



PET/CT with ^{18}F -choline: Physiological whole bio-distribution in male and female subjects and diagnostic pitfalls on 1000 prostate cancer patients^{☆,☆☆,★}



^{18}F -choline PET/CT bio-distribution and pitfalls. A southern Italian experience

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ABSTRACT

Introduction: The $^{11}\text{C}/^{18}\text{F}$ -choline is a PET/CT radiopharmaceutical useful in detecting tumors with high lipogenesis. $^{11}\text{C}/^{18}\text{F}$ -choline uptake can occur in physiological conditions or tumors. The knowledge of its bio-distribution is essential to recognize physiologic variants or diagnostic pitfalls. Moreover, few information are available on the bio-distribution of this tracer in female patients. Our aim was to discuss some documented ^{18}F -choline PET/CT pitfalls in prostate cancer patients. Our secondary aim was to describe the ^{18}F -choline bio-distribution in the female body. **Methods:** We collected diagnostic pitfalls in three PET centers examining 1000 prostate cancer by ^{18}F -choline PET/CT. All pitfalls were ensured by follow-up, imaging and/or histology. We also performed whole body ^{18}F -choline PET/CT in 5 female patients.

Results: 169/1000 (16.9%) patients showed pitfalls not owing to prostate cancer. These findings were due to inflammation, benign tumors while, in 1% of examined patients, a concomitant neoplasm was found. In the female body, the breast showed low physiological uptake.

Conclusions: The accurate knowledge of ^{18}F -choline PET/CT bio-distribution and diagnostic pitfalls is essential. Correlative imaging and histological exam are often necessary to depict pitfalls. In women, the uptake in the breast is due to the physiological gradient of ^{18}F -choline uptake in the exocrine glands.

Advances in knowledge: Our results confirm the possibility of ^{18}F -choline uptake in several diseases other than prostate cancer. However, our experience was acquired on a large population and shows that a conspicuous amount of ^{18}F -choline diagnostic pitfalls are easily recognizable and attributable to inflammation. A new advance in knowledge is the minimal difference in terms of physiological tracer bio-distribution between male and female patients.

Implications for patient care: The knowledge of the physiological bio-distribution and of the potential pitfalls linked of a tracer could help physicians to choose the best diagnostic and therapeutic approaches for a better patient quality of life.

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1. Introduction

The $^{11}\text{C}/^{18}\text{F}$ -choline has become a useful positron emission tomography/computed tomography (PET/CT) radiopharmaceutical, for its capability to be enhanced in neoplastic lesions with low rate of glucose metabolism, as for prostate cancer (PC) cells. The choline is a marker of lipogenesis, being the precursor of phosphatidylcholine, an important element of the cell membrane. The biosynthesis of the cell membrane is particularly increased in PC, inducing high uptake of the tracer [1].

Several studies, mostly developed in western Europe and USA, have been depicted PET/CT with radiolabeled choline as a useful technique in the management of PC patients [2–4], especially in relation to absolute PSA and PSA kinetics value at the time of the scan [5].

Unfortunately, an intrinsic property of this tracer is the tendency to be enhanced in benign conditions and malignant diseases other than PC, due to the high rate of cell membrane synthesis, inducing a rise of intra-cellular lipogenesis. Similarly to the ^{18}F -FDG, the variation of the tracer uptake can be due to physiological and inflammatory effects or to neoplastic processes [6].

Various groups of authors have been described the potential false positive cases, physiological variants and diagnostic pitfalls linked to the variability of the bio-distribution of the radiolabeled choline, as a series [7–12] or in several reports of a case [13–16]. All these experiences probably contributed to develop new clinical applications for radiolabeled choline PET/CT; some recently published papers investigate the possible role of this tracer in imaging brain tumors (BT) [17,18], parathyroid adenomas [19] and urothelial carcinoma [20]. In fact, the uptake of

radiolabeled choline can provide important information about the extension and growth of tumors [21] or inflammation [22].

All the experiences expressed above helped to reach a satisfactory knowledge on the “*in vivo*” bio-distribution of the various kinds of radiolabeled choline, which is essential for nuclear physicians.

On a theoretical basis, still needs to be addressed is the possibility of radiolabeled choline uptake in other diseases, in order to improve the accuracy and the expertise of nuclear physicians in this field. From this point of view, sharing different clinical experiences of various groups of researchers could bring an added value on the overall skill on this topic.

It is noteworthy to introduce that, despite few differences linked to the faster urinary excretion of ^{18}F -ethylcholine in comparison to ^{18}F -methylcholine and slightly different acquisition protocols for ^{11}C -choline PET/CT, for the shorter half-decay of ^{11}C [1,23], all these kinds of tracer follow the same metabolic pathway, being all markers of lipogenesis. Unfortunately, being the experience with radiolabeled choline PET/CT largely linked to studies developed on PC patients, few information are available

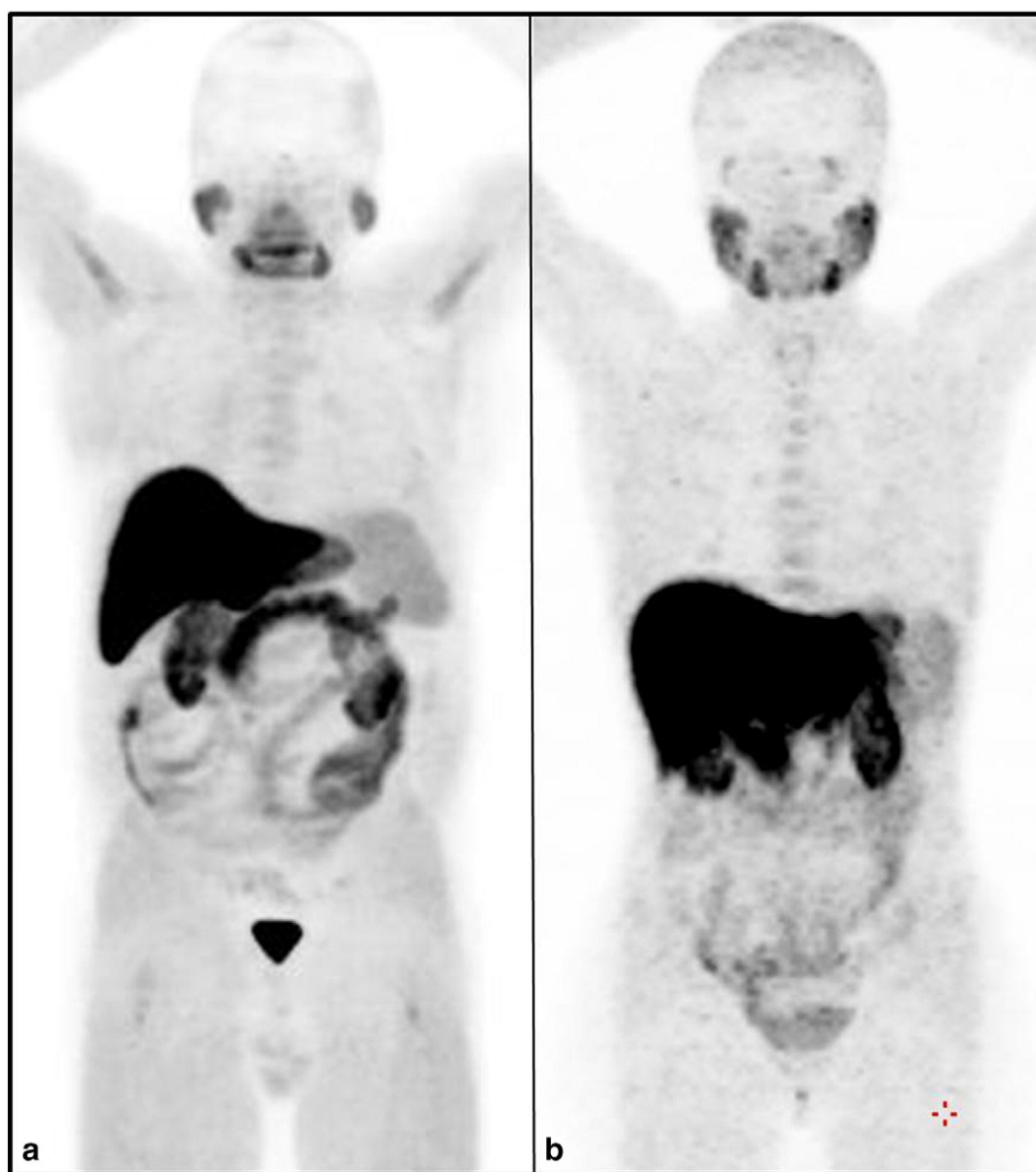


Fig. 1. Maximum intensity projection of two whole body ^{18}F -choline PET/CT scans respectively performed in a man (a) and in a woman (b). In both patients a ^{18}F -choline dose of 330 MBq was administered, without anesthesia and the length of the scan was 3 min per bed position (7 beds). No pathologic foci of uptake are evident in both images. Therefore, this figure can be representative of the physiological bio-distribution of radiolabeled choline in the male and female body.

Table 1
Mean values of registered SUVmax in various organs in 5 female patients submitted to whole body ¹⁸F–choline PET/CT.

Organs	Mean SUVmax	SD	RANGE
Liver	12.8	5.5	8.9–16.7
Pancreas	6.8	4.5	3.6–10.0
Lacrimal glands	1.4	1.2	0.5–2.3
Salivary glands	3.4	2.7	1.5–5.3
Spleen	3.1	1.9	1.8–4.5
Bone marrow	1.5	1.2	0.6–2.3
Kidneys	7.6	4.2	4.6–10.5
Breast	0.8	0.5	0.4–1.1
Uterus	1.2	0.7	0.7–1.7

on its “*in vivo*” bio-distribution in female patients. In fact, this radiopharmaceutical was administered in female patients only in few papers investigating parathyroid adenomas [24] or BT [25]. As a matter of fact, in these last cited papers, the acquisition protocols were developed with segmental scans of brain and/or neck, not including the rest of the female body. For the best of our knowledge, no data are available on the whole bio-distribution of radiolabeled choline in the female body.

For the reasons expressed above, in the last years we collected a large series diagnostic pitfalls in three PET centers performing PET/CT with ¹⁸F–choline for imaging PC patients. The aim of our study was to show our results in a multicenter acquired experience, trying to explain the possible meaning of these findings. Moreover, our secondary aim was to describe the “*in vivo*” bio-distribution of the tracer in the female and male body, with the help of semi-quantitative analysis of maximum standardized uptake value (SUVmax) in the target organs [26].

2. Materials and methods

We registered 169 cases of diagnostic pitfalls on a population of 1000 male patients undergoing whole body ¹⁸F–choline PET/CT during the staging or restaging of PC.

