

Personalized Imaging Approach in the Clinical Diagnosis of Prostate Cancer with Suspicion of Liver Metastases

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Abstract

The diagnostics of liver metastases in prostate cancer is challenging, while liver is seldom the primary site, and rarely the only primary metastatic organ.

Here we present two cases where liver metastases were suspected in prostate cancer patients. The differential diagnostics was successful by using ¹⁸F-choline PET/CT. The findings were confirmed by liver biopsy and consequent immunohistochemistry including PSA-staining. The first case verified liver as only metastatic site of prostate cancer and the second case appeared to be another primary cancer.

Keywords: Prostate cancer; Liver metastases; Fluorocholine PET; Immunohistochemistry

Received: October 24, 2015; **Accepted:** December 14, 2015; **Published:** December 28, 2015

Introduction

Liver metastases are not rare in prostate cancer (PCa), in a large autopsy material of more than 1500 patients 25% cases had liver metastases [1] and in a large clinical material of more than 4000 patients liver metastases was found approximately in 4% of all cases [2]. In the large autopsy material bone (90%) and lung (46%) were more common sites for hematogenic metastatic spread [1]. But there are seldom conditions where the primary metastatic site is liver. In a French study of 345 patients with metastatic prostate cancer, six patients had liver metastases as the first site of metastatic disease, and for one of them, liver were the only metastatic site [3].

Choline for PET/CT is a routine diagnostic agent for prostate cancer which has European Medical Evaluation Agency (EMA) approval in more than 20 European countries, and a recent meta-analysis in more than 3000 patients demonstrates its capability especially in nodal and metastatic PCa [4]. The sensitivity is dependent on Gleason score [5]. ¹⁸F-fluorocholine [chemical name known as [¹⁸F] fluoromethyl-dimethyl-2-hydroxyethyl-ammonium, (FCH)] shows particular promise as a PCa imaging agent [6-9].

At our institution we use FCH routinely for staging of prostate cancer [4] and radiation therapy (RT) dose planning of PCa [10,11].

We present two cases where liver metastases were suspected in prostate cancer patients. The differential diagnostics was successful by using ¹⁸F-choline PET/CT. The findings were

confirmed by liver biopsy and consequent immunohistochemistry including PSA-staining.

Case Histories

The first man was 59 year old having some urge without other urinary symptoms. His initial serum PSA was 9.8 µg/l/12% and clinically he had T3 disease in the left lobe of the prostate. In biopsies he had Grade 3, Gleason Score 7 (4+3), i.e. medium-high risk adenocarcinoma which covered 30% of the sample material. No metastases were seen in bone scintigraphy. Following radical prostatectomy and lymphadenectomy (9 obturator lymph nodes from the left and 11 obturator lymph nodes from the

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right) the staging appeared to be T3bN0M0 and Gleason Score was confirmed to be 7. But due to the marginal positivity he received postoperative radiotherapy of 66 Gy in 2 Gy fractions to the prostate fossa. Following prostatectomy the AMS AdVance XP male sling operation was done due to the incontinence. New

incontinence operation was planned but was cancelled due to the relapse of the prostate cancer.

18 months after the prostatectomy the PSA was zero, but year later PSA increased up to 6.44 and patient became to Docrates Cancer Center where ^{18}F -choline PET/CT and (sodium- ^{18}F -

