Clinical Case Report

Medicine®

OPEN

Osteoblastic bone metastases from neuroendocrine tumor (NET) of unknown origin detected by ^{18}fluorocholine PET/CT and its comparison with ^{68}gallium-DOTATOC PET/CT

Case report and review of the literature

Alberto Bongiovanni, MD[a,*], Federica Recine, MD[a], Monica Celli, MD[b], Giulia Marcantognini, MD[a], Flavia Foca, BSc[c], Chiara Liverani, MSc[a], Valentina Fausti, MD[a], Alessandro De Vita, PhD[a], Giacomo Miserocchi, BSc[a], Laura Mercatali, PhD[a], Dino Amadori, MD[a], Toni Ibrahim, MD[a]

Abstract

Rationale: Choline (CH) positron emission tomography (PET)/computed tomography (CT) with fluorine 18 (^{18}F) CH is increasingly used not only to evaluate patients with biochemically recurrent prostate cancer but also to assess metastatic lesions that are difficult or impossible to identify using more conventional modalities. Our experience with CH PET/CT has shown that it can also be used for many other malignancies.

Presenting concerns: A 71-year-old male with a neuroendocrine tumor (NET) of unknown origin showed osteoblastic bone metastases positive to ^{18}F-CH PET.

Interventions: Diffuse bone and liver metastases were ^{68}gallium-DOTATOC PET-positive with only mild uptake on ^{18}FDG PET/CT. An increased prostate specific antigen (8 μg/L) gave rise to a suspicion of concurrent prostate cancer and the patient underwent ^{18}F-CH PET/CT which showed diffuse uptake in the bone. A CT-guided bone biopsy confirmed osteoblastic bone metastases from NET.

Outcomes: Given the aggressiveness of the tumor, the patient underwent treatment with temozolomide from July 2015 to December 2015, maintaining stable disease. However, progression was documented in January 2016 and the patient was enrolled onto a phase II peptide receptor radionuclide therapy retreatment trial, which is currently ongoing.

Main lesson: Our study highlights that NETs should be taken into consideration in the differential diagnosis of osteoblastic bone metastases showing ^{18}F-CH uptake. A prognostic role for this imaging technique can also be hypothesized.

Abbreviations: CH = choline, CT = computed tomography, ^{18}F = 18 fluoro, ^{68}Ga, 68 gallium, NET = neuroendocrine tumor, PET = positron emission tomography, PRRT = peptide receptor radionuclide therapy.

Keywords: ^{18}F-CH PET/CT, ^{18}FDG PET/CT, ^{68}Ga-PET/CT, neuroendocrine tumor, osteoblastic bone metastases

Editor: Saad Zakko.

Declarations: Ethics approval was not necessary for this study/manuscript due to the type of study design (Case Report). All patient data and photographs are deidentified.

Consent for publication: Written informed consent was obtained from our patient for the publication of this Case Report and accompanying images.

Authorship: AB, GMar, and TI conceived the idea for this case report. CL, FF, VF, ADV, and GMis performed the literature search. MC provided the images and their detailed description. AB, LM, and FR codrafted the manuscript. TI and DA critically evaluated the manuscript for important intellectual content. All authors read and approved the final version of the paper.

The authors have no conflicts of interest to disclose.

[a] Osteoncology and Rare Tumors Center, [b] Diagnostic Nuclear Medicine Unit, [c] Unit of Biostatistics and Clinical Trials, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola, Italy.

[*] Correspondence: Alberto Bongiovanni, Osteoncology and Rare Tumors Center, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Via P. Maroncelli 40, 47014 Meldola, Italy (e-mail: alberto.bongiovanni@irst.emr.it).

Medicine (2017) 96:46(e8567)

Received: 16 June 2017 / Received in final form: 8 October 2017 / Accepted: 18 October 2017

http://dx.doi.org/10.1097/MD.0000000000008567

1. Introduction

Neuroendocrine tumors (NETs) represent a heterogeneous group of relatively rare neoplasms arising from cells of the endocrine system.[1] The incidence of these tumors is low (5.25/100,000/year) but has increased significantly in recent years and prevalence is high (35/100,000/year) given of the long survival of these patients.[2] The medical approach to metastatic disease takes into account the anatomical origin, degree of differentiation, and endocrine function of the tumor, and includes numerous therapeutic options. NETs can be classified as functioning or nonfunctioning according to the presence or not of peptide or hormone secretion. In about 20% to 50% of cases, the primary tumor is of unknown origin, accounting for 2% to 4% of all cancers of unknown primary origin.[3–5]