The term “*diagnostic pitfall*” was intended as an area of potentially pathologic tracer uptake, higher than surrounding background, not related to the disease under study.

All 1000 patients were included from three different centers:

- 1) University Hospital “*Tor Vergata*” in Rome, Italy (n = 300);
- 2) IRCCS INM Neuromed, Pozzilli (IS), Italy (n = 410);
- 3) University Hospital “*Magna Græcia*”, Catanzaro, Italy (n = 290).

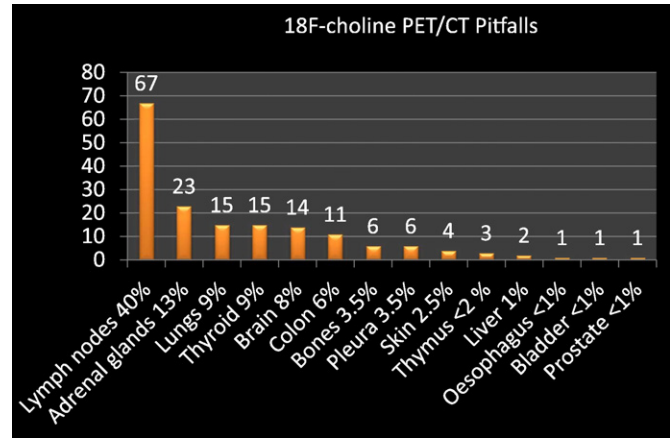
All PET centers contributed to the study joining the diagnostic pitfalls registered during the routinely clinical practice.

All these three centers used ¹⁸F–methylcholine (¹⁸F–choline) to perform PET/CT scans. Examined patients fasted 6 h before ¹⁸F–choline intravenous administration; they were also asked, in the week before the exam, to avoid foods containing high levels of choline [7,27]. Patients received 300–400 MBq of ¹⁸F–choline with an intravenous injection and hydrated *per os* (500 ml) to reduce pooling of the radiotracer in the kidneys.

Table 2
Mean values of registered SUVmax in various organs in 30 male patients submitted to whole body ¹⁸F–choline PET/CT.

Organs	Mean SUVmax	SD	RANGE
Liver	11.4	4.6	8.1–14.6
Pancreas	7.8	5.4	3.9–11.6
Lacrimal glands	1.2	1	0.5–1.9
Salivary glands	3.4	2.4	1.7–5.1
Spleen	4.3	3	2.2–6.4
Bone marrow	1.7	1.4	0.7–2.7
Kidneys	7.9	5.3	4.1–11.6
Testicles	1.9	0.4	1.6–2.4

Table 3
The table summarizes the documented 169 cases of ¹⁸F–choline PET/CT pitfalls on a *per tissues* analysis.



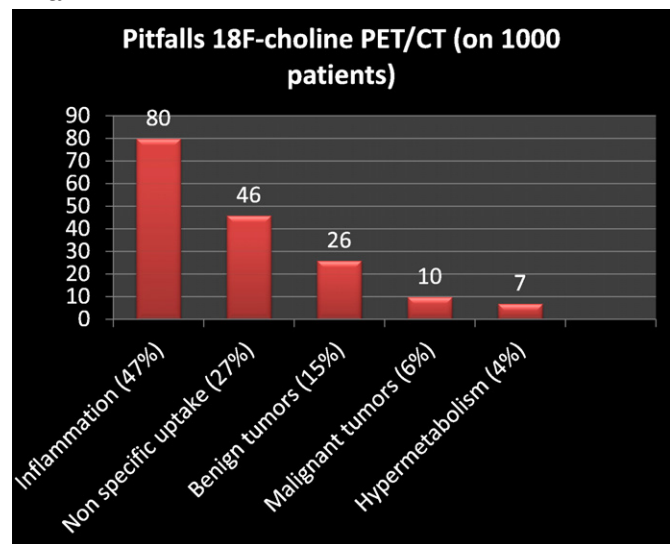
In all the three centers PET/CT scans were acquired using a Discovery ST scanner (Discovery ST16 GE Medical Systems, Tennessee, USA). This system combines a high-speed ultra 16-detector row (912 detectors per row) CT unit and a PET scanner. With 10,080 bismuth germanate crystals in 24 rings.

A low amperage CT scan was performed for attenuation correction of PET images (80 mA, 140 kV, field of view about 420–500 mm; CT slice thickness 3.75). Just after CT, whole-body PET images were acquired 45 min after ¹⁸F–choline administration, 5–7 bed positions, 4 min per bed, from upper thighs to vertex; images were reconstructed using a standard iterative algorithm, Ordered Subsets Expectation Maximization (OSEM). All patients gave their written informed consent for the exam.

The ¹⁸F–choline PET/CT data set was evaluated by 6 nuclear physicians on a dedicated workstation (Advantage–Windows 4.4, GE; General Electric Medical System, Tennessee, USA). All clinical, histological, radiological, nuclear medical information, available within the 3–6 months months before examination, were consulted to verify suspected ¹⁸F–choline findings.

In some cases, magnetic resonance imaging (MRI), CT with or without contrast agents and/or histological exam were performed to verify some uncertain findings.

Table 4
The table summarizes the documented ¹⁸F–choline PET/CT pitfalls according to their etiology.



Finally, in the Department of Nuclear Medicine of the University Hospital “Magna Græcia”, a ^{18}F -choline whole body PET/CT was performed in 5 female patients, examined for suspected BT relapse, beyond the brain PET/CT. Patients were administered 300–400 MBq of ^{18}F -choline intravenously. The acquisition protocol was the same described above for male patients.

Therefore, in these 5 female patients, the SUVmax in liver, uterus, breast, pancreas, salivary and lacrimal glands, spleen, bone marrow and kidneys, was recorded, in order to compare these data to those obtained in 30 male patients submitted to whole body PET/CT with ^{18}F -choline for PC and a scan negative for secondary localizations. SUVmax was measured by placing spherical regions of interest (ROIs) on the cited organs in the maximum intensity projection (MIP).

All patients gave their written consent to the study. The study was approved by our local ethic committees.

3. Results

3.1. Physiological distribution of ^{18}F -choline in female and male patients

The most relevant physiological tracer uptake of ^{18}F -choline, in both male and female patients, was documented in the liver and pancreas; moderate-to-high uptake was observed in the spleen and in salivary and lachrymal glands. Less intense uptake was registered in bone marrow. Other further sites of mild uptake were the small and large intestines, probably due to the peristalsis. Testicles presented mild uptake. Due to the urinary excretion of the tracer, high rate of tracer uptake was documented in kidneys and bladder. The uptake of ^{18}F -choline in

the brain was usually negligible, except in the choroid plexus and pineal gland, occasionally visualized in PET imaging. No significant differences in ^{18}F -choline physiological bio-distribution were recorded at the visual analysis of PET data (Fig. 1) and with the semi-quantitative analysis with SUVmax in the whole body, between female (Table 1) and male (Table 2) patients.

In the examined women, low uptake was detected in the breast, with a mean SUVmax of 0.8 (range 0.4–1.1), and in the uterus, with a mean SUVmax of 1.2 (range 0.7–1.7). Ovaries were not detectable in the CT component of the exam, being performed without contrast agent administration. No differences in terms of bio-distribution were recorded between male and female populations.

3.2. General overview of diagnostic pitfalls in 1000 male patients

Among the 1000 examined male patients with PC, we collected 169 cases (16.9%) of abnormal sites of uptake of ^{18}F -choline, dubious or unexpected, not related to PC.

Globally, on a per-organ analysis, the abnormal sites of uptake were observed in lymph nodes (67/169 patients; 40% of overall findings), in the adrenal glands (23/169, 13%), lungs (15/169, 9%); thyroid (15/69, 9%); brain (14/169, 8%); colon (11/169, 6%); bones (6/169, 3.5%), skin (4/169, 2.5%); thymus (3/169, <2%); liver (2/169, \approx 1%); esophagus (1/169, <1%), bladder (1/169, <1%) and prostate (1/169, <1%) (Table 3).

Considering the diagnostic results, pitfalls were due to inflammation in 80/169 patients (47%), to non-specific uptake in 46/169 patients (27%), to benign tumors in 26/169 patients (15%), to malignant tumors

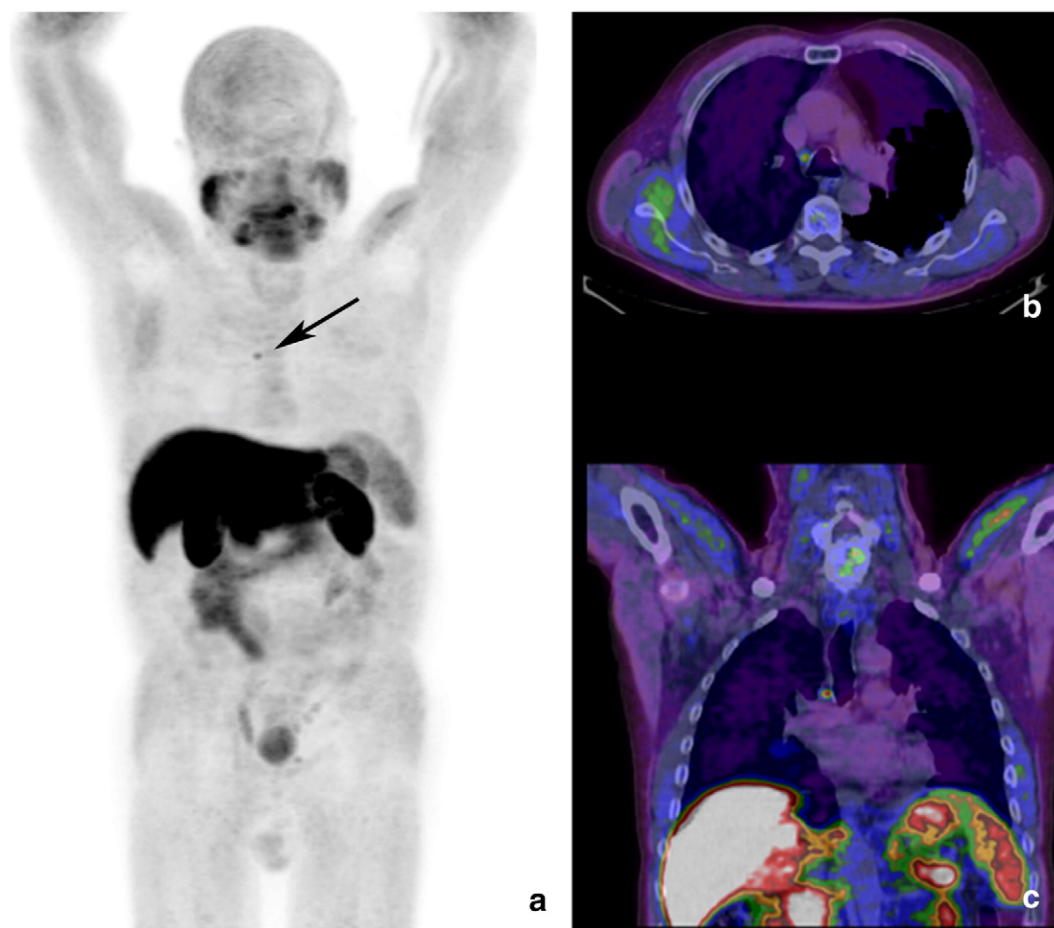


Fig. 2. Maximum intensity projection of the whole body ^{18}F -choline PET (a) shows single area of focal uptake in the mediastinum, corresponding to a 6 mm wide lymph node in the Baretz's space, in corresponding axial (b) and coronal (c) PET/CT views. SUVmax was 3.6 and the finding was considered as inflammatory due to the low PSA serum level and referred persistent cough since one month before the exam.

in 10/169 patients (6%), to a condition of hypermetabolism in 7/169 patients (4%) (Table 4).