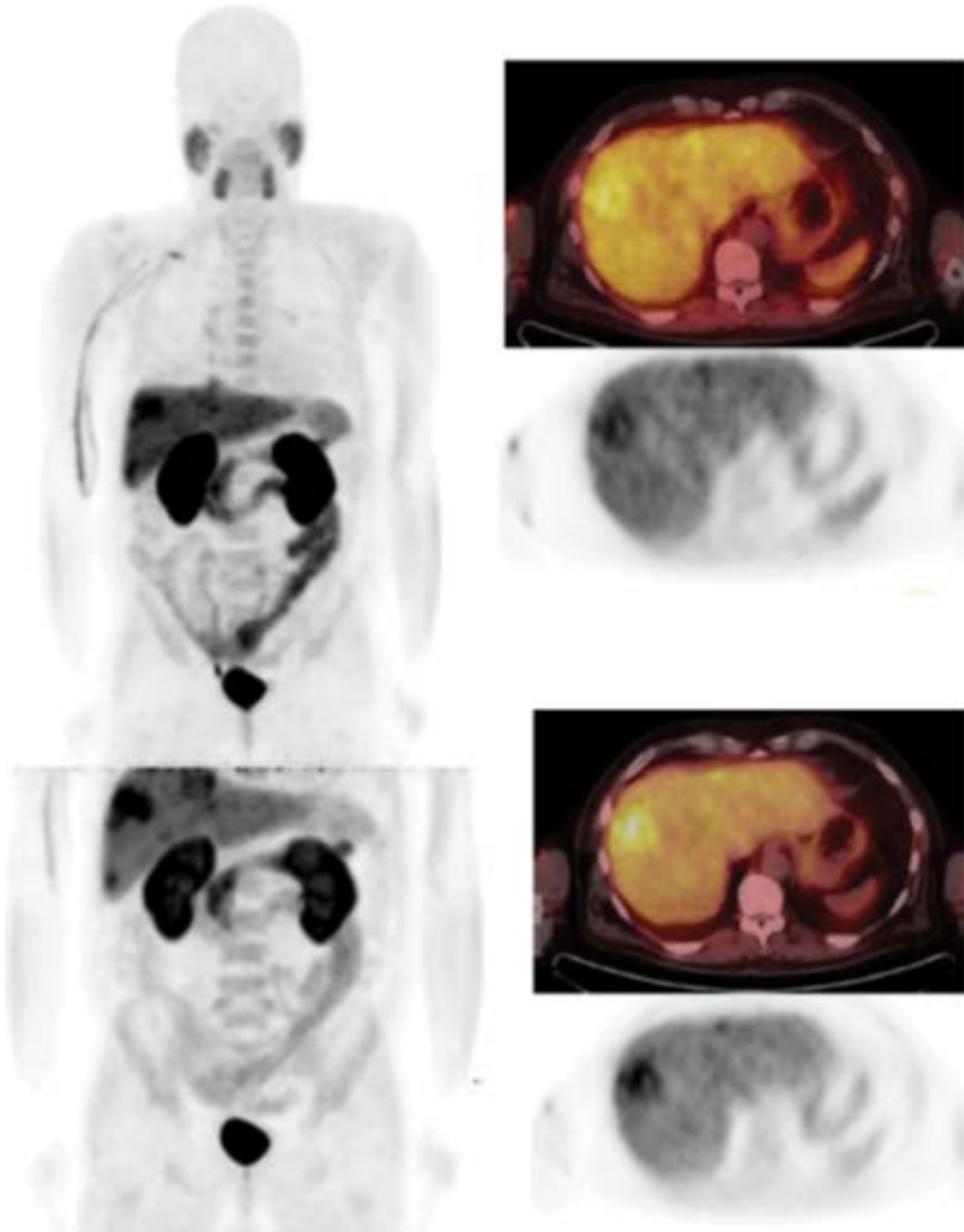


Figure 1 MIP (maximum intensity)-projection of the ^{18}F -FCH-PET study demonstrates 4 larger liver lesions and no other pathologic uptakes (upper panel, left) in the early imaging. In the late imaging at 60 min the MIP-projection of the ^{18}F -FCH-PET study delineates better these 4 larger liver lesions (lower panel, left). One uptake is shown in the transaxial images (PET/CT fusion images and PET images) in the early imaging (upper panel, right) and the signal is better in the late PET/CT fusion images and PET images (lower panel, right). The SUV maximum in liver lesions varied from 9.3 to 12.6 in the early images, from 9.4 to 13.0 in the late images. PSA staining was positive from the liver biopsy specimen consistent with prostate carcinoma metastases (**Figure 3**).

