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ORIGINAL ARTICLE

Role of ^{11}C-choline positron emission tomography/computed tomography in evaluating patients affected by prostate cancer with suspected relapse due to prostate-specific antigen elevation

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Abstract
Purpose. The aim of this study was to evaluate the accuracy of ^{11}C-choline positron emission tomography/computed tomography (PET/CT) in restaging patients affected by prostate cancer and suspected relapse due to prostate-specific antigen (PSA) increase. We also aimed to determine a PSA cutoff that is most suited to the study in terms of best compromise between sensitivity and specificity. Secondary endpoints were a comparison between ^{11}C-choline PET/CT and histological results, clinical findings, and radiological imaging (CT and magnetic resonance imaging).
Materials and methods. We retrospectively evaluated 210 patients (median ± SD age 70 ± 7 years) affected by prostate cancer who underwent ^{11}C-choline PET/CT.
Results. ^{11}C-choline PET/CT imaging was positive in 116 (55.2%) patients and negative in 94 (44.8%). Receiver operating characteristic (ROC) analysis showed that the highest accuracy (sensitivity 76.8%, specificity 92.5%) for the whole population was achieved when the PSA level of 1.26 ng/ml level was used as the cutoff value for interpreting the results ($P = 0.0001$ and the area under the ROC curve AUC = 0.897). For patients treated with surgery or surgery plus radiotherapy the cutoff was 0.81 ng/ml (sensitivity 73.2%, specificity 86.1%). For patients treated with radiotherapy alone, the cutoff was 2.0 ng/ml (sensitivity 81.8%, specificity 92.9%).
Conclusion. Our results indicate that ^{11}C-choline PET/CT is a useful diagnostic tool in patients affected by prostate cancer and a relapsed PSA level. The highest accuracy for all patients is obtained with a PSA cutoff level of 1.26 ng/ml, above which the imaging study is performed (0.81 ng/ml for patients treated with surgery or surgery plus radiotherapy and 2.0 ng/ml for patients treated with radiotherapy alone).

Key words PET · ^{11}C-choline · Prostate cancer

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Introduction

Prostate cancer (PCa) is one of the most commonly diagnosed forms of cancer in men and is often characterized

by a long natural history and a wide variety of clinical behaviors. It continues to be a major health problem in developed countries. The wide availability of an assay for total prostate-specific antigen (PSA), a 34-kD androgen regulated by exocrine serine protease and produced by both normal and diseased prostate cells, has revolutionized PCa screening, resulting in earlier PCa detection and an increase in incidence.

The natural history of PCa from asymptomatic organ-confined disease to locally advanced, metastatic (hormone-dependent or hormone-refractory) disease reflects the complexity of this tumor and justifies the need for a collaboration between urologists, oncologists, pathologists, radiologists, and nuclear medicine physicians for accurate management.[1–3] As a result of screening, many patients are found to have low-risk PCa based on their PSA level, Gleason score, and clinical stage of disease at the time of diagnosis.[4–6] These patients have choices for primary treatment: (1) active surveillance in which patients defer therapy and undergo monitoring for disease progression, or (2) active treatment, which may include prostatectomy, radiation therapy (brachytherapy, intensity-modulated radiotherapy, and/or external beam) alone or in combination with hormonal therapy or cryotherapy. There is currently no consensus regarding the optimal treatment strategy as there are no or very small differences in mortality between treatment options and each treatment has side effects that can significantly affect the quality of life.[7,8] Patients who are unlikely to benefit from curative therapy (patients with locally advanced disease, T4N0 and T1-4N1, or metastatic disease, M1) could be treated with androgen deprivation (hormonal treatment), chemotherapy for castration-refractory prostate cancer, radiation therapy/radiopharmaceuticals, and bisphosphonates.[9]

Routine tools for early diagnosis and localization of the cancer include digital rectal examination and assessment of serum PSA followed by transrectal ultrasonography (US)-guided biopsy. However, a substantial effort has been made to develop and evaluate new diagnostic techniques for staging and restaging purposes.[10] Nowadays, in addition to traditional radiological and nuclear medicine imaging [traditional radiology, computed tomography (CT), bone scintigraphy], magnetic resonance imaging (MRI), three-dimensional (3D) pelvic MRI spectroscopic imaging, carbon-11 (^{11}C)-choline positron emission tomography/CT (^{11}C-choline PET/CT) are also available. These diagnostic tools allow better staging and restaging evaluations, reaching a more accurate diagnosis of relapse and metastases.

The aims of our study were to evaluate the accuracy of ^{11}C-choline PET/CT for restaging patients affected by PCa and suspected relapse (indicated by a PSA increase) and to determine a PSA cutoff over which it is appropriate to perform the study in terms of the best compromise between sensitivity and specificity. Secondary endpoints were a comparison between ^{11}C-choline PET/CT and the histological results, clinical findings, and radiological imaging (CT and MRI).

Materials and methods

We retrospectively evaluated 210 patients aged 70 ± 7 years (median ± SD) affected by PCa histologically documented after surgical intervention or biopsy. The patients had to have undergone ^{11}C-choline PET/CT from March 2007 to December 2009 for restaging consequent to PSA elevation [5.9 ± 19.6 ng/ml (mean ± sd)]. Relapsed disease was defined as PSA elevation of >0.2 ng/ml at two measurements in patients treated with surgery or surgery plus radiotherapy (it was empirically considered 0.1 ng/ml in cases clinically judged less favorable on the basis of histological findings and the Gleason score and pT stage). The same criteria were used for patients treated with radiotherapy alone and not-dosable PSA after the end of treatment. In patients treated with radiotherapy alone and with a still dosable but stable PSA level after the end of irradiation, relapsed disease was defined as an increase of at least 1 ng/ml from the nadir after radiotherapy.

A total of 114 patients had previously undergone radical surgery (PSA 2.0 ± 3.5 ng/ml), 26 had undergone surgery and radiotherapy (PSA 5.5 ± 14.2 ng/ml), and 70 had had radiotherapy alone (PSA 12.6 ± 31.8 ng/ml). Among all patients treated by surgery, 3.3% were staged pT2a at histological examination, 4.5% were pT2b, 28.9% were pT2c, 32.2% were pT3a, 18.9% were pT3b, 3.3% were pT3c, and 8.9% were pT4. The Gleason score was ≤6 in 26.5% of patients, 7–8 in 52.3%, and 9–10 in 21.2%.