The inflammatory findings were localized in lymph nodes ($n = 64$), bones ($n = 5$), skin ($n = 4$), thyroid ($n = 4$), lungs ($n = 2$) and esophagus ($n = 1$).

Nonspecific uptake was considered as a condition of high radiolabeled choline uptake without clinical evidence, laboratory tests and correlative imaging positive for benign or malignant disease. This feature was documented in adrenal glands ($n = 21$), lungs ($n = 12$ solitary pulmonary nodes), thyroid ($n = 8$) and pleura ($n = 5$).

Benign tumors were represented by meningiomas ($n = 12$), colon adenomas ($n = 9$), thymomas ($n = 3$), a papilloma of the choroid plexus ($n = 1$) and a neuroendocrine lung tumor ($n = 1$).

Malignant tumors were lymphomas ($n = 2$), colon cancers ($n = 2$), a lymphadenopathy due to bladder cancer relapse ($n = 1$), a glioma ($n = 1$), a case of multiple myeloma ($n = 1$), a pleural mesothelioma ($n = 1$), a case of bladder cancer ($n = 1$) and a primary squamous cell carcinoma of the prostate ($n = 1$).

A condition of hypermetabolism was supposed when clinical and laboratory data confirmed the ^{18}F -choline findings of uptake in conditions of hyperthyroidism ($n = 3$), adrenal adenomas ($n = 2$) and hepatic focal nodular hyperplasia ($n = 2$).

The mean SUVmax registered in inflammatory findings, nonspecific uptake cases, benign tumors, malignant tumors and in conditions of hypermetabolism was respectively 2.9, 2.5, 4.5, 8.9 and 4.2 while the SUVmax documented in the vascular lesion was 11. Differences between these groups were not statistically significant.

All the cited findings are described below more accurately, following the order of Table 3.

3.3. Lymph node uptake

A large amount of patients (67/169; 40% of overall documented pitfalls) showed low/mild uptake of ^{18}F -choline in lymph-nodes. In the most part of these cases the uptake was confined in a single lymph-node, generally localized in axillary regions, neck, mediastinum or inguinal regions. Rarely this finding was recorded in the abdominal district.

In 64 cases the uptake was considered as inflammatory with the help of anamnestic data and CT features. Among these patients, in particular, in a 67-year-old patient in restaging of PC, 1 year after radical prostatectomy (PSA 0.36 at the time of the scan), a single area of focal, mild uptake was detected in a 6 mm lymph node, with recognizable hilum, of the Baret's space. Registered SUVmax was 3.6 (Fig. 2). The patient referred persistent cough since one month before the exam.

Conversely, in two cases a lymphoma was documented. In the first case a low grade lymphoma was detected in multiple supra- and infra-diaphragmatic lymph-adenopathies [7]. In the second case, we examined for restaging PC a patient previously submitted to radiotherapy on the prostate for curative intent (PSA 1.8 at the time of the scan). Intense ^{18}F -choline uptake was observed in three small lymph nodes without recognizable hilum (diameter ≈ 1 cm) in the left inguinal region. Moreover, the patient presented splenomegaly at the CT component of the exam, with low ^{18}F -choline uptake (SUVmax 2.8). Being these findings not congruent with the diagnosis of secondary localizations of PC a histological specimen was obtained in the left inguinal region. Histological diagnosis was positive for non-Hodgkin lymphoma (Fig. 3).

Finally, in a patient in restaging of PC after radiotherapy (PSA 1.1 ng/ml), a focal area of intense uptake (SUVmax 8.3) was detected

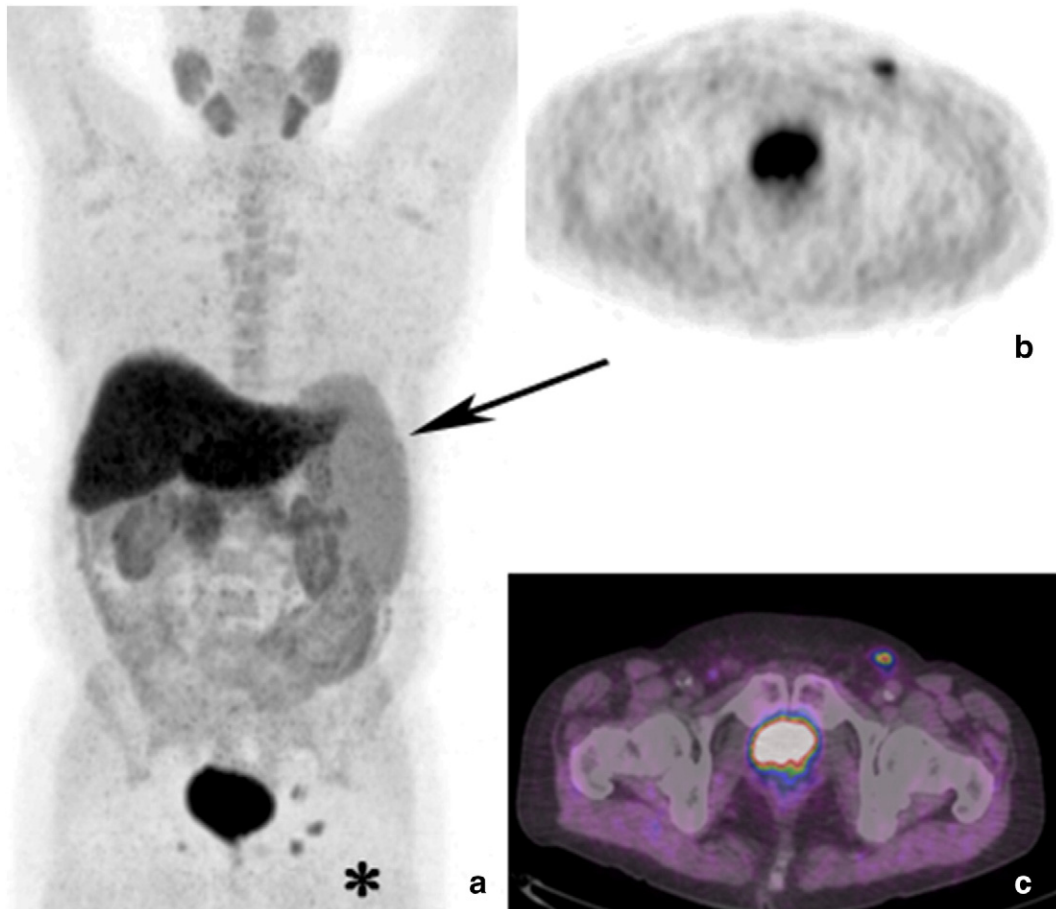


Fig. 3. PET/CT maximum intensity projection (a) shows splenomegaly (black arrow) and intense ^{18}F -choline uptake in the left inguinal region, with a focal area evident in axial PET detail (b) corresponding to a centimetric lymph node in axial PET/CT view (c). Histological exam diagnosed non-Hodgkin lymphoma.

in correspondence of a 2.3 cm wide lymph node in the pre-sacral region (Fig. 4). The patient had also diagnosis of bladder cancer and was submitted to chemotherapy two years before the scan. Considering also the relatively low PSA serum level, this finding was considered as pelvic lymph nodal relapse of bladder cancer.

3.4. Adrenal glands

In 23/169 patients mild uptake of the tracer was documented in adrenal glands (13%). Generally, the uptake was mono-lateral. In 21 cases the uptake was not related to meaningful morphological abnormalities, this finding was therefore considered as exclusively functional, non-specific. In two cases the uptake was in correspondence of a nodular hypodense area in right ($n = 1$) or in left adrenal gland ($n = 1$): these findings were considered suspicious for adrenal adenomas [9].

3.5. Lungs

The pulmonary district was the third most important district for prevalence of unexpected findings of ^{18}F -choline uptake (15/169; 9%). Twelve patients showed focal uptake in correspondence of a solitary pulmonary node, generally with a low SUVmax (range: 1.5–2.6). In most of these cases, the suspicion of benign lung nodule was done,

standing to the clinical history or the comparison with previous imaging [7]. In one case a neuro-endocrine tumor of the lung was diagnosed in a mass in the right lung with SUVmax 4.5 and diameter 10 cm [9]. Finally, in two cases the diagnosis of sarcoidosis was done: in particular, in a 58-year-old patient in restaging of PC 3 years after radical prostatectomy (PSA 2.6 ng/ml), a focal area of uptake was detected in the right pulmonary hilar region (SUVmax 4.1) in correspondence of a 1 cm wide lymph node (Fig. 5). This finding was suspicious for secondary localization of PC but anamnestic data of the patients were also suggestive for chronic respiratory disease (cough, fatigue, and shortness of breath since 6 years before the exam). Thus, a suspicion of sarcoidosis was done, accordingly with the pulmonologist. Histological sampling from the mediastinal lymph nodes, by endobronchial ultrasound-guided transbronchial needle aspiration, confirmed non-caseating granulomas with epithelioid cells.