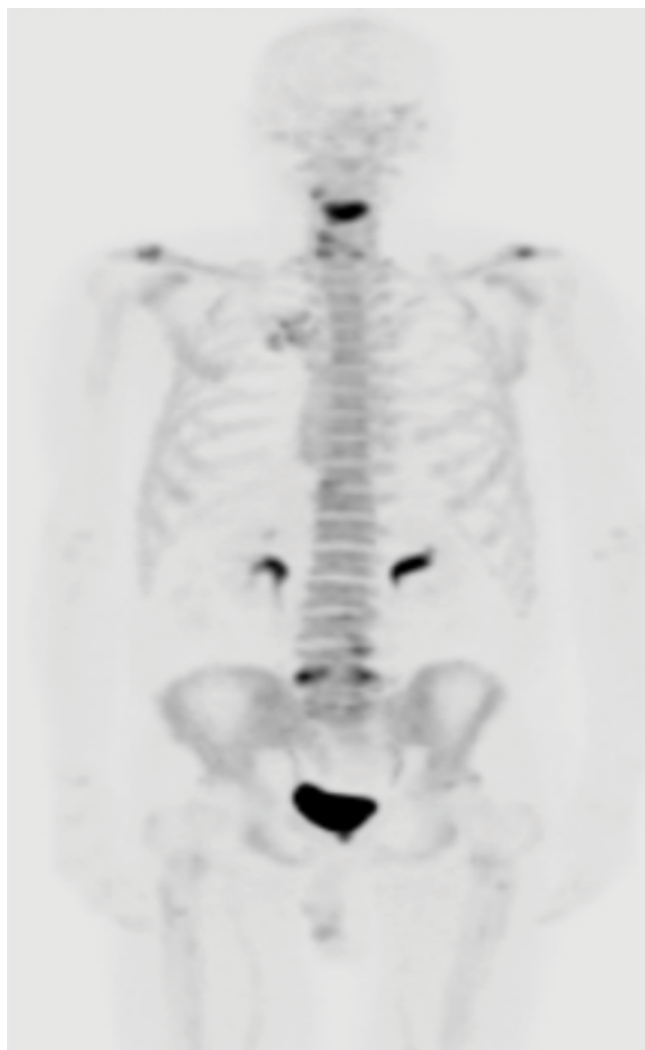


Figure 2 MIP-image of the whole body Na¹⁸F-PET/CT study. No metastatic findings were seen on Na¹⁸F-PET. Only weak degenerative changes were observed in the cervical and lumbar spine.

fluoride) Na¹⁸F-PET/CTs were performed. FCH-PET-study revealed four larger liver lesions, where SUVmax-values varied from 9.3 to 12.6 in the early images, and from 9.4 to 13.0 in the late images. Normally PCa spreads into the bone and/or local lymph nodes, but these regions did not demonstrate any pathologic findings (**Figure 1**). Also, the skeleton was free from metastatic findings, as Na¹⁸F-PET study demonstrates (**Figure 2**).

Liver metastases were biopsied and the histological analysis revealed PSA positive prostate cancer (**Figure 3**). Docetaxel chemotherapy started.

The second man was 75 year old in good general condition who had regular clinical follow-up visits due to the mild unspecific kidney failure. Due to his age he wanted more complete urological check-up although he had no urological symptoms. Clear resistance in the apex of the prostate was observed by digital rectal examination and his initial PSA appeared to be elevated up to 10.4. In endorectal multiparametric MRI the size of the prostate was measured to be 36 g having some central hypertrophy. The tumor in the apex had ADC (apparent diffusion coefficient) of $0.7 \times 10^{-3} \text{ mm}^2/\text{s}$. In dynamic contrast enhanced images it was hypervascular and the tumor diameter was 1 cm. According to the radiologist's analysis it looked more aggressive than Gleason Score 6 disease. Gleason Score 7 (3+4) diagnosis was also confirmed from biopsies. The cancerous transformation covered 10% of the biopsy sample. In choline- and Na¹⁸F-PET-CT we could not see any disseminated uptake of markers outside the prostate (**Figure 4**). However, in the liver there seemed to be unclear tumorous focus of 7 cm surrounding ligamentum falciforme. Based on abdominal CT the tumor in the liver was hypovascular arising suspicion more about cholangiocarcinoma than Hepatocellular Carcinoma (HCC). Tumor was biopsied and seemed to be PSA negative metastatic adenocarcinoma. The values of tumor markers were AFP 15 IU/l, CEA 3.6 $\mu\text{g}/\text{l}$ and CA19-9 4 IU/l.

Patient received prophylactic single fraction irradiation of the mamillas and Degarelix + Bicalutamide started.

Left lobe of the liver resected 3 months after primary prostate cancer diagnosis. The histopathological diagnosis of the liver