Tumor grade is determined on the basis of Ki67 proliferation index within the neoplastic cell population; low and medium grade lesions are classified as NETs, whereas high grade lesions are considered to be more aggressive and are classified as neuroendocrine carcinomas.[6] These neoplasms are characterized by an overexpression of somatostatin receptors. ^{68}Gallium (^{68}Ga)-DOTATOC positron emission tomography (PET)/computed tomography (CT) plays a crucial part in the diagnostic and therapeutic management strategies of these tumors.[7–9]

F-fluorodeoxyglucose (FDG) is the most widely used glucose analog for PET imaging studies and is particularly sensitive for tumors exhibiting rapid and aggressive growth.[10] FDG uptake is closely linked to tumor vascularization and hydrocarbon metabolism and, therefore, to its replicating power.[11]

Although radiolabeled choline (CH) PET/CT is widely accepted as a useful tool in prostate cancer staging, several human tumor-derived cell lines of different cancer histologies including breast, colon, prostate, lung, brain, and liver have shown an increased CH metabolism.[12,13] Some authors have also indicated the potential usefulness of ^{11}C- and 18 fluoro (^{18}F)-labeled CH PET/CT in bronchial NETs. No data are available on NETs of different origin.[14,15]

We present the case of a 71-year-old patient with osteoblastic bone metastases positive to ^{18}F-CH PET/CT from a metastatic NET of unknown origin. A comparison was also performed between ^{18}F-CH PET/CT findings and ^{68}Ga PET/CT and ^{18}FDG PET/CT results. We also performed a brief review of the literature, focusing on solid tumors other than from prostate cancer detected by ^{18}F-CH PET/CT. Institutional review board approval and informed consent were waived as this was a retrospective case report with no identifying patient information presented.

2. Case presentation

Ethics approval was not necessary for this work due to its design (Case Report). Written informed consent was obtained from our patient for the submission of this manuscript and accompanying images.

A 70-year-old male with no comorbidities other than essential hypertension was diagnosed with liver metastases from a NET of unknown origin in 2004 and came to our institute for a second opinion. Eastern Cooperative Oncology Group performance status was 0. After a careful review of the patient's medical history, the multidisciplinary medical team recommended a wedge resection of liver segments IV and V, hepatic hilum lymphadenectomy, appendectomy, and cholecystectomy, performed in November of the same year. The histology report revealed liver and lymph node metastases from a well differentiated NET and chronic mild cholecystitis. No evidence of neoplastic disease was found in the other surgical specimens.

In 2010, a whole body CT scan and ^{68}Ga PET/CT showed systemic recurrence with skeletal and liver involvement. The patient also performed a ^{18}FDG-PET/CT which, however, did not show increased metabolic uptake. Given the indolent course of the patient's disease, the multidisciplinary team decided to start 1st-line therapy with long-acting release (LAR) octreotide at a dose of 30 mg following subcutaneous induction. After the 1st subcutaneous administration of octreotide the patient developed dyspnea and glottis edema which rapidly resolved with corticosteroid and antihistamine therapy. Following reevaluation by the multidisciplinary team, the patient was enrolled onto a phase II trial of peptide receptor radionuclide therapy (PRRT).

From August 2010 to May 2011 he completed 5 cycles of ^{177}Lutetium-DOTATATE-PRRT with a cumulative dose of 720 mCi, obtaining a partial response documented in both morphological and metabolic imaging studies. From August 2014 to April 2015 the patient underwent 1st-line metronomic capecitabine, showing a partial response in the liver lesions but progression in terms of the increased number and extension of bone metastases. These unusual findings were discussed by our institute's Osteoncology Multidisciplinary Group and a new radionuclide evaluation with both ^{68}Ga PET/CT and ^{18}F-FDG PET/CT was performed. The former showed widespread, intensely ^{68}Ga-avid skeletal disease (standardized uptake value (SUV)max at the left iliac crest: 83) and liver involvement (SUVmax: 47.6) (Fig. 1A). The ^{18}F-FDG PET/CT revealed very mild to mild tracer uptake in a few pelvic and vertebral bone lesions (SUVmax at the left iliac crest: 4.1) (Fig. 1B).

Given the discrepancy between the visceral and skeletal response to 1st-line chemotherapy and the suspicion of the presence of a concurrent prostatic tumor, a ^{18}F-CH PET/CT was performed. Corresponding ^{18}F-CH PET/CT images documented mild-to-moderate uptake in a number of axial and appendicular skeletal lesions (SUVmax at the left iliac crest: 7.5) (Fig. 1C). Coregistered CT imaging showed a sclerotic pattern of some prominent lumbosacral and pelvic bony lesions that were positive to ^{68}Ga-DOTATOC.