3.6. Thyroid

The thyroid was interested by uptake of ^{18}F -choline in 15 patients (9% of overall amount of pitfalls). In 8 cases laboratory data and/or correlative imaging did not show abnormalities and this finding was considered as non-specific. In 4 patients laboratory data were suggestive for a condition of thyroiditis [7]. In the remaining 3 patients, laboratory

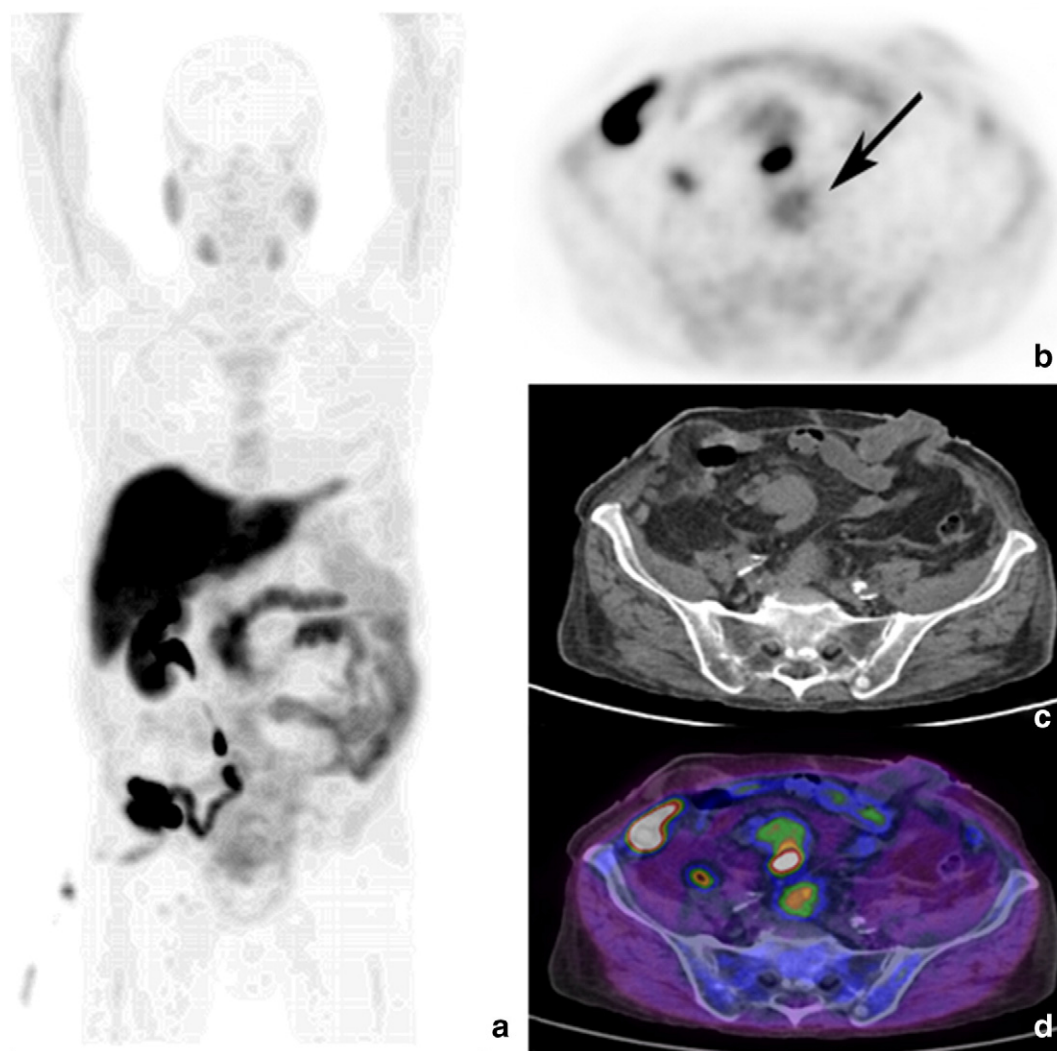


Fig. 4. PET/CT maximum intensity projection (a) of a patient in biochemical relapse of PC after radiotherapy (PSA 1.1 ng/ml), previously also submitted to cystectomy and ileo-cutaneous ureterostomy for bladder carcinoma. The axial PET view (b) shows diffuse uptake in the pre-sacral region, corresponding to a 2.3 cm wide lymph node in CT (c) and PET/CT (d) views, indicative of lymph nodal pelvic bladder cancer relapse.

data allowed to diagnose a condition of hyperthyroidism, due to the concomitant rise of thyroid hormones and reduction of TSH serum levels.

3.7. Brain

Abnormal uptake of ^{18}F -choline was documented in the brain in 14/169 cases (8%). In 12 patients the uptake was linked to a meningioma (Fig. 6); in one patient a single area of ^{18}F -choline uptake in the brain was related to a glioma, as confirmed by MRI [7]. Finally, in a patient examined for restaging PC, 1 year after radiotherapy for curative intent (PSA 1.6 ng/ml at the time of the scan), a focal area of uptake (SUVmax 4.5) was observed in the occipital horn of the right cerebral ventricle, associated with hyperdense area in the CT. MRI diagnosed a papilloma of the choroid plexus (Fig. 7).

3.8. Colon

In 11 patients (6%) abnormal focal uptake of ^{18}F -choline was documented in the colon. Among these, in 9 patients the colon endoscopy allowed to diagnose colic adenomatosis. In two cases the histological sample, performed by endoscopy, diagnosed colon carcinoma. In particular, in a 74-year-old patient in restaging of PC, focal uptake was detected in a thickening of the superior tract of the sigma, due to colon cancer (Fig. 8).

3.9. Bones

In 6/169 patients (3.5%) we observed abnormal tracer uptake in the skeleton. In particular, in 3 patients the uptake was detectable in the

maxillary sinus, extended to mucosal thickenings respectively of the right ($n = 1$) [9] and left ($n = 2$) maxillary sinus. All patients were then evaluated with CT of the cranial bones within 10 days. The CT scan showed soft tissue in the right maxillary sinus without erosion of the osseous cortex. All the imaging findings were considered suggestive for maxillary sinusitis. Similarly, in one patient presenting ^{18}F -choline uptake in the right middle ear and in the ipsilateral mastoid cells, a right otomastoiditis was documented. In one patient a multiple myeloma was diagnosed due to multiple ^{18}F -choline avid, lytic bony lesions. In this patient, examined for restaging PC for low rise in PSA serum level (0.9 ng/mL), 2 years after radical prostatectomy, the diagnosis was already obtained from elevated γ -globulin levels and bone marrow biopsy.

Finally, the last patient showed was examined due to a bone scan suspicious for a PC metastasis in the right femoral neck: the PET/CT scan confirmed a single area of focal uptake in this site, with SUVmax 6 and without morphological abnormalities in the corresponding CT [9]. The PSA serum level was too low to support the diagnosis of bone metastasis (0.2 ng/ml). Moreover, the patient reported a severe post-traumatic pain in that region. The biopsy of the right femoral neck was performed and diagnosed reactive fibrous cells without malignancy.

3.10. Pleura

In the pleural district we encountered 6 pitfalls (3.5%): in 5 of them a solitary area of uptake was observed in correspondence of a single pleural thickening in the thoracic wall. In all these cases the anamnesis, follow-up and/or correlative imaging allowed to consider the uptake as non-specific. Unfortunately, in these patients histological exam was not available.

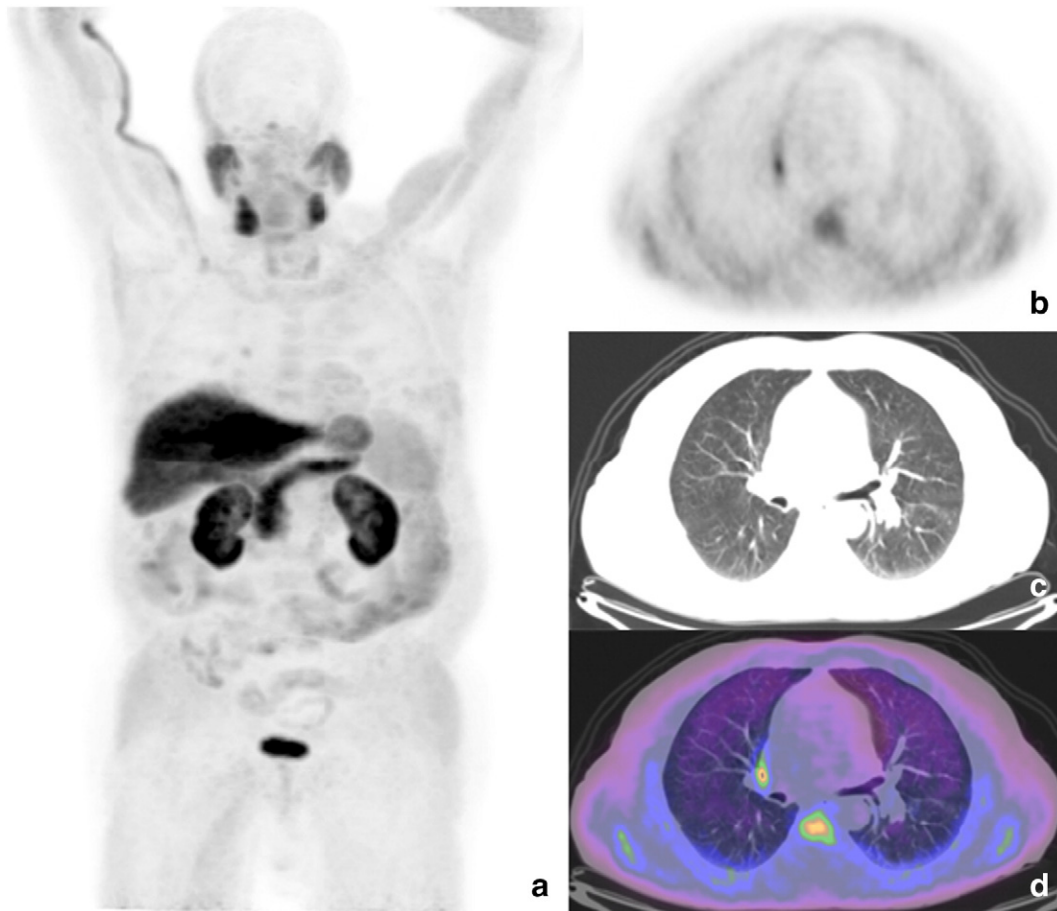


Fig. 5. PET/CT maximum intensity projection (a) and axial PET view (b) show a focal area of ^{18}F -choline uptake in the right pulmonary hilar region (SUVmax 4.1), corresponding to a 1 cm wide lymph node in axial CT (c) and PET/CT views (d). Histological sample allowed to diagnose active sarcoidosis.

In the last patient, examined for restaging PC and rise of PSA serum level (1 ng/ml at the time of the scan) one year after surgical intervention of radical prostatectomy, we observed multiple areas of intense ^{18}F -choline uptake in several pleural thickenings in the right lung, with some areas of confluence producing consolidation as detectable in the CT component of the exam. Considering the radiologic criteria and the high SUVmax documented in the lesions (range 7.2–16) a CT-guided pleural needle biopsy was performed. Histological exam diagnosed pleural mesothelioma (Fig. 9).