Altogether, 34.6% of patients underwent ^{11}C-choline PET/CT under total androgenic blockade (TAB), and 65.4% did not. In all, 45 patients underwent prostate site mapping after the PET study, 56 patients underwent abdominopelvic contrast-enhanced computed tomography (CECT), and 22 underwent pelvic MRI within 3 months before or after PET/CT.

^{11}C-11-choline was produced using Tracerlab FxC module (General Electric, Milwaukee, WI, USA). $^{11}C\text{-}CO_2$ produced by cyclotron was reduced to $^{11}C\text{-}CH_4$ on nickel catalyzing shimalite (Shimadzu, Kyoto, Japan) and trapped with carbosphere (Alltech, Deerfield, IL, USA). $^{11}C\text{-}CH_3I$ was produced in the presence of iodium (Merck, Darmstadt, Germany) sublimated in a gas phase reaction and trapped on Porapak (type Q 50–80 mesh; Waters,

Milford, MA, USA). ^{11}C-CH_3I was transferred on helium flow in anhydrous acetonitrile (Merck) containing 2.5 µl of 99% dimethylethanolamine (DMAE) (Riedel-de Haen, Seelze, Germany). After the synthesis reaction, acetotrile was distilled by heat. ^{11}C-choline produced was solved in H_2O (ABX, Radeberg, Germany), trapped on SepPak Accell CM (Waters), further washed with 10 ml of H_2O (ABX), and eluted with saline solution (ABX). The ^{11}C-choline solution was sterilized with a 0.22-µm filter and was ready for use.

^{11}C-choline PET/CT, performed using a standard activity of 555 MBq, was administered intravenously and a two-dimensional (2D) mode ordered-subset-expectation-maximization (OS-EM) imaging (with septa) was acquired 5 min after injection on a Discovery ST PET/CT tomograph (General Electric) with standard CT parameters (80 mA, 120 kV without contrast; 3 min per bed-PET-step of 15 cm). The reconstruction was performed in a 128×128 matrix and 60 cm field of view (FOV). The PET images, from the pelvis to the base of the skull, were analyzed visually and semi-quantitatively by measuring the maximum standardized uptake value (SUVmax). SUV was expressed as SUV-body weight (SUVbw in g/ml) and automatically calculated by software (Volumetrix for PET/CT; Xeleris Functional imaging workstation; GE) on the basis of the following parameters: weight of the patient expressed in kilograms; height expressed in centimeters; tracer volume expressed in milliliters; radioactivity at injection time expressed in megabecquerels (MBq); postinjection activity in the vial expressed in MBq; injection time; starting time acquisition; decay half-time of the radioisotope (standard 20.38 min for ^{11}C).

Images readout was performed on a Xeleris Functional imaging workstation (GE) by two readers who had knowledge of the clinical history and other diagnostic technique results of patients. In the event of disagreement the cases were reexamined, and a consensus was reached. Every focal tracer uptake deviating from physiological distribution was considered suggestive of disease. Faint bilateral tracer uptake in inguinal, axillary and pulmonary hilar lymph nodes was considered as being inflammatory. Whole-body analysis was carefully performed, and particularly studied were the typical sites of metastases, such as lymph nodes, lungs, and bones. No specific SUV value cutoff was considered to discriminate benign from malignant lesions; only the deviation from the physiological distribution and background or from the normal tissue activity around the suspect lesion was considered. All patients underwent ^{11}C-choline PET/CT according to a Phase II protocol approved by the local ethics committee, and written consent was obtained from all patients before each study.

Contrast-enhanced CT was performed on a Somatom Sensation 16-slice tomography (Siemens Medical Solutions, Forchheim, Germany) using Iomeron contrast medium (Bracco Imaging; 350–120 ml; speed injection 2 ml/s) with a three-phase protocol (precontrast phase, venous phase after 90 s, delayed phase 5 min after injection; 120 kV; 180 mA). Written consent was obtained from all patients before each study. Pelvic MRI was performed on a 1.5-T superconducting MRI unit (Magnetom Avanto; Siemens Medical Solutions, Erlangen, Germany) with precontrast images (FOV 220×220 mm; matrix 256×512; 3 mm slice thickness T2-weighted turbo spin echo 2d 512, sagittal, axial, coronal, and axial fat-saturation sequences; 3 mm slice thickness T1-weighted turbo spin echo 2D axial sequences; 5 mm slice thickness trufi 2D axial sequences; T1-weighted spin-echo axial precontrast sequences and T1-weighted spin-echo axial sequences after injection of Gadovist-Bayer-Schering Pharma, 0.1 mmol/kg, 1 ml/s). Written consent was obtained from all patients before each study.

Statistical analysis was performed using receiver operating characteristics (ROC) curve analysis (a graphic plot of the sensitivity, or true-positive rate, versus the false-positive rate; 1—specificity or 1—true-negative rate) to assess a PSA cutoff over which it is deemed best to perform the study. Student's *t*-test was performed to correlate the PSA value and ^{11}C-choline PET/CT. Fisher's exact test and contingency tables analysis were performed to assess a possible correlation between the PET results and clinical or pathological findings.

Results

^{11}C-choline PET/CT imaging was positive in 116 (55.2%) patients and negative in 94 (44.8%). A local relapse was diagnosed in 23.2% of patients; local relapse and lymph nodes metastases in 20.7%; local relapse, lymph nodes, and distant metastases in 3.4%; local relapse and distant metastases in 10.4%; lymph node metastases in 21.6%; distant metastases in 12%; and lymph node and distant metastases in 8.7% (Figs. 1–5).

For the entire population, ROC curve analysis showed that the highest accuracy in terms of best compromise between sensitivity and specificity (sensitivity 76.8%, specificity 92.5%) was achieved when the 1.26 ng/ml level is used as the PSA cutoff value to interpret the results ($P = 0.0001$ and the area under the ROC curve: AUC = 0.897) (Fig. 6).