A CT-guided bone biopsy of an osteoblastic lesion at the left iliac crest positive to both ^{18}F-CH and ^{68}Ga PET/CT was carried out (Fig. 2), the histology revealing a bone localization from a NET G1 according to the 2010 WHO classification. Immunohistochemical assays were positive for synaptophysin and negative for prostate specific antigen, chromogranin A, transcription termination factor 1, and caudal type homeobox 2. Ki67 proliferation index was 1% (Fig. 3). The patient underwent treatment with temozolomide from July 2015 to December 2015, maintaining stable disease. However, progression was documented in January 2016 and the patient was enrolled onto a phase II PRRT retreatment trial, which is currently ongoing.

3. Discussion

Over the past decade, the advent of new diagnostic tools such as ^{68}Ga-DOTA-peptide PET/CT and the use of novel therapeutic agents have led to an increase of survival of patients with NETs.[1–4] Thus, the identification of easily assessable prognostic parameters is crucial for an accurate evaluation both at baseline and during the course of the disease because an initially indolent tumor may become aggressive. To this purpose, PET/CTs provide a functional evaluation of the whole tumor burden that is not feasible with the commonly used Ki-67 parameter.[16–19] CH PET/CTs

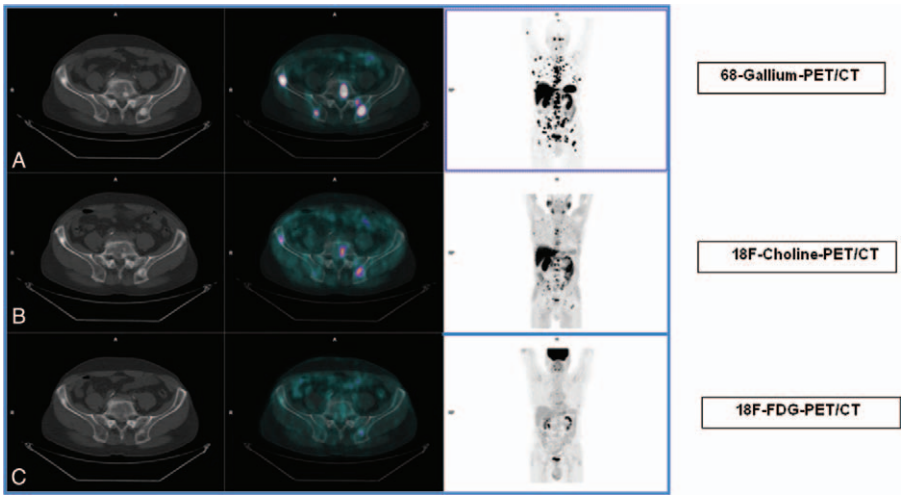

Figure 1. A 71-year-old male treated with temozolomide for advanced NET of unknown origin with widespread bone disease, liver metastases, and increased serum PSA (8.0 ng/mL). (A) ^{68}Ga-DOTATOC PET/CT axial, sagittal, and maximum intensity projection views show widespread intensely ^{68}Ga-DOTATOC-avid skeletal disease (SUVmax at the left iliac crest: 83); and liver involvement (SUVmax: 47.6). (B) Corresponding ^{18}F-FDG PET/CT axial and sagittal views showing very mild-to-mild tracer uptake in a few pelvic and vertebral bone lesions (SUVmax at the left iliac crest: 4.1). (C) Corresponding ^{18}F-FCH PET images document mild-to-moderate ^{18}F-FCH uptake in a number of axial and appendicular skeletal lesions (SUVmax at the left iliac crest: 7.5). ^{18}F-FCH coregistered low-dose CT shows the sclerotic pattern of some prominent lumbosacral and pelvic bone lesions, all positive to ^{68}Ga-DOTATOC. CT = computed tomography, ^{18}F = ^{18}fluoro, FCH = fluorocholine, ^{68}Ga = ^{68}gallium, NET = neuroendocrine tumor, PET = positron emission tomography, PSA = prostate specific antigen, SUV = standardized uptake value.