3.11. Skin

We registered 4 cases (2.5%) of a single area of focal uptake in the skin. In all cases the uptake was localized in correspondence of a sub-centimetric nodule in the skin of the neck ($n = 2$), of the right axilla ($n = 1$) and right inguinal region ($n = 1$). In all these patients the anamnesis or the direct clinical investigation allowed to diagnose a common cutaneous furuncle.

3.12. Thymus

In three patients we documented abnormal tracer uptake in the thymus. Considering the age-related thymic involution in all adult patients,

we further examined this finding with follow-up or histological exam. In all cases a thymoma was diagnosed. In particular, in a patient examined for staging PC (PSA 6 ng/ml), we observed prominent ^{18}F -choline uptake in the upper mediastinum (SUVmax 7), corresponding to a well-defined, hypodense area of 2.8 cm. The patient did not suffer any symptoms related to a “mediastinal mass”. Subsequently, histopathological analysis, after a CT-guided biopsy, diagnosed epithelial thymoma. No lymph node or bone metastases from PC were detected on the exam (Fig. 10).

3.13. Liver

In 2 patients we observed a single hepatic area of focal uptake. Considering the clinical suspicion of hepatic secondary lesions, in both case histological CT-guided sampling allowed to diagnose focal nodular hyperplasia (FNH). Particularly, in a 67-year-old patient a focal area of ^{18}F -choline uptake was documented in the 4th hepatic segment (SUVmax 7), corresponding to a non-homogeneous hypodense area in the CT. The subsequently performed MRI of the upper abdomen did not help to reach the correct diagnosis, being dubious for the differential diagnosis between secondary localization of PC and FNH (Fig. 11). Only the histological exam allowed to obtain the correct diagnosis.

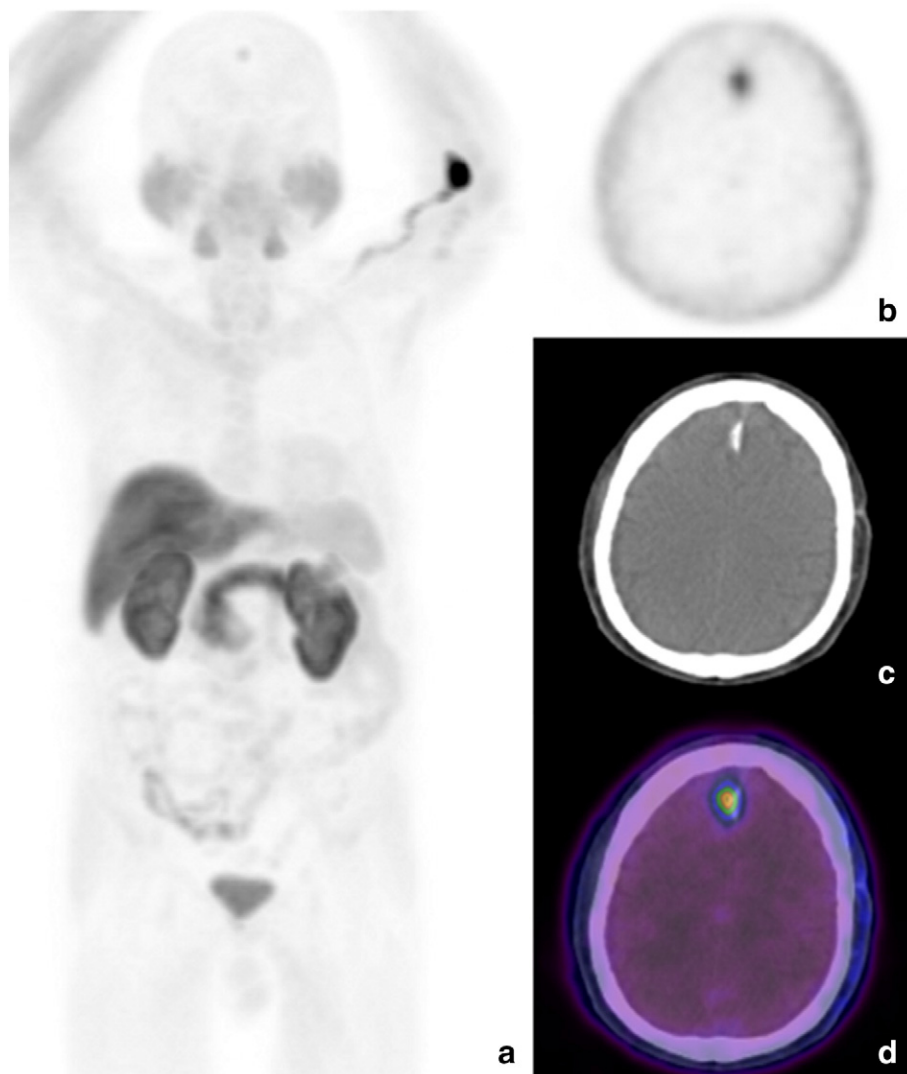


Fig. 6. Maximum intensity projection (a) and axial PET view (b) show focal ^{18}F -choline uptake in right, parasagittal frontal lobe, corresponding to hyperdense area with calcifications in related CT (c) and PET/CT (d) views. Patient anamnesis was positive for meningioma.

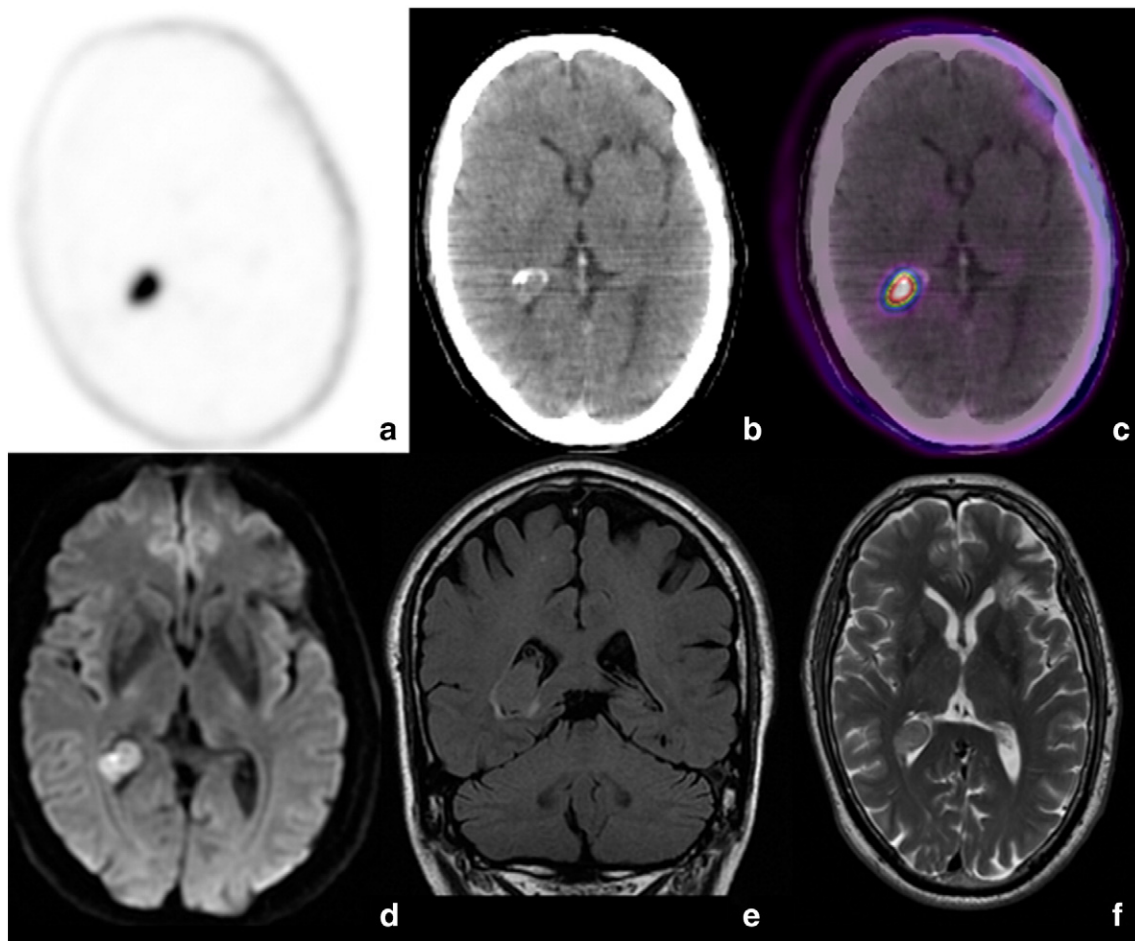


Fig. 7. Axial PET (a), CT (b) and PET/CT (c) views show focal ^{18}F -choline uptake a hyperdense area in the occipital horn of the right cerebral ventricle. MRI diagnosed a papilloma of the choroid plexus, with high signal on diffusion-weighted imaging (d), hypersintensity signal in FLAIR sequences (e) and regular margins on T2 weighted view (f).

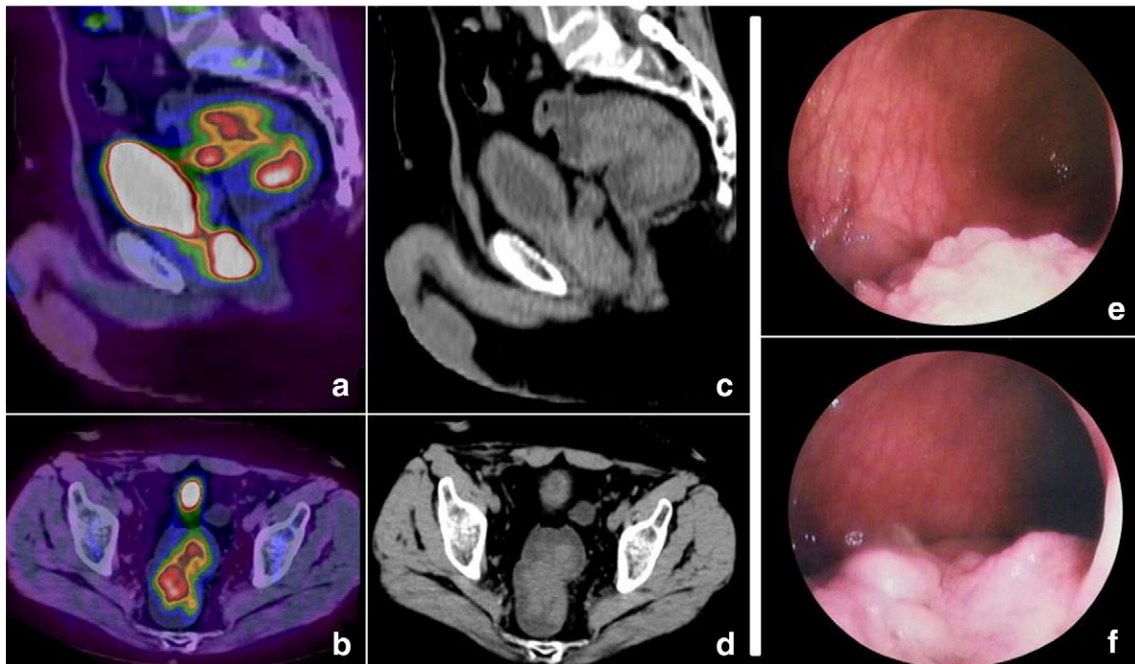


Fig. 8. Sagittal (a) and axial (b) PET/CT views show focal tracer uptake in the superior sigmoidal tract, in correspondence of a thickening in related sagittal (c) and axial (d) views. The colonoscopy (e, f) displayed a pedunculated malignant lesion, as confirmed by subsequent histological exam.