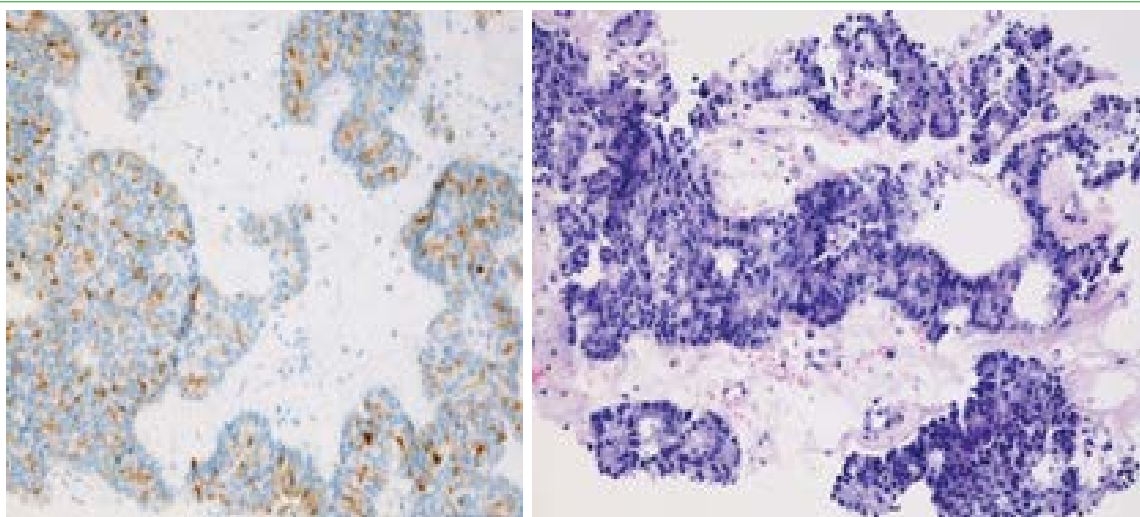


Figure 3 PSA-staining and HE-staining.