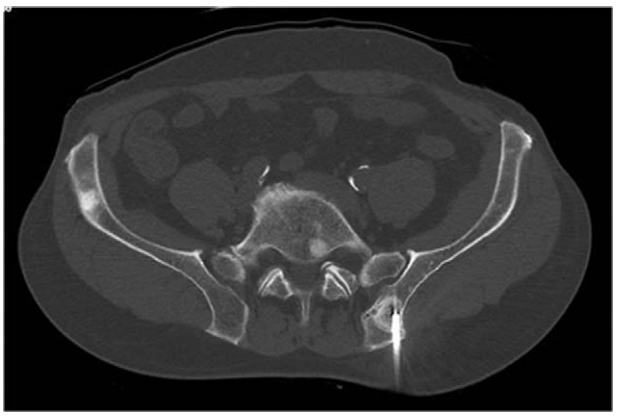

Figure 2. Computed tomography (CT)-guided bone biopsy: CT-guided needle biopsy of the 22-mm oval-shaped sclerotic bone lesion located at the left iliac crest, close to the sacroiliac synchondrosis.

also represent an optimal imaging modality for the assessment of bone metastases from prostate cancer, showing high specificity.[20] Beheshti et al evaluated 70 patients with biopsy-proven prostate cancer submitted to ^{18}F-CH PET/CT for either preoperative staging (n = 32) or follow-up evaluation (n = 38). The accuracy of bone metastasis detection was 84%.[21]

Comparing ^{11}C-CH PET/CT with MRI in prostate cancer staging, Eschmann et al observed similar high accuracy in the detection of bone metastases for both imaging modalities.[22]

Radiolabeled CH uptake reflects the increased demands of this precursor for the synthesis of membrane phospholipids in tumor cells with a high proliferation rate.[21] Based on this, radiolabeled CH was introduced as a PET tracer for brain tumors and prostate cancer in 1970.[12,15] Numerous case reports and clinical studies have also been published on ^{18}F-CH PET/CT positivity in other solid tumors.[13,22] In a recent paper by Sollini et al,[23] 7 patients with biochemical prostate cancer recurrence underwent ^{18}F-CH PET/CT and positive lesions were biopsied. Lung cancer was found in 5 patients, colorectal cancer in 1 patient, and lymph

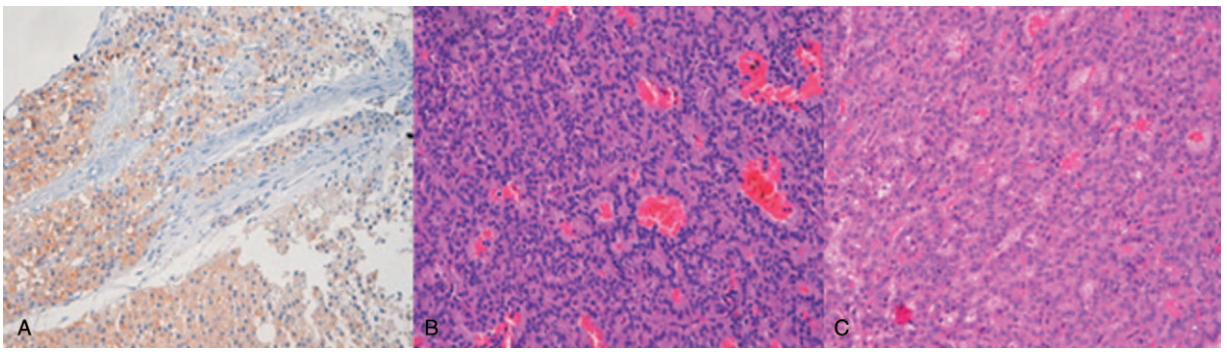

Figure 3. Bone biopsy histology report: osteoblastic bone metastases from NET G1 according to WHO classification, synaptophysin-positive (A) and negative for PSA, chromogranin A, TTF1, and CDX2. Ki67 was 1%. Mitosis and tumor cell necrosis not detected (B, C). CDX2 = caudal type homeobox 2, NET = neuroendocrine tumor, PSA = prostate specific antigen, TTF1 = transcription termination factor 1, WHO = World Health Organization.

node metastases from melanoma in 1 patient. In a case report by Vadrucci et al,[24] a 79-year-old patient with prostate cancer showed ^{18}F-CH uptake in a left pelvic lymph node and the right breast, the latter histologically diagnosed as infiltrating ductal carcinoma. Piccardo et al[25] observed that a lymph node metastasis in the left laterocervical region of a patient with differentiated thyroid cancer was negative to ^{18}F-FDG PET/CT but correctly diagnosed by ^{18}F-CH PET/CT, indicating that F-CH PET/CT may provide more accurate information than ^{18}F-FDG PET/CT on aggressive cancers. Calabria et al[26] reported that benign tumors such as thymoma, adrenal adenoma, sarcoidosis, and meningioma can also be detected by ^{18}F-CH PET/CT, suggesting that these diseases should be evaluated by a nuclear physician because of the intrinsic pharmacologic property of the tracer. How Kit et al[27] reported that there were no apparent differences that could help to distinguish prostate cancer recurrence from other solid tumors in a large series of patients with increasing prostate specific antigen levels who were positive to 18F-FDG and 18F-CH PET/CT. The authors concluded that when more than 1 diagnosis is a possibility, lesions should be biopsied.

