European Journal of Radiology 81 (2012) e893–e896

Contents lists available at SciVerse ScienceDirect

European Journal of Radiology

journal homepage: www.elsevier.com/locate/ejrad

Role of ^{11}C-choline PET/CT in the re-staging of prostate cancer patients with biochemical relapse and negative results at bone scintigraphy

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ARTICLE INFO

Article history:
Received 15 July 2011
Accepted 26 April 2012

Keywords:
Prostate cancer
Positron emission tomography (PET)
^{11}C-choline
PSA
Bone scan

ABSTRACT

Aim: to evaluate the utility of ^{11}C-choline PET/CT in prostate cancer (PC) patients who have demonstrated a biochemical recurrence and a negative bone scintigraphy (BS).
Materials and methods: 123 consecutive PC patients (mean age 67.6 years; range 54–83) with a biochemical relapse (mean PSA value 3.3 ng/mL; range 0.2–25.5) after radical prostatectomy (RP) were included in our retrospective study. Patients underwent a BS that resulted negative and a ^{11}C-choline PET/CT within 4 months from BS (range: 1 day to 4 months; mean: 2.5 months). Validation of results was established by: (1) a positive biopsy, (2) a positive subsequent BS, CT or MR and (3) a normalization of ^{11}C-choline uptake after systemic therapy or a progression of the disease.
Results: ^{11}C-choline PET/CT was positive in 42/123 patients (34.1%). ^{11}C-choline PET/CT detected lesions in: bone (10 patients), lymph-nodes (20 patients), bone and lymph nodes (7 patients), bone and lung (1 patient), lymph-nodes and lung (1 patient), local relapse (3 patients). Overall, ^{11}C-choline PET/CT showed a total of 30 unknown bone lesions in 18/123 (14.6%) patients.
Conclusion: ^{11}C-choline PET/CT showed a better sensitivity than BS in patients with biochemical relapse after RP: ^{11}C-choline PET/CT detected unknown bone lesions in 18/123 (14.6%) patients.

1. Introduction

The follow up of patients with prostate cancer (PC) after radical prostatectomy (RP) is based on measurement of PSA serum levels. Biochemical relapse is defined as a PSA value over 0.2 ng/mL [1]. Bone metastases are a frequent complication of PC: about 65–75% of men with advanced disease demonstrate bone localizations [2].

Conventional imaging (CI) methods, such as computed tomography (CT), magnetic resonance (MR), trans-rectal ultrasound (TRUS) and bone scan (BS), have been widely used during restaging of the disease, although they have shown a low sensitivity [3,4]. BS itself rarely detects skeletal metastasis in patients with PSA levels lower than 10 ng/mL [5,6].

In recent years PET/CT has emerged as a promising molecular imaging tool for detection of PC recurrences in patients with biochemical relapse. Good results were obtained by choline, that can be labeled with either ^{11}C (^{11}C-choline) and ^{18}F (^{18}F-fluorocholine). Choline is a substrate for the synthesis of phosphatidylcholine, which is the major phospholipid in the cell membrane [7]. Choline kinase activity is substantially up-regulated in tumor cells [8]. The uptake of ^{11}C-choline seems to be mediated by a selective choline transporter as showed by a recently published *in vitro* study by Muller et al. [9].

Even though the detection rate for recurrent disease with ^{18}F or ^{11}C-choline PET/CT decreases at lower levels of PSA, overall the technique seems to be more sensitive than CI modalities [10,11]. Since the metastatic spread to the skeleton in the natural history of patients with PC is frequent and the sensitivity of BS is low, we wanted to assess the added value of PET/CT with ^{11}C-choline in the early detection of bone lesions in patients with prostate cancer during follow up.

The aim of our retrospective study was to assess the utility of ^{11}C-choline PET/CT in the restaging of PC patients who showed negative result at BS.

2. Material and methods

2.1. Patient population

The study was performed according to the declaration of Helsinki and to national regulations. All patients gave informed

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http://dx.doi.org/10.1016/j.ejrad.2012.04.027

consent to participate and for the anonymous publication of data.

One hundred and twenty-three consecutives PC patients (mean age 67.6 years; range 54–83) treated by RP as a primary treatment and showing a biochemical relapse (mean PSA value 3.3 ng/mL; range 0.2–25.5) were included in our retrospective study. All patients underwent a BS to re-stage the disease that resulted negative for the presence of bone metastasis. All patients underwent a ^{11}C-choline PET/CT within 4 months from BS (Mean time = 2.5 months; range 1 day to 4 months). Twenty-two out of 123 patients received anti-hormonal therapy at the time of the two scans. In the window period between BS and ^{11}C-choline PET/CT none of the patients received any additional therapy or changed the on going therapy (Table 1).

2.2. Radiopharmaceuticals

BS was performed after the injection of ^{99m}Tc-DPD (3,3-diphosphono-1,2-propane-dicarbon acid) (TECEOS; CIS bio international). ^{11}C-choline was synthesized according to the solid-phase method, essentially as described by Pascali et al. [12], in a modified commercial synthesis module (TRACERlab; GE Healthcare).