For the subgroup of patients treated with surgery or surgery plus radiotherapy, ROC curve analysis showed that the best PSA cutoff was 0.81 ng/ml ($P = 0.0001$;

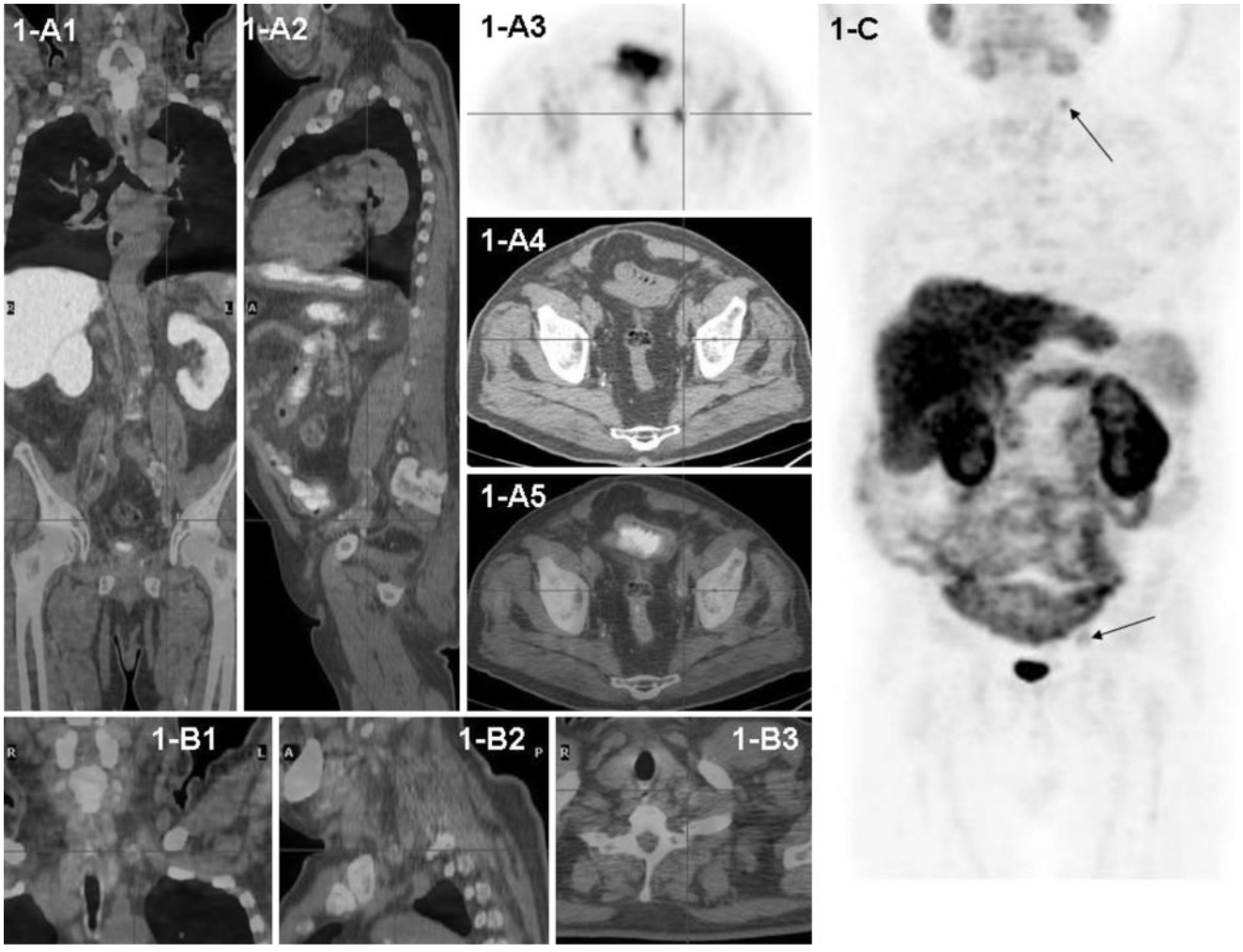

Fig. 1. Positive positron emission tomography/computed tomography (PET/CT) study in a patient treated with prostatectomy with a PSA level of 7.93 ng/ml and pathological uptake by the external left iliac and left supraclavicular lymph nodes. In particular, ^{11}C-choline PET/CT images are shown: maximum intensity projection (MIP) image (**1-C**); fused coronal (**1-A1**), fused sagittal (**1-A2**), PET axial (**1-A3**), CT axial (**1-A4**), and fused axial (**1-A5**) images of the external left iliac lymph node (*arrow* and *cross*). There are also fused coronal (**1-B1**), fused sagittal (**1-B2**), and fused axial (**1-B3**) images of the left supraclavicular lymph nodes (*arrow* and *cross*)

AUC = 0.845; sensitivity 73.2%; specificity 86.1%) (Fig. 7). For the subgroup of patients treated with radiotherapy alone, ROC curve analysis showed that the best PSA cutoff was 2.0 ng/ml ($P = 0.0001$; AUC = 0.925; sensitivity 81.8%; specificity 92.9%) (Fig. 8).

Based on ROC curve analysis schemes (PSA levels higher or lower than 1.26 ng/ml, 0.81 ng/ml, and 2.0 ng/ml), the following observations were made: among the entire population, for patients with PSA ≤ 1.26 ng/ml the study was positive in 22.5% and negative in 77.5%, whereas for patients with PSA > 1.26 ng/ml the study was positive in 91% and negative in 9%. These results have shown statistical significance with Fisher's exact test analysis ($P < 0.0001$). Among the group treated with surgery or surgery plus radiotherapy, for patients with PSA < 0.81 ng/ml the study was positive in 20% and negative in 80%, whereas for patients with PSA > 0.81 ng/ml the study was positive in 84% and negative in 16% ($P < 0.0001$). Among the group treated with radiotherapy alone, for patients with PSA < 2 ng/ml the study was positive in 43% and negative in 57%, whereas for patients with PSA > 2 ng/ml the study was positive in 98% and negative in 2% ($P < 0.0001$).