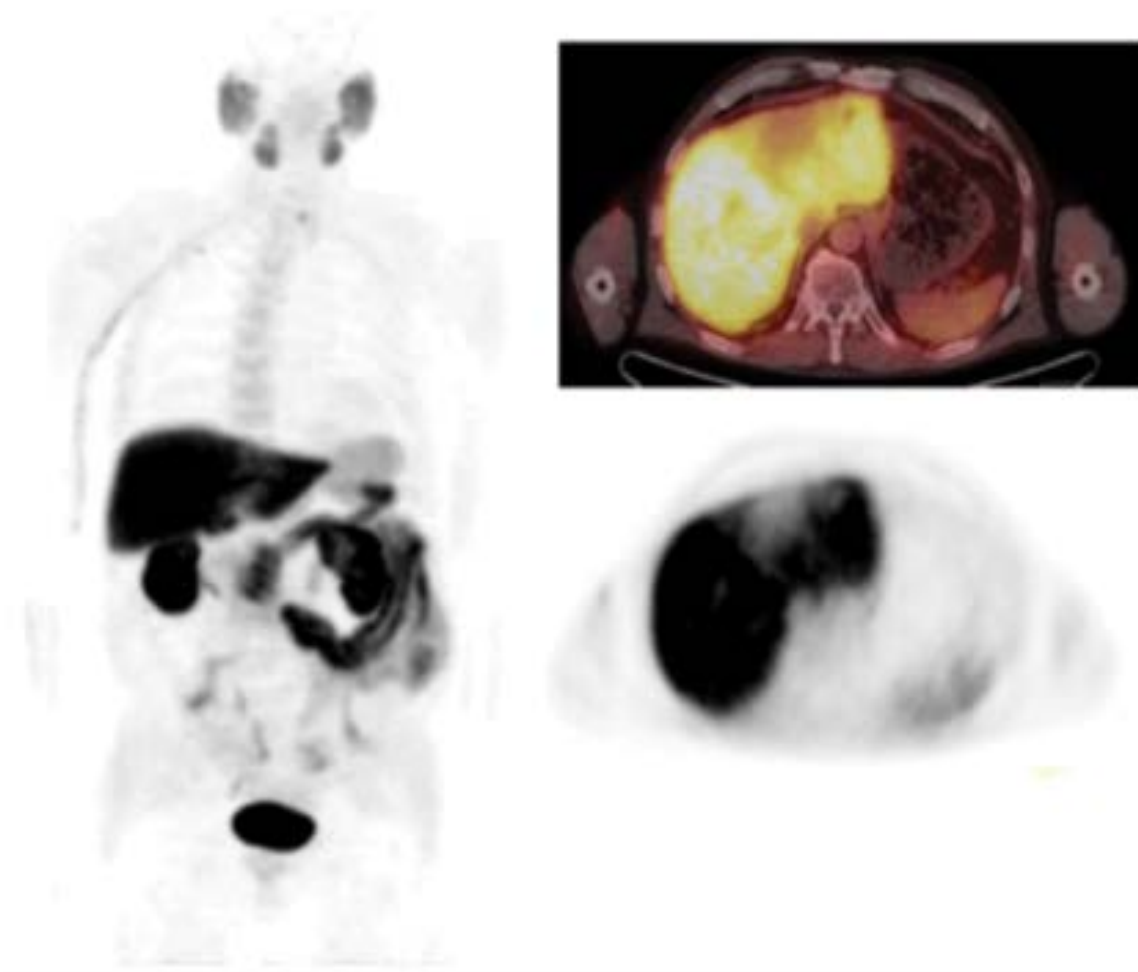


Figure 4 MIP-projection of the FCH-PET study demonstrates defect in the liver, weak uptake in the prostate (right apex) and another uptake in the left lobe of the thyroid (on the left). The defect in the liver is seen better in transaxial images; PET/CT fusion images (upper panel, right) and PET images (lower panel, right). The average SUV in liver was 9.3 whereas in the lesion it was only 4.6. PSA staining was negative from the liver biopsy consistent with histological diagnosis of cholangiocarcinoma.

tumor was confirmed to be cholangiocarcinoma and the resection was radical.

T3N0M0 prostate cancer radiotherapy with VMAT RapidArc technique was given 5-7 months following initial diagnosis as image guided radiotherapy giving 45/1.8 Gy to the pelvic lymph nodes, 50 Gy to the seminal vesicles and 80 Gy in 2 Gy fractions to the prostate. Hormone therapy was not continued after radiotherapy.

Written informed consent was obtained from both of the patients for publication of this case report and accompanying images. Copies of the written consents are available for review by the Editor-in-Chief of this journal.

Discussion

Liver metastases are uncommon although not very rare, but appear to be a rather late event in the course of the disease [2]. They are frequently associated with neuroendocrine characteristics [2,3]. Hematogeneous metastases were present in

35% of 1,589 patients with prostate cancer, with most frequent involvement being bone (90%), lung (46%), liver (25%), pleura (21%), and adrenals (13%) [1].

In the literature one example with prostate liver metastases, C-11-choline [12] was not able to demonstrate metastatic liver disease, in contrast to our findings. C-11 has a short half-life, 20 min, which is a drawback in the diagnosis. In normal metabolism choline in the liver gives some background, but it decreases significantly already e.g. at 60 min. The lesions are clear in **Figure 1**.

It is known from the literature that hepatocellular carcinoma and similar conditions are hypometabolic, i.e. cause a defect in the FCH-PET-studies [13]. Also, quantitative differential diagnosis of hepatocellular adenoma and focal nodular hyperplasia is possible using ^{18}F -fluorocholine PET/CT based on hypometabolism degree [14].

FDG may demonstrate liver metastases [15], but FDG is not a good tracer for PCa [4]. There are other tracers [11,16], which may play pivotal role in the differential diagnosis of PCa by molecular

imaging -one of them is ^{68}Ga -PSMA. In the literature a case is presented where ^{68}Ga -PSMA was able to detect liver metastases [17]. We also know that FCH is helpful in the differential diagnosis of liver metastases in PCa, especially if late imaging is applied to improve the signal in liver (**Figure 1**). FCH is known to specific for prostate cancer: The sensitivity of FCH was 46-49%, whereas specificity was 92-95% in two large reviews of more than 2000 patients [4,18].

At this moment FCH-imaging is considered as a standard method in the staging and detection of biochemical relapse

in PCa. Thousands of patients have been studied (4,5). Very little is known about detection liver metastases. Therefore, we recommend that late imaging covers liver region and it should be performed at least 60 minutes after injection. With ^{11}C liver metastasis detection might be problematic, because of its short half-life of 20 minutes very late imaging is not possible.

Conflicts of Interest

Written informed consents were obtained from the patients for publication of this Case report and all accompanying images. Copies of the written consents are available for review by the Editor-in-Chief of this journal.