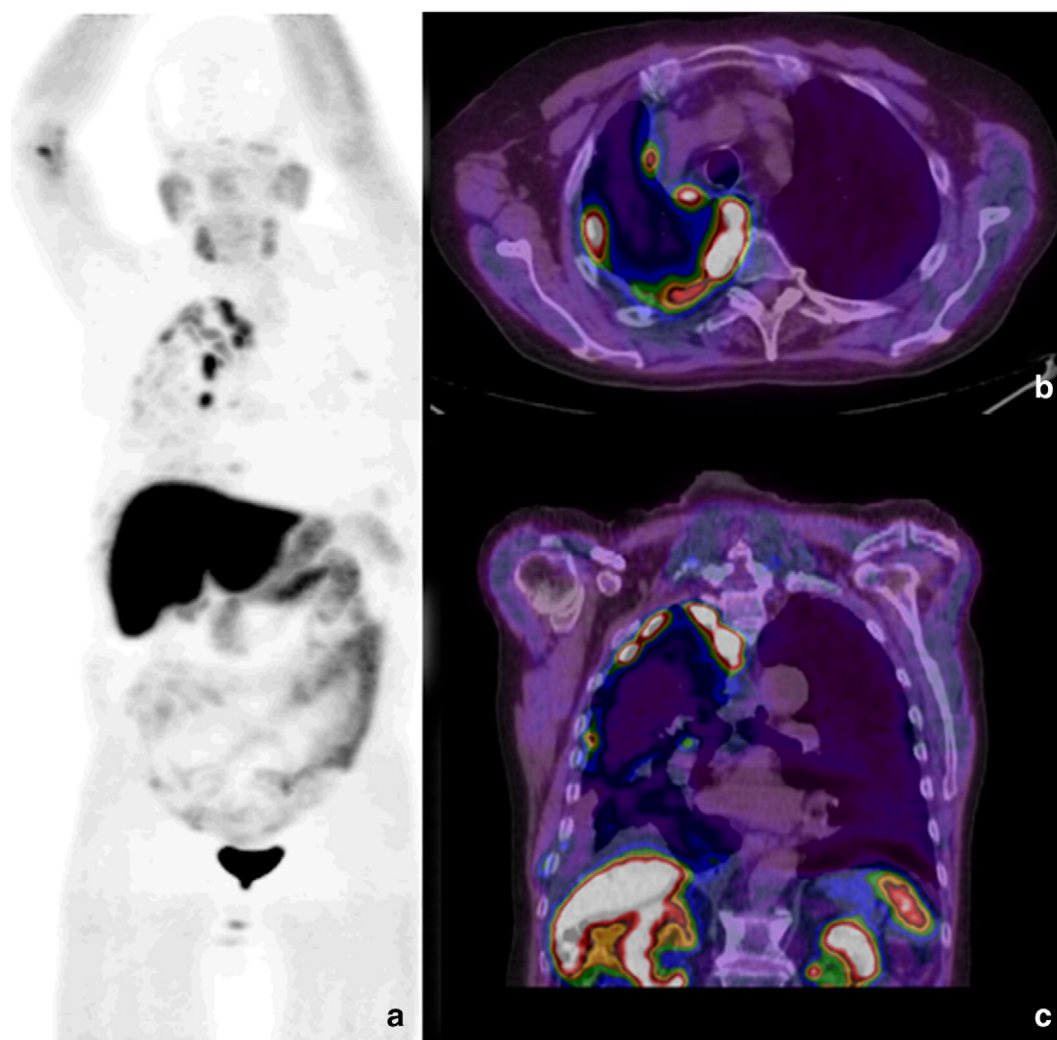


Fig. 9. Maximum intensity projection (a) shows multiple areas of pathologic ^{18}F -choline uptake in the right lung, corresponding to several pleural thickenings in axial (b) and coronal (c) details. The CT-guided pleural needle biopsy allowed histological diagnosis of pleural mesothelioma.

3.14. Esophagus

A 72-year-old patient was referred for ^{18}F -choline PET-CT staging of PC (PSA serum levels of 11 ng/ml; Gleason score = 8). Only an area of focal and intense uptake in the distal tract of esophagus was documented. Contrast enhanced CT did not show suspected abnormal tissue in correspondence of the site of uptake. This finding was highly suggestive for oesophagitis, according to clinical symptoms referred by the patient (dyspepsia and dysphagia), as subsequently confirmed by gastroscopy [7].

3.15. Bladder

A patient was submitted to the exam because of suspicion of bone metastases in a bone scan 2 years after radical prostatectomy (PSA serum level, 1.5 ng/ml at the time of the scan). No bone metastases were detected at PET/CT; nevertheless, a focal area of intense uptake (SUVmax 18.1) was detected in a thickness of the trigonal area of the bladder higher than the surrounding physiological high rate of radioactive urine in the bladder. A contrast enhanced CT of the pelvis showed a lesion of the trigone with irregular margins and high contrast enhancement. Histological sample diagnosed a bladder carcinoma.

3.16. Prostate

A patient was examined with ^{18}F -choline PET/CT to stage PC histologically proven (PSA 7.7 ng/ml). The exam showed intense tracer uptake in the prostate gland, with remarkable increase in size, non-homogeneous density and air bubbles in the prostatic tract of the urethra. Furthermore, an important quote of air-fluid level was observed in the bladder, by evaluating the CT component of the exam.

Finally, some areas of ^{18}F -choline uptake were observed in several mediastinal lymphadenopathies (Fig. 12). The patient referred to suffer of pelvic pain and haematuria from three months. Considering that these data were suggestive for a particularly aggressive kind of neoplasm, not completely in agreement with the biological behavior of PC and with the PSA serum level, a new biopsy, done in accordance with urologists, allowed to diagnose a primitive squamous cells cancer of the prostate.

4. Discussion

Being a marker of lipogenesis and cell membrane synthesis, the $^{11}\text{C}/^{18}\text{F}$ -choline is a tracer with a clear role in the management of PC patients, superior to ^{18}F -FDG in different clinical settings [28,29]. Numerous studies deepen the knowledge of the diagnostic pitfalls in clinical

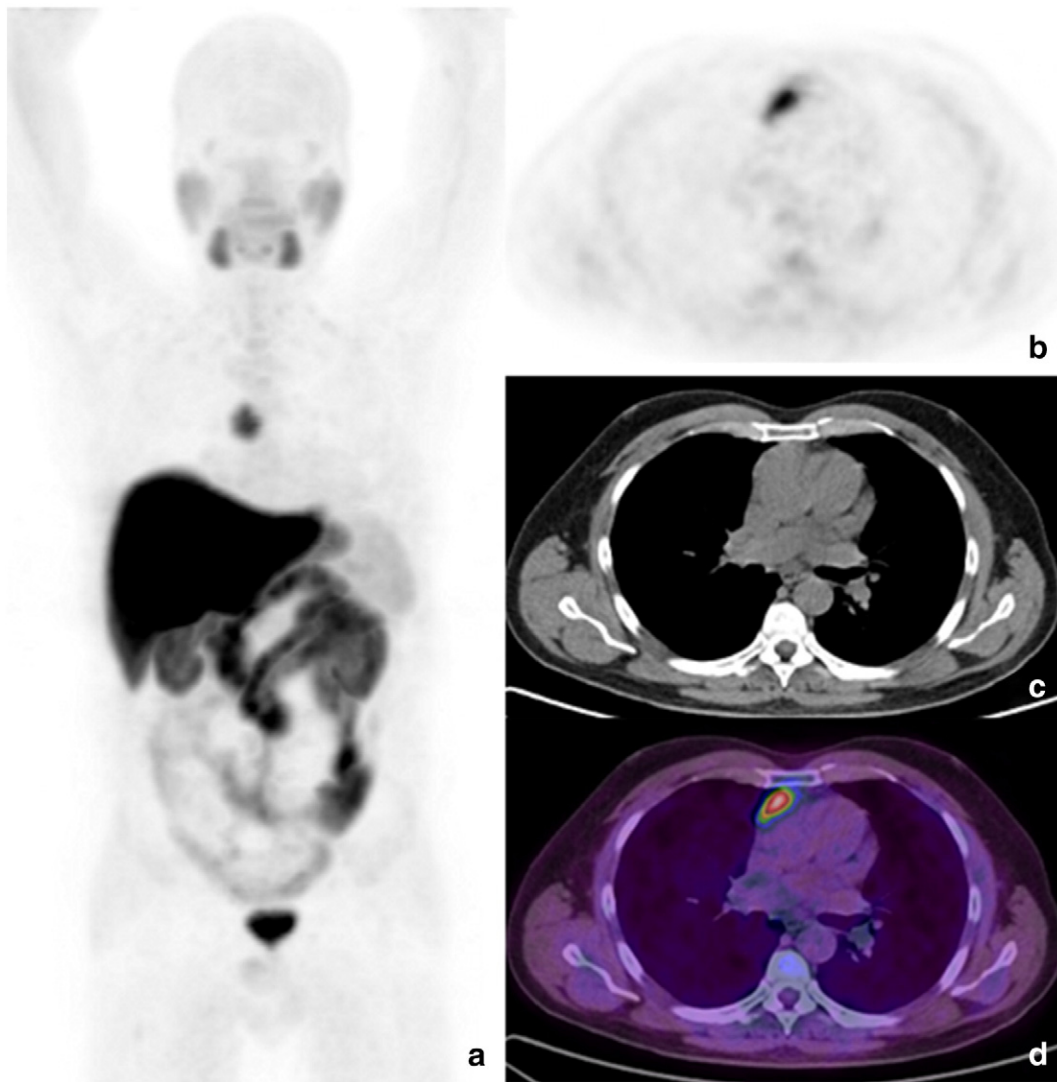


Fig. 10. Maximum intensity projection (a) and axial PET view (b) show ^{18}F -choline uptake in the upper mediastinum, corresponding to a well-defined, hypodense, 2.8 cm wide area in related CT (c) and PET/CT views (d). The CT-guided biopsy diagnosed epithelial thymoma.

practice with the ^{18}F -FDG [6,30–32]: all these experiences allowed to reach a satisfactory knowledge on the physiological bio-distribution of this tracer, its physiologic variants and the potential diagnostic errors linked to its intrinsic properties of a glucose-analogue, non-tumor specific marker. On the other hand, few data are actually available on this topic on the radiolabeled choline. Nevertheless, the radiolabeled choline is becoming one of the most useful PET tracers, beyond ^{18}F -FDG.