The PSA levels were significantly statistically different among the groups selected according to the ROC analysis ($P < 0.05$, Student's t-test). Moreover, we noted a significant statistical correlation between ^{11}C-choline PET/CT results and PSA values and a statistically sig-

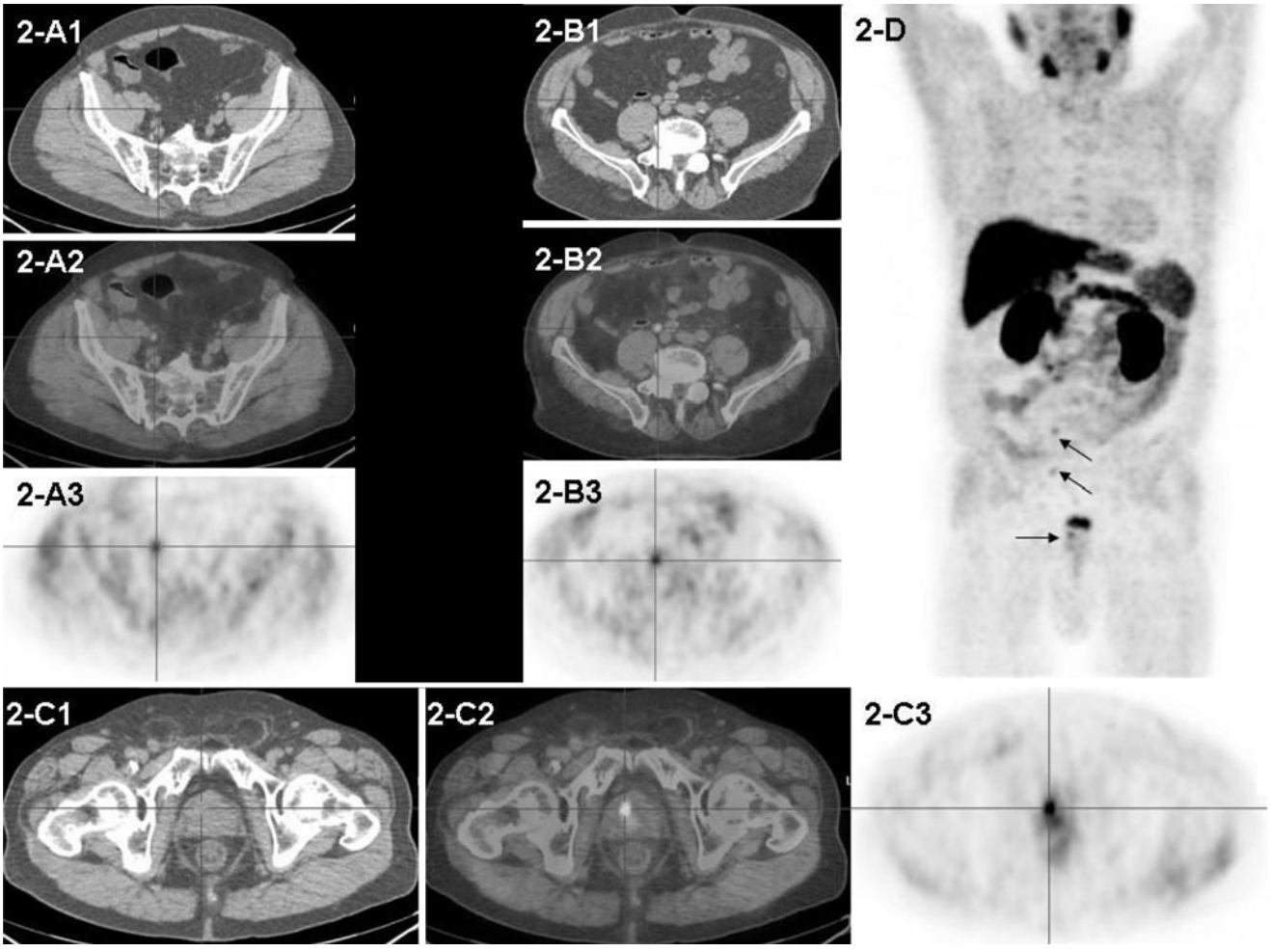

Fig. 2. Positive PET/CT study in a patient with a PSA level of 3.57 ng/ml and pathological uptake at a right common and an internal iliac lymph node and in the right prostate lobe. He was treated with radiotherapy. In particular, ^{11}C-choline PET/CT showed MIP (**2-D**), axial CT (**2-A1**), axial fused (**2-A2**), and axial PET (**2-A3**) images of the right internal iliac lymph node (*arrow* and *cross*); axial CT (**2-B1**), axial fused (**2-B2**), and axial PET (**2-B3**) images of the right common iliac lymph node; and axial CT (**2-C1**), axial fused (**2-C2**), and axial PET (**2-C3**) images of the right prostate lobe (*arrow* and *cross*)

nificant difference ($P < 0.05$, Student's *t*-test) between PSA values of the ^{11}C-choline PET/CT positive and negative patient groups considering the entire population and the groups of patients treated with surgery and surgery plus radiotherapy. There was no statistically significant difference ($P = 0.12$) in the group of patients treated with radiotherapy only. There was a statistically significant difference ($P < 0.05$, Student's *t*-test) between the PSA levels of patients treated by surgery or radiotherapy alone, between those treated by surgery and radiotherapy and by surgery alone, but not between those treated by surgery plus radiotherapy and radiotherapy alone ($P = 0.266$).

We have not noted a statistical significant difference, using Fisher's exact test, between ^{11}C-choline PET/CT results in patients whose studies were performed under total androgenic blockage (TAB) and patients without TAB ($P = 0.76$). We also did not note a significant correlation in the contingency tables analysis between the Gleason scores at the time of surgical intervention and the restaging-PET results in three groups of patients based on the Gleason scores (≤6, 7–8, or 9–10, respectively). Nor did we find a significant correlation with contingency tables analysis between the pT stage at the time of surgical intervention and restaging-PET results in three groups of patients classified as pT2 (36.7%), pT3 (54.4%), and pT4 (8.9%), respectively.

A confrontation was performed between PET and prostate mapping results to evaluate and eventually confirm local disease relapse. On the basis of histological confirmation regarding exclusively local disease relapse and considering PET findings in the prostate site only,