To the best of our knowledge, this is the first study to document NET-derived osteoblastic bone metastases detected by ^{18}F-CH PET/CT. The case described highlights some important points. First, it confirms that osteoblastic bone lesion positivity to ^{18}F-CH PET/CT is not only specific for metastases from prostate cancer but also for other solid neoplasms such as NETs. Furthermore, in our patient the shift from negative to positive in ^{18}FDG PET/CT imaging was suggestive of a transformation from indolent to more aggressive disease not detected by bone biopsy and less responsive to treatment.

CH is a precursor of phosphatidylcholine which is a membrane lipids component. The synthesis of lipid membrane and DNA takes place during cell proliferation.[28] Aberrant CH metabolism characterized by increased phosphocholine and total CH-containing compounds reflects the complex interactions between cellular metabolism and proliferative signaling.[29] An increased CH metabolism related to a greater activity of choline kinase-α has been reported in various human malignancies, suggesting a prognostic role of choline kinase-α overexpression.[14] In our patient, ^{68}Ga PET/CT showed a high expression of somatostatin receptors that correlated with a more indolent clinical course, whereas ^{18}F-FDG PET/CT uptake indicated more aggressive disease. Of note, ^{18}F-CH PET/CT was more sensitive than ^{18}F-FDG PET/CT in several of the bone lesions, reflecting the capacity of the former scan to detect early changes in the metabolic behavior of the tumor. This could be useful for tumors in which prognostic factors are lacking.

4. Conclusions

^{18} F-CH PET/CT interpretation can be challenging because of the possibility of tracer uptake from other solid malignancies and benign lesions. NETs should also be included in the differential diagnosis of osteoblastic bone metastases showing ^{18}F-CH PET/CT uptake. Our findings suggest a potential prognostic role of ^{18}F-CH PET/CT, which proved more sensitive than ^{18}F-FDG PET/CT in our patient, in NETs. Further investigation is warranted.

Acknowledgements

The authors thank Gráinne Tierney for editorial assistance.