References

- 1 Bubendorf L, Schöpfer A, Wagner U, Sauter G, Moch H, Willi N, et al. (2000) Metastatic patterns of prostate cancer: An autopsy study of 1,589 patients. *Human Pathology* 31: 578–583.
- 2 Wang H, Li B, Zhang P, Yao Y, Chang J (2014) Clinical characteristics and prognostic factors of prostate cancer with liver metastases. *Tumour Biol* 35: 595-601.
- 3 Pouessel D, Gallet B, Bibeau F, Avancès C, Iborra F, et al. (2007) Liver metastases in prostate carcinoma: clinical characteristics and outcome. *BJU Int* 99: 807-811.
- 4 von Eyben FE, Kairemo K (2014) Meta-analysis of ¹¹C-choline and ¹⁸F-choline PET/CT for management of patients with prostate cancer. *Nucl Med Commun* 35: 221-230.
- 5 Cimitan M, Evangelista L, Hodolič M, Mariani G, Baseric T, et al. (2015) Gleason score at diagnosis predicts the rate of detection of ¹⁸F-choline PET/CT performed when biochemical evidence indicates recurrence of prostate cancer: experience with 1,000 patients. *J Nucl Med* 56: 209-215.
- 6 Schmid DT, John H, Zweifel R, Cservenyak T, Westera G, et al. (2005) Fluorocholine PET/CT in Patients with Prostate Cancer: Initial Experience. *Radiology* 235: 623–628.
- 7 Jadvar H (2011) Prostate Cancer: PET with ¹⁸F-FDG, ¹⁸F- or ¹¹C-Acetate, and ¹⁸F- or ¹¹C-Choline. *J Nucl Med* 52: 81–89.
- 8 Beheshti M, Imamovic L, Broinger G, Vali R, Waldenberger P, et al. (2010) ¹⁸F Choline PET/CT in the Preoperative Staging of Prostate Cancer in Patients with Intermediate or High Risk of Extracapsular Disease: A Prospective Study of 130 Patients. *Radiology* 254: 925-933.
- 9 Kwee SA, Wei H, Sesterhenn I, Yun D, Coel MN (2006) Localization of Primary Prostate Cancer with Dual-Phase ¹⁸F-Fluorocholine PET. *J Nucl Med* 47: 262–269.
- 10 Weber DC, Wang H, Cozzi L, Dipasquale G, Khan HG, et al. (2009) RapidArc, intensity modulated photon and proton techniques for recurrent prostate cancer in previously irradiated patients: a treatment planning comparison study. *Radiation Oncology* 34.
- 11 von Eyben FE, Kairemo K, Kiljunen T, Joensuu T (2015) Planning of External Beam Radiotherapy for Prostate Cancer Guided by PET/CT. *Curr Radiopharm* 8: 19-31.
- 12 García JR, Franquet E, Romera N, Moragas M, Jorcano S, et al. (2014) Bajo rendimiento diagnóstico de la PET/TC con ¹¹C-colina en la detección de metastasis hepaticas de origen prostático [Low diagnostic yield of the ¹¹C-choline PET/CT in the detection of liver metastasis from prostate cancer]. *Rev Esp Med Nucl Imagen Mol* 33: 56-57.
- 13 Talbot JN, Fartoux L, Balogova S, Nataf V, Kerrou K, et al. (2010) Detection of hepatocellular carcinoma with PET/CT: a prospective comparison of ¹⁸F-fluorocholine and ¹⁸F-FDG in patients with cirrhosis or chronic liver disease. *J Nucl Med* 51: 1699-1706.
- 14 van den Esschert, Bieze M, Beuers UH, van Gulik TM, Bennink RJ (2011) Differentiation of hepatocellular adenoma and focal nodular hyperplasia using ¹⁸F-fluorocholine PET/CT. *Eur J Nucl Med Mol Imaging* 38: 436-440
- 15 Shreve PD, Grossman HB, Gross MD, Wahl RL (1996) Metastatic prostate cancer: initial findings of PET with 2-deoxy-2-[F-18]fluoro-D-glucose. *Radiology* 199: 751-756.
- 16 Jadvar H (2015) Imaging cellular proliferation in prostate cancer with positron emission tomography. *Asia Oceania J Nucl Med Biol* 3: 72-76.
- 17 Afshar-Oromieh A, Zechmann CM, Malcher A, Eder M, Eisenhut M, et al. (2014) Comparison of PET imaging with a ⁶⁸Ga-labelled PSMA ligand and ¹⁸F-choline-based PET/CT for the diagnosis of recurrent prostate cancer. *Eur J Nucl Med Mol Imaging* 41: 11-20.
- 18 Evangelista L, Guttilla A, Zattoni F, Muzzio PC, Zattoni F (2013) Utility of choline positron emission tomography/computed tomography for lymph node involvement identification in intermediate- to high-risk prostate cancer: a systematic literature review and meta-analysis. *Eur Urol* 63: 1040-1048.