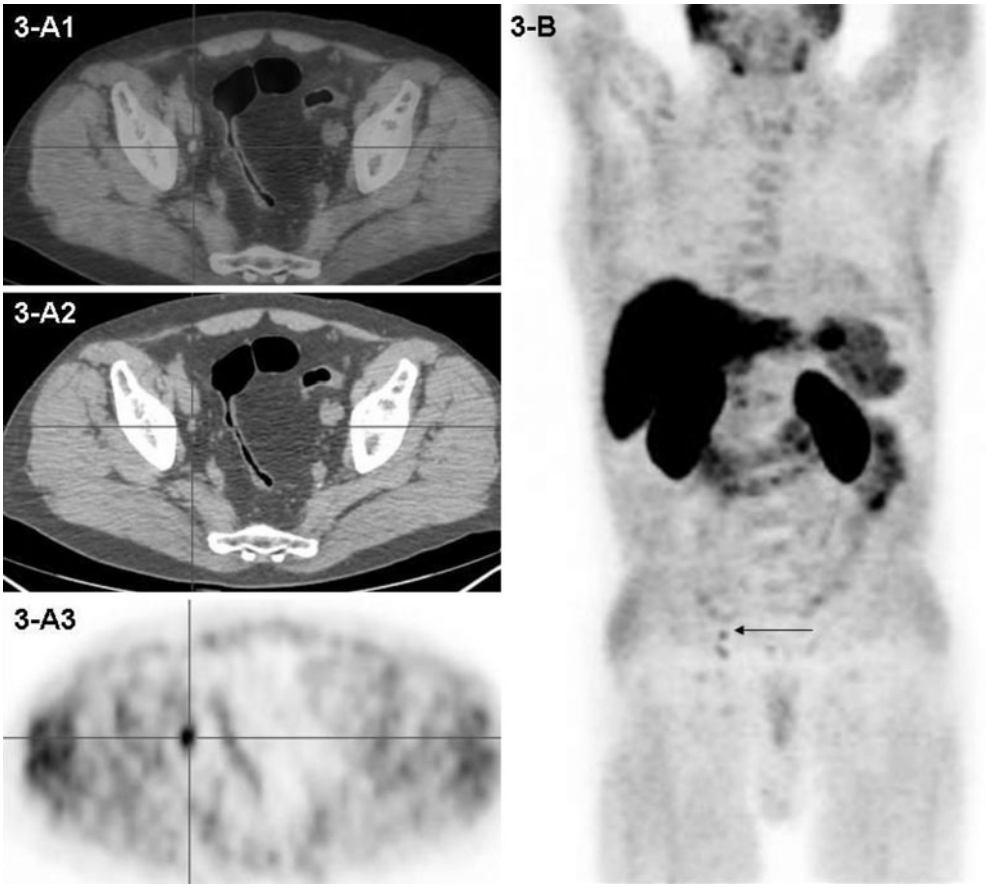

Fig. 3. Positive PET/CT study in a patient with A PSA level of 1.54 ng/ml and pathological uptake in a small right external iliac lymph node. He was treated with radiotherapy. In particular, the ^{11}C-choline PET/CT images show MIP (**3-B**), axial fused (**3-A1**), axial CT (**3-A2**), and axial PET (**3-A3**) images of the right external iliac lymph node (*arrow* and *cross*)

the ^{11}C-choline PET/CT study was true-negative in 32, true-positive in 6, false-positive in 3, and false-negative in 4. Sensitivity, specificity, accuracy, and the negative (NPV) and positive (PPV) predictive values for these patient subgroups considering disease relapse at the prostate site were 60%, 91%, 84%, 89%, and 67%, respectively.

A confrontation was also performed between patients who underwent ^{11}C-choline PET/CT and abdominopelvic CECT. A concordance in terms of disease relapse diagnosis was achieved in 66.7% of patients (27.3% negative results in both studies and 39.4% positive) even if in 10% of the patients PET/CT revealed more lesions than CECT and PET/CT was positive in 33.3% of the patients who were negative at CECT. In both of the latter situations, the diagnostic incremental value of PET/CT was the detection of skeletal metastases and of lymph nodes. No patient negative at PET/CT was positive at CECT.

Finally, a confrontation was performed between patients who underwent ^{11}C-choline PET/CT and pelvic MRI. A concordance in terms of local disease relapse diagnosis was achieved in 86.3% of patients (40.9% negative results in both studies and 36.4% positive). Pelvic MRI was positive in 13.6% of patients negative at PET/CT and 9.1% vice versa.

Discussion

Prostate cancer is the most common malignancy among men in the Western world. It is the second most common cause of death from cancer,[11] and it relapses in about 20%–40% of patients after radical surgery within 5 years and up to 53% within 5 years after external beam radiotherapy.[12] Serum PSA, clinical stage, and Gleason score can help predict the aggressiveness of PCa, but it is essential to identify local recurrence and metastatic disease early for optimal management of the relapse.

After primary treatment, PSA, produced by acinar and ductal epithelial cells in prostate cancer, is the most sensitive method of detecting biochemical recurrence, and its elevation is usually the first sign of disease relapse.[13] It is consequently mandatory to confirm the suspicion, possibly to identify sites of disease and espe-