References

[1] Oberg K, Eriksson B. Endocrine tumours of the pancreas. Best Pract Res Clin Gastroenterol 2005;19:753–81.
[2] Halfdanarson TR, Rubin J, Farnell MB, et al. Pancreatic endocrine neoplasms: epidemiology and prognosis of pancreatic endocrine tumors. Endocr Relat Cancer 2008;15:409–27.
[3] Clark OH, Benson AB3rd, Berlin JD, et al. NCCN Neuroendocrine Tumors Panel Members: NCCN Neuroendocrine Tumors Panel Members NCCN Clinical Practice Guidelines in Oncology: neuroendocrine tumors. J Natl Compr Canc Netw 2009;7:712–47.
[4] Modlin IM, Oberg K, Chung DC, et al. Gastroenteropancreatic neuroendocrine tumours. Lancet Oncol 2008;9:61–72.
[5] Kirshbom PM, Kherani AR, Onaitis MW, et al. Carcinoids of unknown origin: comparative analysis with foregut, midgut, and hindgut carcinoids. Surgery 1998;124:1063–70.
[6] Klimstra DS, Modlin IR, Coppola D, et al. The pathologic classification of neuroendocrine tumors: a review of nomenclature, grading, and staging systems. Pancreas 2010;39:707–12.
[7] Treglia G, Castaldi P, Rindi G, et al. Diagnostic performance of gallium-68 somatostatin receptor PET and PET/CT in patients with thoracic and gastroenteropancreatic neuroendocrine tumours: a meta-analysis. Endocrine 2012;42:80–7.
[8] Kayani I, Conry BG, Groves AM, et al. A comparison of 68Ga-DOTATATE and 18F-FDG PET/CT in pulmonary neuroendocrine tumors. J Nucl Med 2009;5:1927–32.
[9] Jindal T, Kumar A, Venkitaraman B, et al. Role of (68)Ga-DOTATOC PET/CT in the evaluation of primary pulmonary carcinoids. Korean J Intern Med 2010;25:386–91.
[10] Reske SN, Kotzerke J. FDG-PET for clinical use. Results of the 3rd German Interdisciplinary Consensus Conference, "Onko-PET III". Eur J Nucl Med 2001;28:1707–23.
[11] Bombardieri E, Aktolun C, Baum RP, et al. FDG-PET prodeure guidelines for tumour imaging. Eur J Nucl Med Mol Imaging 2003;30: BP115-124.
[12] Bauman G, Belhocine T, Kovacs M, et al. (18)F-fluorocholine for prostate cancer imaging: a systematic review of the literature. Prostate Cancer Prostatic Dis 2012;15:45–55.
[13] Peng Z, Liu Q, Li M, et al. Comparison of (11)C-choline PET/CT and enhanced CT in the evaluation of patients with pulmonary abnormalities and locoregional lymph node involvement in lung cancer. Clin Lung Cancer 2011;13:312–20.
[14] Vallabhajosula S. 18F-labeled positron emission tomographic radiopharmaceuticals in oncology: an overview of radiochemistry and mechanisms of tumor localization. Semin Nucl Med 2007;37: 400–19.
[15] Hara T, Kosaka N, Shinoura N, et al. PET imaging of brain tumor with [methyl-11C]choline. J Nucl Med 1997;38:842–7.
[16] Ramirez de Molina A, Rodríguez-González A, Gutiérrez R, et al. Overexpression of choline kinase is a frequent feature in human tumor-derived cell lines and in lung, prostate, and colorectal human cancers. Biochem Biophys Res Commun 2002;296:580–3.
[17] Treglia G, Lococo F, Petrone G, et al. Pulmonary neuroendocrine tumor incidentally detected by 18F-CH PET/CT. Clin Nucl Med 2013;38: e196-169.
[18] Ambrosini V, Campana D, Bodei L, et al. 68Ga-DOTA-NOC PET/CT clinical impact in patients with neuroendocrine tumors. J Nucl Med 2010;51:669–73.
[19] Pavel M, O'Toole D, Costa F, et al. ENETS consensus guidelines update for the management of distant metastatic disease of intestinal, pancreatic, bronchial neuroendocrine neoplasms (NEN) and NEN of unknown primary site. Neuroendocrinology 2016;103:172–85.
[20] Kitajima K, Murphy RC, Nathan MA. Choline PET/CT for imaging prostate cancer: an update. Ann Nucl Med 2013;27:581–9.
[21] Beheshti M, Vali R, Waldenberger P, et al. The use of F-18 choline PET in the assessment of bone metastases in prostate cancer: correlation with morphological changes on CT. Mol Imaging Biol 2010;12: 98–107.
[22] Eschmann SM, Pfannenberg AC, Rieger A, et al. Comparison of 11C-choline-PET/CT and whole body-MRI for staging of prostate cancer. Nuklearmedizin 2007;46:161–8.
[23] Sollini M, Pasqualetti F, Perri M, et al. Detection of a second malignancy in prostate cancer patients by using [18F]Choline PET/CT: a case series. Cancer Imaging 2016;16:27.
[24] Vadrucci M, Gilardi L, Grana CM. Breast cancer incidentally detected by 18F-choline PET/CT in a patient with recurrent prostate carcinoma. Clin Nucl Med 2016;41:892–3.

[25] Piccardo A, Massollo M, Bandelloni R, et al. Lymph node metastasis from tall-cell thyroid cancer negative on 18F-FDG PET/CT and detected by 18F-Choline PET/CT. Clin Nucl Med 2015;40:e417–9.
[26] Calabria F, Chiaravalloti A, Schillaci O. (18)F-choline PET/CT pitfalls in image interpretation: an update on 300 examined patients with prostate cancer. Clin Nucl Med 2014;39:122–30.
[27] How Kit N, Dugué AE, Sevin E, et al. Pairwise comparison of 18F-FDG and 18F-FCH PET/CT in prostate cancer patients with rising PSA and known or suspected second malignancy. Nucl Med Commun 2016;37:348–55.
[28] Yoshimoto M, Waki A, Obata A, et al. Radiolabeled choline as a proliferation marker: comparison with radiolabeled acetate. Nucl Med Biol 2004;31:859–65.
[29] Glunde K, Bhujwalla ZM, Ronen SM. Choline metabolism in malignant transformation. Nat Rev Cancer 2011;11:835–48.