2.3. Imaging protocol

In 40/123 patients BS was performed in our centers following standard procedure: simultaneous anterior/posterior whole-body images were obtained 3 h after the intravenous injection of about 750 MBq ^{99m}Tc-DPD. Images were acquired with a dual headed gamma-camera ECAM (SIEMENS, Germany) equipped with low energy high resolution (LEHR) collimators. Doubtful findings were investigated with additional planar or SPECT acquisitions on selected regions. In the remaining 83 patients BS was performed in other centers with planar and/or SPECT acquisitions and reported as negative. Images (on film = 52 pts; on paper = 31 pts) were retrospectively reviewed in our departments by two nuclear medicine physicians and, according to previous report, defined as negative.

All ^{11}C-choline PET/CT scans were performed at Bologna center and obtained with Discovery LS or Discovery STE (GE Healthcare). Patients received an intravenous injection of 370–555 MBq of ^{11}C-choline. PET/CT scan started 3–5 min after the injection, emission data were acquired at 5–6 bed positions from the mid thigh to the base of the skull, taking 4 min for each position. The CT parameters were 120 kVp, 60 mA, 0.8 s per tube rotation, slice thickness of 5 mm, pitch of 1.5, and a table speed of 30 mm/rotation. CT images were used for both attenuation correction of emission data and image fusion.

All ^{11}C-choline PET/CT images were assessed visually, and interpreted by consensus of two experienced nuclear medicine physicians aware of the clinical data. In doubtful cases diagnosis was reached by consensus. Attenuation correction CT images were interpreted also using bone window and bone lesions were visually classified as osteoblastic, lytic or mixed.

2.4. Final assessment

Positive ^{11}C-choline PET/CT findings were considered to be true positive if they were confirmed by any one of the following: (1) a positive biopsy (only three cases: one bone lesion an two local relapses); (2) confirmation of the same lesion by other imaging procedures that had been carried out within 6 months after ^{11}C-choline PET/CT scan, including a subsequent BS, CT or MR; (3) positive lesions showing a normalization of ^{11}C-choline-uptake in a subsequent scan following systemic therapy and a clear alteration on CT images or an evidence of malignancy on other CI modalities; (4) a progression of the disease.

Table 1
Patient population characteristics.

No of patients	123
Age (years)	
Mean (range)	67.6 (54–83)
Gleason score	
Median (range)	7 (6–9)
TNM staging	
T2N0/Nx M0	29 pts
T3N0/Nx M0	34 pts
T3N1M0	35 pts
T4N0M0	15 pts
T4N1M0	10 pts
PSA (ng/mL)	
Mean (range)	3.3 (0.2–25.5)
Median	6.0

3. Results

^{11}C-choline PET/CT was positive in 42/123 patients (PET/CT detection rate 34.1%). Mean PSA value in ^{11}C-choline PET/CT

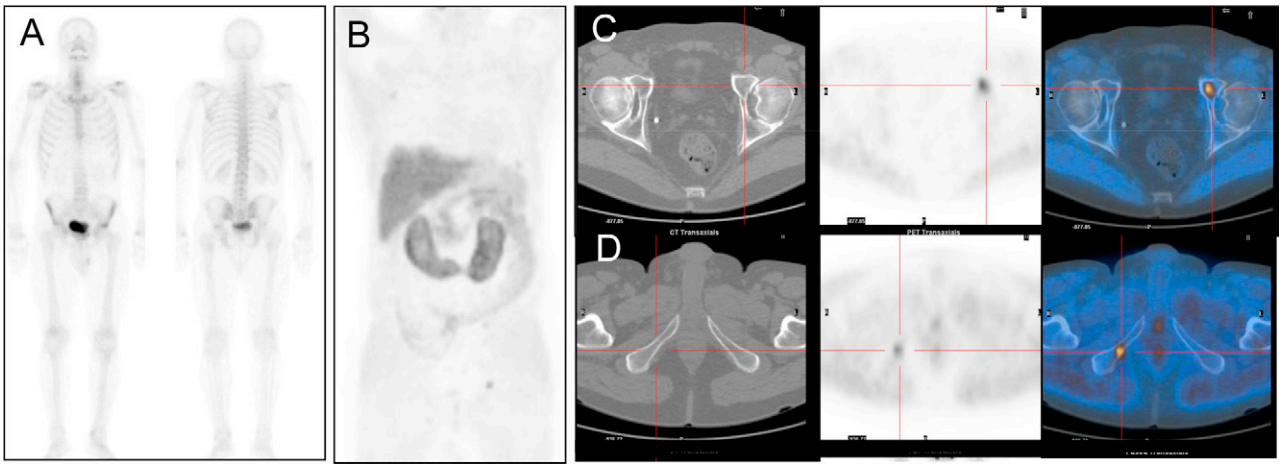

Fig. 1. Patient # 9. Seventy-nine-years old patients; RP in 2008; pT3bN0Mx; PSA value at the time of BS study 3.55 ng/mL. BS resulted to be negative (A). ^{11}C-choline PET/CT (B) performed one month after BS showed bone metastasis in the left pubic bone, proximal to acetabolum (C), and a bone metastasis in the right ischium (D). In the MIP projection (A) it is possible to note other small areas of increased uptake in the left iliac bone and in two ribs bilaterally. To note the absence of any structural alteration at CT attenuation correction images.