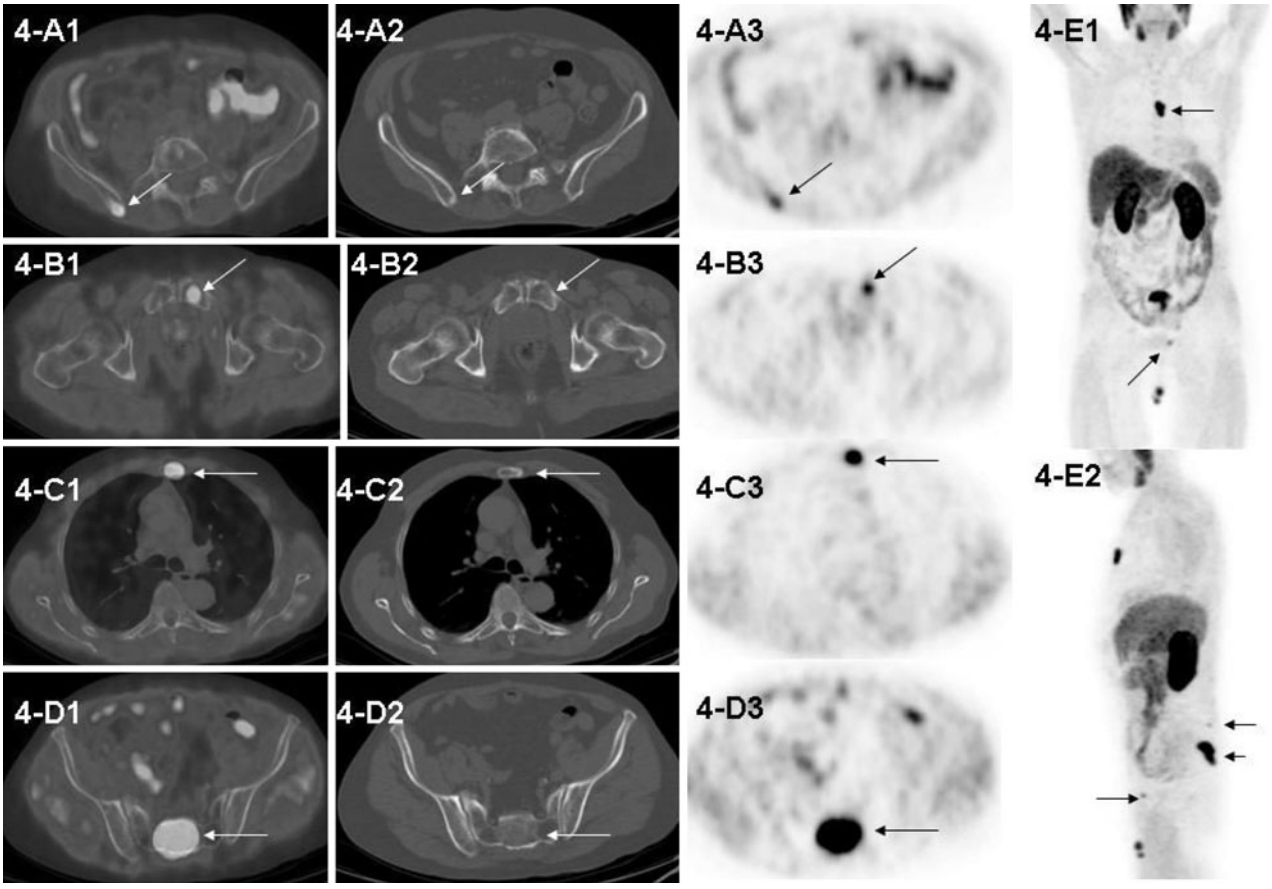

Fig. 4. Positive PET/CT study in a patient with a PSA level of 14.02 ng/ml and pathological uptake in the sternum, sacrum, right iliac bone, and left pubis. He was treated with prostatectomy. In particular, ^{11}C-choline PET/CT shows anterior (**4-E1**) and lateral (**4-E2**) MIP, axial fused (**4-A1**), axial CT (**2-A2**), and axial PET (**4-A3**) images of the right iliac bone lesion (*arrows*); axial CT (**4-B1**), axial fused (**4-B2**), and axial PET (**4-B3**) images of the left pubis lesion (*arrows*); axial fused (**4-C1**), axial CT (**4-C2**), and axial PET (**4-C3**) images of the sternal lesion (*arrows*); and axial fused (**4-D1**), axial CT (**4-D2**), and axial PET (**4-D3**) images of the sacral lesion (*arrows*)

cially to establish whether the disease is locally confined or systemic. This information is needed for planning the best treatment for each patient, which is selected on the basis of disease status, expected efficacy, and side effects. Despite the many diagnostic methods—bone scintigraphy, CECT, transrectal US, MRI, PET/CT—currently available for clinical practice, with ranging sets of information and accuracy, the optimal tool for imaging evaluation of men with PSA relapse is still uncertain. The goal of imaging is to determine whether there is recurrence in the treated prostate bed and if there are metastases. Although bone scintigraphy, which has been and still is one of the most frequently used nuclear medicine tools and is useful for detecting osseous metastases, the false-positive rate is high.[14] Also, it cannot detect soft tissue or lymph nodal involvement, which is quite prevalent with metastatic spread of this disease. Bone scintigraphy has limited sensitivity in detecting metastases when the serum PSA level is <2 ng/ml and only correlates well at high PSA levels (>16 ng/ml).[3,15,16]

Although in recent years ^{11}C-choline PET/CT has proven to be useful for restaging PCa patients with biochemical failure, a PSA cutoff value (Table 1) at which these patients should undergo ^{11}C-choline PET/CT has not been established even if many threshold ranges (from 1 ng/ml to 5 ng/ml) have been proposed.[17–27]

In particular, Giovacchini et al.[23] performed a retrospective analysis of 358 patients previously treated by radical prostatectomy and with subsequent biochemical failure (defined as at least two consecutive PSA measurements of >0.2 ng/ml). The ROC analysis showed that ^{11}C-choline PET/CT and PET/CT-negative patients could be best distinguished using a PSA cutoff value of 1.4 ng/ml. Sensitivity, specificity, PPV, NPV, and overall accuracy for ^{11}C-choline PET/CT were, respectively, 85%, 93%, 91%, 87%, and 89%.