Concerning the physiological bio-distribution of ^{18}F -choline in the whole body, our data (Tables 1 and 2) show that the ^{18}F -choline exhibits a high uptake gradient in the exocrine and endocrine glands: in liver is registered the highest uptake while pancreas, salivary and lachrymal glands, normally enhance ^{18}F -choline. It is known that hepatic and pancreatic cells present an endodermal lineages, also common to salivary glands and lachrymal glands [33,34]: as reported in two studies comparing ^{11}C -choline and the two fluorinated kinds of choline [1,23], all these tracers present an high uptake gradient in liver, being this organs the main site of phospholipids metabolism and catabolism in the human body. The uptake in the other exocrine glands can be due to an alternative excretion, being pancreas and salivary and lachrymal glands associated by a common embryologic origin [33].

Other sites of physiological uptake are bone marrow and spleen: this could be due to a slight gradient of choline enhancement in the reticuloendothelial system.

The kidneys and bladder are usually visualized due to the urinary excretion of the tracer. Interestingly, we did not observe significant differences in the bio-distribution in the whole body between female and male patients (Fig. 1). Testicles show mild uptake and breast show low-mild uptake, due to their exocrine function, that in the breast is normally absent. The uptake in the uterus is negligible. Nevertheless, our data on the bio-distribution of the tracer in female body need to be considered preliminary, considering the poor examined population.

The main feature that our results in 1000 patients examined for PC, shows the high probability to detect ^{18}F -choline uptake in inflammatory conditions (47%, 80 cases on 169 pitfalls), in particular in reactive lymph nodes. In our series, a large number of documented pitfalls were linked to inflammation in lymph nodes, lung nodes and skin. The uptake of ^{18}F -choline in inflammatory conditions could be due to the activation of cellular types as in the monocyte-to-macrophage differentiation, expressing a high rate of lipogenesis and cell membrane synthesis [35]. However, the recognition of the most part of these false positive cases is easily reachable with an accurate collection of the anamnesis. Nevertheless, among all the cases of lymph node uptake, we documented one case of pelvic lymph nodal relapse of bladder cancer and two lymphomas. Both these cases were not congruent with a diagnosis of lymph nodal metastases of PC, due to the anamnestic data and their peculiar anatomic localizations, as in a case of low grade

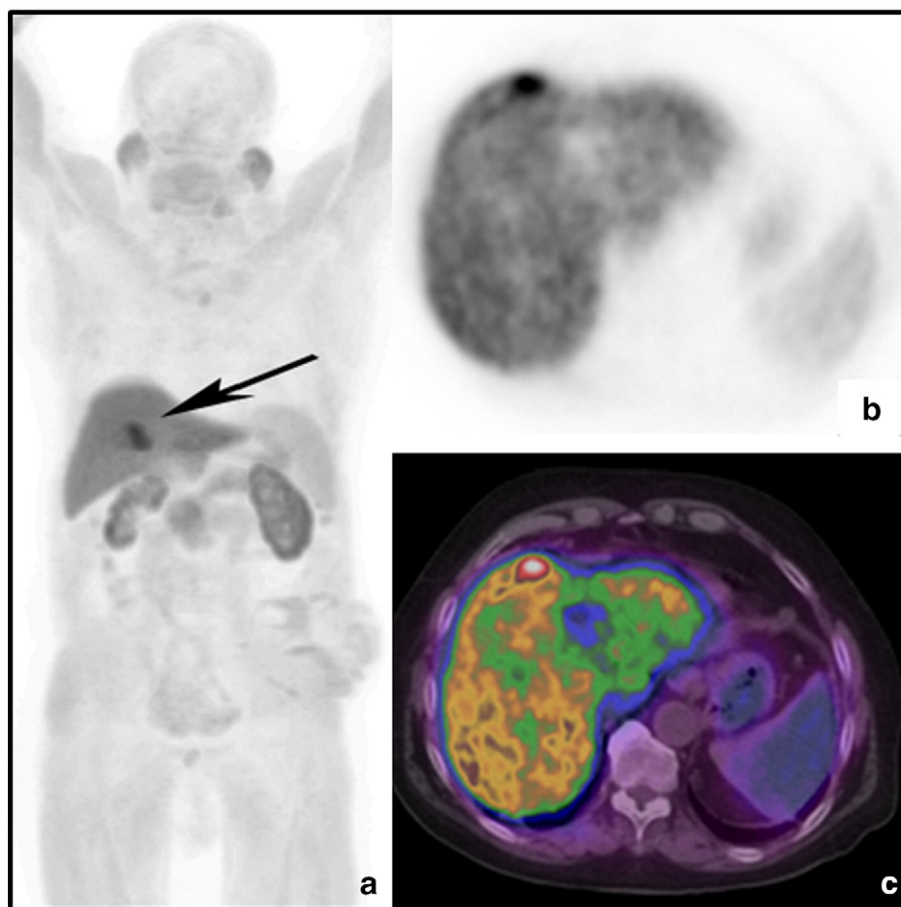


Fig. 11. In this patient, a focal area of ^{18}F -choline uptake was documented in the 4th hepatic segment, as evident in maximum intensity projection (a, arrow) and axial PET (b) and PET/CT (c) views. Histological exam diagnosed focal nodular hyperplasia.

lymphoma with supra and infra-diaphragmatic localizations. Only few papers have been already described the possibility of ^{18}F -choline uptake in non-Hodgkin and Hodgkin lymphomas [16,36] and we must consider the incidental detection of a lymphoma as a rare but not unusual condition.

The molecular pathway of lipogenesis is also at the basis of the ^{18}F -choline uptake documented in benign tumors: thymomas, a neuroendocrine tumor of the lung, colic adenomas, meningiomas, representing the 15% of all registered pitfalls (25/169, Table 3). Also in these cases, a clinical approach, aware of the clinical history of the patients, allowed to recognize these findings as non-related with PC. In particular, it is well known that some mediastinal diseases can show $^{18}\text{F}/^{11}\text{C}$ -choline uptake, as already reported for thymomas [13,37] and mediastinal inflammatory lymph nodes [38] while the uptake in thoracic granulomatous diseases as sarcoidosis, anthracosis and tuberculosis is also known the possibility of uptake in thoracic granulomatous diseases as sarcoidosis [39], anthracosis [40] and tuberculosis [41]: in these cases, a deepen clinical anamnesis was sufficient to reach the final diagnosis. On the other hand, caution is needed when observing tracer uptake in numerous pleural thickenings as in the case of malignant mesothelioma we reported (Fig. 10). In this last case the accurate knowledge of the CT component of the exam can help in correctly diagnosing a concomitant malignant tumor other than PC.

Regarding the liver, we documented a case of focal nodular hyperplasia. In the liver, we observed a single case of focal nodular hyperplasia; in fact, it is known that some benign hepatic lesions as focal nodular hyperplasia and hepatocellular adenoma can show radiolabeled choline uptake, with different uptake rate [42]. Interestingly, in our case, the uptake in the focal nodular hyperplasia was a clearly visible respect to the

surrounding background of the liver, which is commonly the site with the highest rate of radiolabeled choline uptake.

As known, the uptake in the brain is usually negligible with all the kinds of radiolabeled choline [1,23]. As already reported by our group [7] and by the experience of Mertens et al.[43], only the pineal gland and the choroid plexus can occasionally show a minimal rate of physiological uptake, not associated with morphological lesions. In our series, we described a case of ^{18}F -choline uptake linked to a benign tumor in the choroid plexus (Fig. 8): in this asymptomatic case a hyperdense area was detectable on the CT but only correlative MRI allowed to reach the correct diagnosis. The possibility of uptake in benign and malignant tumors of the brain was described in several papers [44–46]: all these studies support the usefulness of radiolabeled choline PET/CT in the management of brain tumors, due to the low rate of physiological uptake in the normal white and gray matter that allows the recognition of tumors expressing high synthesis of cell membrane. In our series, we documented 1 papilloma of the choroid plexus, 1 glioma and 11 meningiomas. Therefore, 1% of examined patients for PC (11/1000) presented a ^{18}F -choline avid meningioma at the whole body scan. Interestingly, these data are similar to the experience of Fallanca et al.[11], which reported the possibility to incidentally detect meningiomas in patients undergoing a whole body ^{11}C -choline PET/CT for PC. The inclusion of the brain in the whole body scan of PC patients examined with radiolabeled choline PET/CT should be recommended in order to ensure the possibility to detect malignant tumors or benign lesions of the brain and also the verify the possibility of PC metastases in the cranial teca or in the brain that can occur in a significant minority of PC patients [47,48].

