year old man (case no.6) with a focal thyroid choline uptake in the right thyroid lobe at axial CT **a**, PET **b**, and PET/CT **c** images then diagnosed as indeterminate at cytological examination. A 78-year old man (case no.7) with a diffuse thyroid uptake and a focal area of increased choline uptake in left lobe at axial CT **d**, PET **e**, and PET/CT **f** images, finally classified as follicular adenoma

in several organs, possibly modifying clinical management and treatment options [23].

As aforementioned, thyroid gland may show a mildly increased uptake on choline PET but it is not clear whether there is any relationship between this finding and the presence of a pathologic or physiologic condition [16]. Similar to 18F-FDG, the incidental diffuse uptake pattern of 18F-choline in the thyroid gland has been already described and often correlated to thyroiditis [24]. In our study, average SUVmax and SUVmean of thyroid gland on 18F-metylcholine PET/CT was described as 2.7 ± 0.74 and 1.87 ± 0.51, respectively[17]; these values are similar to ours (3 and 1.8, respectively). These evidences underlined that thyroid is an endocrine gland with physiological moderate choline uptake.

The potential relationship between differentiated thyroid cancer and choline uptake, especially in evaluating persistence or recurrence of disease in patients affected by high-risk differentiated thyroid cancer and inconclusive or negative 18F-FDG PET/CT findings, has been already studied with promising evidences [5, 25].

FTIUs are a challenge for the clinicians due to their different nature: some of these findings are benign; nevertheless, the risk of malignancy is not negligible [26]. Thyroid incidental findings can be detected in different imaging modalities, such as neck ultrasonography, CT, magnetic resonance imaging or PET/CT. Several studies have reported the prevalence and the malignancy risk of thyroid incidentalomas detected by 18F-FDG PET/CT [3, 26]. The detection of focal thyroid incidental uptake in 18F-FDG PET-CT scan is a well-known issue with an estimated incidence of 2–4% and a risk of carcinoma of 20–30%. In our centre [27], we showed a prevalence of 1.4% (161/11278 patients) of focal thyroid incidental uptake considering 18F-FDG PET/CT, a value lower than what we have identified in this study using choline PET/CT, but probably due to the different period analyzed and because choline PET/CT analyse only male population. Despite this, the percentage of malignant lesions identified with 18F-FDG-PPET/CT (34%) and with choline PET/CT (25%) are not so different.

The incidence of 18F-choline FTIU, as well as the nature of FTIU, has not been widely analyzed and not well established. FTIU in choline PET/CT can have different biological substrates: both benign [7, 8, 10, 11] and malignant [6, 12–15] diseases are described in the literature (Table 2). Moreover, Wu et al. [5] have compared 18F-FDG and 11C-choline detection rate in four patients with thyroid cancer showing that malignant thyroid carcinomas may take up radiolabelled choline due to an increased choline metabolism.

In our study, FTIUs were related to both malignant and benign disease; we found two cases of thyroid cancer with high SUV values, but, due to the low number of cases, it is

Table 2 Summary of studies in the literature about focal thyroid incidentaloma detected by choline PET

First author	Year of publication	Radiotracer	No. of cases	Final diagnosis	SUVmax
Paone G	2013	18F-choline	1	Hurtle cell adenoma	NA
Garcia Vicente AM	2013	18F-choline	1	Nodular hyperplasia	NA
Eccles A	2014	18F-choline	1	Thyroid lymphoma	NA
Treglia G	2014	18F-choline	1	Benign nodule	8
Hodolic M	2014	18F-choline	2	1 adenoma;1 papillary carcinoma	3.3NA
Aziz AL	2015	18F-choline	1	Oncocytic adenoma	NA
Lalire P	2016	18F-choline	1	Oxyphilic papillary thyroid carcinoma	NA
Outtara A	2017	11C-choline	1	Encapsulated follicular variant of papillary carcinoma	NA
Thanseer NTK	2017	18F-choline	1	Papillary carcinoma	NA
Ciappuccini R	2018	18F-choline	1	follicular variant of papillary carcinoma	NA

NA not available

not possible to hypothesize a threshold of SUV to discriminate between benign and malignant lesions, despite malignant lesions seeming to be more choline-avid.

The limitations of our study are the retrospective nature of the study design, a population consisting only of males, and the relatively low number of patients analyzed.

In conclusion, 18F-choline PET/CT FTIUs, despite being rare, are a diagnostic reality, which requires further investigations and clinical management, especially considering that, despite mainly benign, approximately one-fourth of focal thyroid uptakes are malignant.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required.

Informed consent Informed consent was obtained from all individual participant included in the study.

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