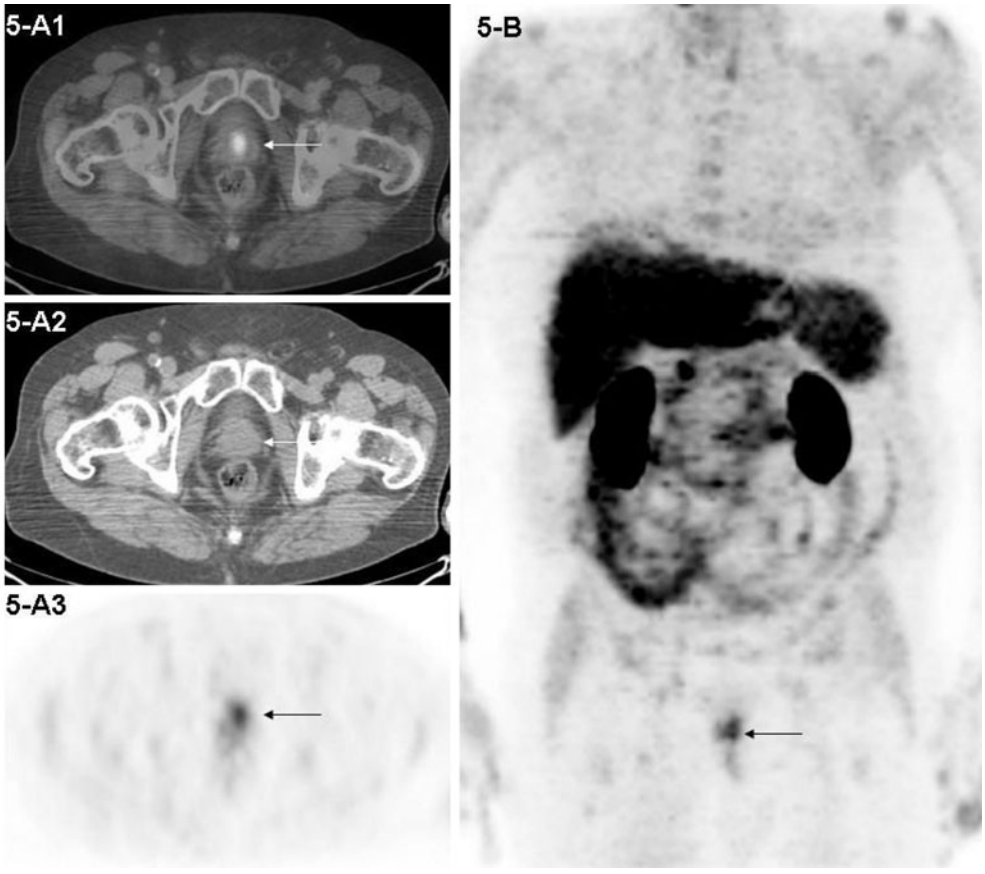

Fig. 5. Positive PET/CT study in a patient with a PSA level of 2.6 ng/ml and pathological uptake in the left prostatic lobe, indicating local disease relapse. He was treated with radiotherapy alone. In particular, ^{11}C-choline PET/CT shows MIP (**5-B**), axial fused (**5-A1**), axial CT (**5-A2**), and axial PET (**5-A3**) images of the left prostatic lobe (*arrows*). This finding was confirmed at histological examination after prostate mapping

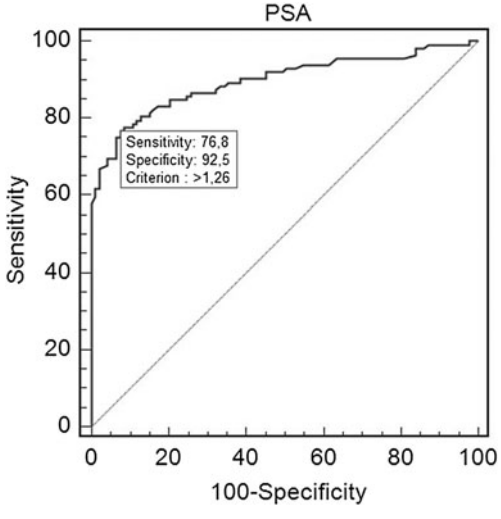

Fig. 6. Receiver operating characteristic (ROC) curve analysis performed considering the entire population shows PET/CT results correlated with PSA levels in terms of sensitivity and specificity. The identified cutoff value was 1.26 ng/ml—the level over which it is better to perform the imaging study in terms of the best compromise between sensitivity and specificity

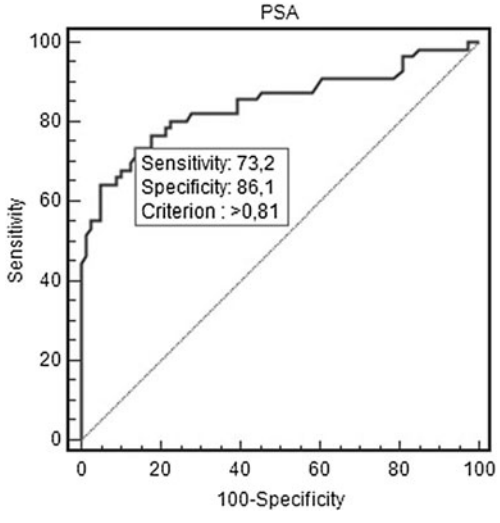

Fig. 7. ROC curve analysis performed for patients treated with surgery or surgery plus radiotherapy shows that the PET/CT results correlated with PSA levels in terms of sensitivity and specificity. The identified cutoff value was 0.81 ng/ml

Castellucci et al.[24] retrospectively grouped 190 patients treated with radical prostatectomy according to the trigger PSA (PSA ≤ 1 ng/ml; PSA > 1 but ≤2 ng/ml; PSA > 2 but ≤5 ng/ml; PSA > 5 ng/ml). The detection rates of ^{11}C-choline PET/CT were 19%, 25%, 41%, and 67% in those four subgroups, respectively; and ROC analysis showed an optimal cutoff point for the trigger PSA at 2.43 ng/ml (AUC = 0.76). There was no statistical difference between PET-positive and PET-negative scan detection rates according to the Gleason score, pT and N status, patient age, or time between surgery and biochemical relapse. Also in our study we did not note significant differences considering these parameters.

Richter et al.[25] studied 73 patients after radical treatment with 60.6% sensitivity for ^{11}C-choline PET to detect cancer recurrence. Negative ^{11}C-choline PET scans were observed in 70% of patients with serum PSA values <1.9 ng/ml, and positive ^{11}C-choline PET scans were seen in 84% of patients with serum PSA values >1.9 ng/ml. When those patients with PSA values <1.9 ng/ml were excluded, the sensitivity of ^{11}C-choline PET and FDG-PET increased to 80%.

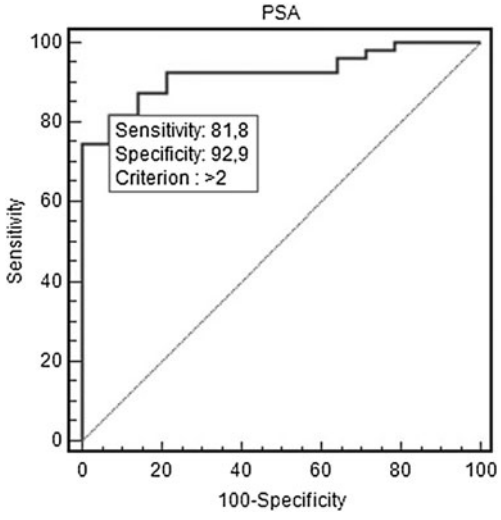

Fig. 8. ROC curve analysis performed for patients treated with radiotherapy alone shows PET/CT results correlated with PSA levels in terms of sensitivity and specificity. The identified cutoff value was 2.0 ng/ml

Krause et al.[18] studied 63 patients after primary treatment and biochemical relapse with a global detection rate of 56% and a positive relation with the serum PSA value. In particular, the detection rate was 36% when the PSA was <1 ng/ml, 43% for PSA of 1–2 ng/ml, 62% for PSA of 2–3 ng/ml, and 73% for PSA of >3 ng/ml.

Breeuwsma et al.[26] prospectively evaluated 70 patients with histologically proven PCa treated with external beam radiotherapy (EBRT) and biochemical recurrence. Among the 70 patients, 57 had an abnormal uptake pattern (locoregionally and/or distant) with a sensitivity of 81%. Overall, the PPV and NPV for ^{11}C-choline PET were 100% and 44%, respectively, with an accuracy of 84%. They concluded that ^{11}C-choline PET is a sensitive technique for identifying the site of recurrence in patients with PSA relapse after EBRT.