In our opinion, the most peculiar finding we encountered was the squamous cell carcinoma of the prostate: probably, for the best of our

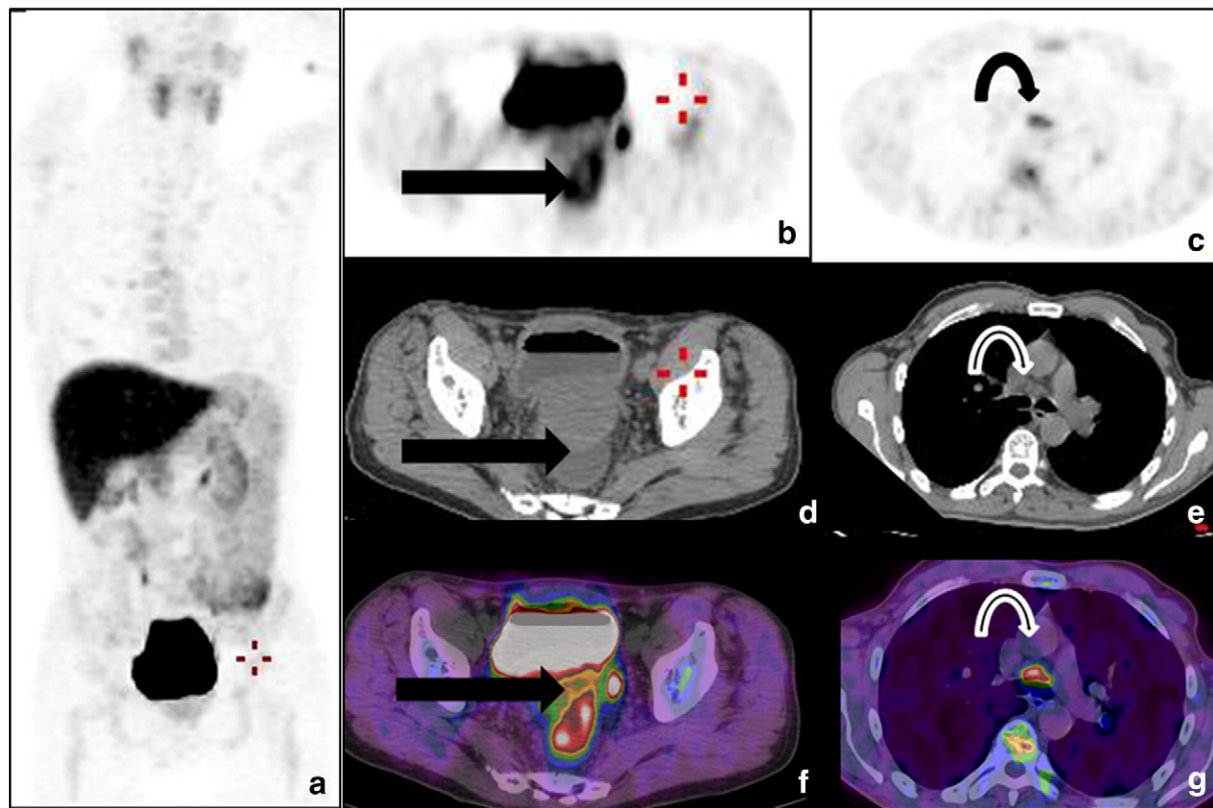


Fig. 12. Maximum intensity projection (a) of a patient with primitive squamous cell cancer of the prostate. High tracer uptake is more evident in axial PET views in the pelvis (a, black arrow) and the mediastinum (b, curved arrow), corresponding to respectively the prostate and to metastatic mediastinal lymph node in related axial CT (b, c) and PET/CT views. Only the repeated histological sample allowed to reach the final diagnosis.

knowledge, this is the first case described in literature as ^{18}F -choline avid [49]. Also in this case, the high rate of tracer uptake was probably due to a faster synthesis of cell membrane expressed by this cancer [50].

Globally, the uptake of radiolabeled choline in malignant tumors could be due to the highest synthesis of cell membrane induced by the faster mitosis of cellular types expressing a high rate of replication, as known for malignant tumors, hepato-cellular [51] and bronchiolo-alveolar carcinoma [21].

Limit of our study was the lack of an adequate follow-up for all described cases, in particular for those cases we classified as non-specific uptake or inflammatory. Furthermore, we did not provide the

histological diagnosis for all registered pitfalls. Anyway, we must state that the recognition of all cited false positive findings, physiological variants and diagnostic pitfalls was of the utmost importance in order to choose the best therapeutic approach when a malignant condition was diagnosed.

In the last decade, several PET radiopharmaceuticals have been proposed for the management of PC patients [28], also taking into account the documented low specificity of radiolabeled choline. Recently, the use of radiolabeled choline PET/CT has significantly reduced its use in the clinical practice due to the marketing of new agents, like ^{68}Ga -Prostate Specific Membrane Antigen (PSMA) [52]. In particular, many

Table 5
The table summarizes some papers developed on patients, suggesting the potential applications of radiolabeled choline, ^{68}Ga -PSMA and ^{18}F -Fluciclovine PET/CT in different clinical settings.

Authors	Journal	Year	Tracer	Clinical setting	Nr. of patients	Trigger PSA	Conclusion
Cimitan et al.[60]	Eur J Nucl Med Mol Imaging	2006	^{18}F -choline	Biochemical relapse	100	4 ng/ml	Useful
Calabria et al.[2]	Nucl Med Commun	2013	^{18}F -choline	Staging	45	18 ng/ml	Limited role
Evangelista et al.[59]	Abdom Imaging	2015	^{18}F -choline	Local recurrence	1031	>2 ng/ml	Limited role
Chiaravallotti et al.[61]	Eur J Nucl Med Mol Imaging	2016	^{18}F -choline	Local recurrence	79	≤2 ng/ml	Limited role
Marzola et al.[5]	Clin Nucl Med	2013	^{18}F -choline	Distant metastases and biochemical relapse	331	>0.2 ng/ml	Useful
Eschmann et al.[3]	Nuklearmedizin	2007	^{11}C -choline	Staging	42	/	Useful only in secondary localization detection.
Castellucci et al.[4]	J Nucl Med	2014	^{11}C -choline	Restaging	605	>0.2 ng/ml	Useful
Freitag et al.[52]	Eur J Nucl Med Mol Imaging	2016	^{68}Ga -PSMA	Restaging	26	/	Useful
Giesel et al.[53]	Eur J Nucl Med Mol Imaging	2016	^{68}Ga -PSMA	Primary tumor location (PET/CT and PET/MRI)	10	/	Useful
Eiber et al.[54]	Eur Urol	2016	^{68}Ga -PSMA	Primary tumor location (PET/MRI)	66	/	Useful
Verburg et al.[55]	Eur J Nucl Med Mol Imaging	2016	^{68}Ga -PSMA	Biochemical relapse	155	/	Useful
Odewole et al.[62]	Eur J Nucl Med Mol Imaging	2016	^{18}F -fluciclovine	Biochemical relapse	53	/	Useful
Nanni et al.[63]	Clin Nucl Med	2015	^{18}F -fluciclovine ^{11}C -choline	Biochemical relapse	50	/	^{18}F -fluciclovine more useful than ^{11}C -choline.

papers documented a good diagnostic performance of ^{68}Ga -PSMA PET/CT and PET/MRI in primary tumor detection and localization [53,54] and in the detection of secondary lymph nodes and bone metastases [52], with a diagnostic accuracy superior or slightly higher than radiolabeled choline PET/CT (Table 5).

Moreover, the detection rate of ^{68}Ga -PSMA PET/CT is also related to the PSA and PSA kinetics at the time of the scan [55]. On a theoretical basis, ^{68}Ga -PSMA is more specific than radiolabeled choline due to its peculiar biological affinity for PC cells; anyway, similarly to radiolabeled choline, it has also been already demonstrated the possibility to detect ^{68}Ga -PSMA uptake in conditions other than PC [56,57]. On the other hand, radiolabeled choline PET/CT shows a very low specificity in the detection of primary PC [58] and local recurrence [59] while ^{68}Ga -PSMA is more useful in these fields due to its specific membrane antigen ligand [54]. However, radiolabeled choline PET/CT remains the most cost-saving technique.

Standing to these considerations, we can hypothesize that radiolabeled choline and ^{68}Ga -PSMA will play complementary roles in different clinical settings of PC.

As future trend, PET/CT with radiolabeled choline should be performed in patients during the restaging of PC with advanced biochemical relapse (in example with PSA higher than 2 ng/ml, supporting the possibility of distant secondary metastases rather than local recurrence) [60,61]. On the other hand, ^{68}Ga -PSMA PET/CT is becoming useful during the staging, for tumor detection or during the early biochemical relapse after surgery or radiotherapy [55]: on this last topic, it has recently demonstrated that, in 32 patients with suspicion of local relapse of prostate cancer after curative therapy (surgery and/or radiotherapy) and a negative ^{18}F -choline PET/CT scan, ^{68}Ga -PSMA PET/CT detected local recurrence in 43.8% (14/32) of the choline negative patients. [62] This study suggests that ^{68}Ga -PSMA is more able than radiolabeled choline in detecting early recurrence of prostate cancer.

However, it is necessary to underline that a conspicuous amount of papers on the diagnostic accuracy of radiolabeled choline PET/CT is actually available with large examined populations, while the interesting results regarding ^{68}Ga -PSMA PET/CT are obtained on limited populations. Moreover, in the panorama of PC imaging, a new tracer, the ^{18}F -fluciclovine [63], is showing encouraging results in terms of diagnostic accuracy in the management of PC patients, even in comparison with ^{11}C -choline [64] (Table 5).

Globally, it is also mandatory to consider the large amount of studies on the diagnostic accuracy of radiolabeled choline PET/CT, which allowed to reach a satisfactory knowledge of the physiologic distribution of this tracer and on the physio-pathologic pathways at the basis of its uptake in several, different conditions as benign lesions, inflammation and malignant tumors that can occur in clinical practice [1,7–16]. Beyond the few cited reports of a case on ^{68}Ga -PSMA [56,57], diagnostic pitfalls linked to the abnormal uptake of ^{68}Ga -PSMA and ^{18}F -fluciclovine still need to be addressed on a large population with studies focused on this topic.

Finally, we must also consider a well-known favorable quality imaging for radiolabeled choline, while preliminary available data suggest a poor quality of imaging due to the entrapment of ^{18}F -fluciclovine in muscular structures, suggesting the necessity of an early imaging window with this tracer, in order to provide the best visual results [65]. On the other hand, ^{68}Ga present high emission positron energy, which could lead a low quality of final imaging [66].

Therefore, despite the potential good diagnostic accuracy of ^{68}Ga -PSMA PET/CT in detecting recurrent PC, especially for low PSA serum levels after primary treatment with curative intent, a *head to head* comparison with radiolabeled choline PET/CT is still missing [67]. The routine use of ^{68}Ga -PSMA in clinical practice is also limited by the registration in several different countries. Considering also this feature, the radiolabeled choline PET/CT still needs to be considered the method of choice in the diagnostic *panorama* of PC imaging. Therefore, the accurate knowledge of its biodistribution and the expertise in the

management of diagnostic pitfalls linked to the increasing growing rate and augmented uptake in cells due to the up-regulation of choline kinase [68], appear to be absolutely necessary.

In conclusion, the interpreting nuclear medicine physician must be aware of the physiological biodistribution of the tracer and about the unusual findings of uptake, in order to avoid misdiagnosis of benign conditions or malignancy, as well as missing out on actual pathology. The clinical history and the exact anatomical evaluation provided by CT are of the utmost importance, in clinical practice. When needed, correlative imaging with MRI is also important. Histological sample is necessary to reach the final diagnosis.

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