Garcia et al.[27] included 38 patients with increased PSA levels (0.8–9.5 ng/ml) after radical treatment for PCa in a study to compare the diagnostic accuracy of PET/CT with ^{18}F-fluorodeoxyglucose (^{18}F-FDG) and ^{11}C-choline for early detection and localization of recurrent prostate cancer. ^{11}C-choline was able to detect 40% of recurrences in patients with PSA < 1 ng/ml, 50% of recurrences in patients with PSA 1–4 ng/ml, and 87% of recurrences with PSA > 4 ng/ml with higher yields as compared to ^{18}F-FDG.

All reported studies have confirmed the statement that ^{11}C-choline PET/CT accuracy is related to the PSA value. Although no definitive PSA cutoff level has been identified, our results corroborate this hypothesis and seem to reduce slightly the threshold beyond which it is considered appropriate to perform the imaging study.

Although some reports have described decreased choline uptake after initiating hormonal therapy,[28] pathological uptake under treatment does occur in those patients with a hormone-resistant tumor, as indicated by increases in PSA. Analysis of the influence of hormone therapy revealed that our results coincide with those

Table 1. Most significant studies correlating ^{11}C-choline PET/CT results and PSA value

Study	Year	No. of patients	PSA cutoff[a] (ng/ml)	Se/Sp (%)	Detection rate (%)
Giovacchini[23]	2010	358	1.4	85/93	
Richter[25]	2010	73	1.9	80	
Castellucci[24]	2009	190	2.43	73/69	
García[27]	2009	38	4		87
Krause[18]	2008	63	3		73

PET, positron emission tomography; PSA, prostate-specific antigen; Se/Sp, sensitivity/specificity
[a] The cutoff is the value over which it is better to perform the study

described by Heinisch et al.,[21] Husarik et al.,[22] and Richter et al.[25] Treatment followed during rising PSA levels has no significant influence on the yield of tracer.[25]

A critical issue is the histological confirmation of pathological findings revealed by PET/CT or any other imaging tools to establish and confirm the presence of relapsed disease. Histology has to be theoretically considered the gold standard. Unfortunately, in daily practice, this is seldom possible because of clinical reasons, the feasibility of the procedure, and effective advantages of this approach in the absence of a radical surgical intent. Imaging compensates for this limit and is clinically acceptable that, in a patient with PSA elevation, pathological uptake during ^{11}C-choline PET/CT (or suggestive CECT and MRI findings) should be considered the site of the disease, even in the absence of systematic histological confirmation. The disappearance of these findings after therapy can be considered confirmation of the correctness of the diagnosis.

Despite the limitation of prostate site mapping due to evaluating a limited portion of tissue—precluding what could be considered definitive diagnostic results or gold standard results—in our study only 45 patients underwent histological prostate site mapping after PET/CT. Considering PET/CT results specifically regarding the prostate site, we had 32 true-negative and 6 true-positive results, reaching a global accuracy of 84%. The four false-negative and three false-positive results were probably due to microscopic extension of the diseases (inferior to the resolution power of the method) and inflammatory uptake at the prostatic site, respectively. Histological verification of lymph nodes or distant metastatic diseases has not been evaluated.

Schilling et al.[29] published an article on histological verification of ^{11}C-choline PET/CT positive lymph nodes in patients with biochemical failure after treatment for localized prostate cancer. In particular, they retrospectively reviewed 10 patients with PSA recurrence after either EBRT or radical retropubic prostatectomy who had undergone laparoscopic lymphadenectomy for suspicious lymph nodes detected on ^{11}C-choline PET/CT. Histology confirmed metastatic involvement in 7 of the 10 positive PET patients with a PPV of 70%.

Scattoni et al.[30] prospectively studied 25 patients with biochemical recurrence and evidence of lymph node metastases on ^{11}C-choline PET/CT or conventional imaging. All patients were scheduled for either bilateral pelvic or pelvic and retroperitoneal lymph node dissection. In all, 21 patients were positive on ^{11}C-choline PET/CT and 19 of 21 had nodal metastases from prostate adenocarcinoma at histological evaluation. A lesion-based analysis showed that ^{11}C-choline PET/CT sensitivity, specificity, PPV, NPV, and accuracy were 64%, 90%, 86%, 72%, and 77%, respectively. The mean maximum diameter of true-positive metastases was larger than in the false-negative ones (15.0 vs. 6.3 mm; $P = 0.0004$). They concluded that ^{11}C-choline PET/CT is an accurate diagnostic tool for the detecting lymph node metastases of recurrent PCa despite the low NPV (probably due to the limited capability of detecting microscopic lesions) in the presence of a high PPV. Consequently, it is reasonable and clinically acceptable to consider a diagnosis of relapsed disease at the sites of pathological uptake during ^{11}C-choline PET/CT in the presence of PSA elevation, even in the absence of biopsy confirmation.

To compare the diagnostic performance regarding disease relapse detection between different methods, despite the small number of patients evaluated, we compared PET/CT, CECT, and pelvic MRI results. The diagnostic concordances between PET/CT and abdominopelvic CECT and between PET/CT and pelvic MRI were 66.7% and 86.3%, respectively. PET/CT seems to have been more accurate than CECT, especially in regard to skeletal metastasis detection. CECT performance in other studies seems less helpful than in ours.[23] Pelvic MRI has shown high concordance with PET/CT but seems to have been slightly more sensitive regarding local relapse detection, although the small number of patients studied and the lack of systematic histological confirmation strongly affect these results and their interpretation.

Conclusion

Despite the limitations of our study—being a retrospective analysis, the lack of histological confirmation in most patients, and a comparison with other imaging techniques available in a small group only—our results confirm that ^{11}C-choline PET/CT is a useful diagnostic tool for patients affected by PCa and a relapsed PSA level. Our results are in agreement with those in the literature. Despite the fact that no definitive PSA cutoff level has been identified in literature, our results seem to reduce slightly the threshold at which it may be deemed appropriate to perform the imaging study. The highest accuracy is obtained when the PSA cutoff levels above which the imaging study is performed are 1.26 ng/ml for the overall population, 0.81 ng/ml for patients treated with surgery or surgery plus radiotherapy, and 2.0 ng/ml for patients treated with radiotherapy alone.

The authors declare that they have no conflicts of interest.

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