Diagnostic performance of bone scintigraphy and $^{11}$C-choline PET/CT in the detection of bone metastases in patients with biochemical recurrence of prostate cancer


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A B S T R A C T

Aim: To compare bone scan (BS) with $^{11}$C-choline PET/CT for the detection of bone metastases in patients with biochemical recurrence of prostate cancer (PC).

Materials and methods: A total of 169 patients with biochemical recurrence of PC (PSA: 2.4–58 ng/ml) who were referred for both exams (0–15 days-in-between) were included. Lesion-detection-rate per patients and lesions were analyzed for both BS and $^{11}$C-choline PET/CT. Metastases were diagnosed by: biopsy, CT/$^{18}$F-fluoride PET/MRI confirmation, or evidence of progression in subsequent imaging procedures.

Results: A total of 91 lesions were found to be active in BS and/or $^{11}$C-choline PET/CT (40 patients), with 78 of which were metastatic. BS detected 38 blastic, 2 lytic and 10 non-CT-evident lesions. $^{11}$C-choline PET/CT detected 41 blastic, 4 lytic and 29 non-CT-evident lesions. BS and $^{11}$C-choline PET/CT sensitivities were 65.4% and 96.1%; specificities are 38.5 and 92.3% ($\chi^2 \p< 0.04$).

Both imaging techniques were negative in 118 patients. Tracer avid lesions were found in 51 patients: with 30/51 being BS and $^{11}$C-choline PET/CT concordant; in 21/51 patients had discordant lesions ($\text{kappa} = 0.712, \p = 0.00$).

Lesions were absolutely discordant in 10/19 patients: 5 FN BS, 2 FP BS (degenerative changes; dysplasia), 1 FN $^{11}$C-choline PET/CT (blastic), 1 FP $^{11}$C-choline PET/CT (degenerative), 1 out of field-of-view lesion with $^{11}$C-choline PET/CT (tibia alone).

$^{11}$C-choline PET/CT showed extraosseous involvement in 26/51 patients with bone metastases: 9 local recurrences, 5 infra-diaphragmatic-lymph-nodes, 2 supra-diaphragmatic, 5 local and infra-diaphragmatic, 4 infra- and supra-diaphragmatic, 1 supra-diaphragmatic and lung metastases.

Conclusion: $^{11}$C-choline PET/CT yielded better sensitivity and specificity than BS for the detection of bone involvement in patients with biochemical recurrence of PC and allowed extraosseous restaging, with an impact in the clinical management of these patients.

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**Introduction**

Prostate cancer is the fourth most frequent cause of cancer. It is the most frequent neoplasm in men, with an incidence of around 56,000 cases per year in the European Union and is the second cause of death after lung cancer.\(^1\)

The clinical outcome of this cancer has great biological variability, going from an indolent low grade limited to the prostate to aggressive types with the development of metastasis and high mortality rates.\(^2\)

The most frequent metastatic dissemination is to the lymph nodes followed by the bones. Involvement by bone metastasis varies from 8% to 35% at the initial diagnosis of the disease to around 65–75% for advanced prostate tumors and up to 85% in patients with death due to prostate cancer. Involvement of other organs such as the lung or liver usually occurs in late phases of the disease.\(^3\)

Early detection of bone metastasis by imaging techniques may prevent possible complications (pain, pathological fractures, medullar compression), determining its extension in order to select the most appropriate therapeutic approach and to serve as a guide for biopsy to obtain diagnostic confirmation.\(^4\)

Bone scintigraphy is classically the technique of choice in bone metastasis in prostate cancer. According to predictive nomograms and accepted criteria this technique is indicated in the staging of high-risk patients and in biochemical relapse after radical therapy.\(^5\)

However, the specificity of bone scintigraphy in the differentiation of benign and malignant lesions is limited. This low specificity is inherent to the mechanism of uptake in relation to the increase in cellular replacement, although it is of note that assessment of the different characteristics of uptake requires a learning curve and represents an improvement in the discrimination of these types of lesions.\(^6,7\)

The use of SPECT has demonstrated an increase in sensitivity. Comparison with computed tomography (CT) in SPECT/CT equipment or fusion by software with CT or magnetic resonance (MR) increases the specificity.\(^8\) Nonetheless, the effectiveness of bone scintigraphy in the detection of bone metastasis has been questioned in recent studies.\(^9\)

The use of \(^18\)F-FDG PET/CT in oncology has exponentially risen, particularly since the introduction of combined PET/CT equipment. However, the role of \(^18\)F-FDG in prostate cancer remains under debate. This is mainly due to the low affinity of the tracer in differentiated tumors such as in prostate cancer and the physiological urinary elimination of the tracer which makes interpretation of pelvic images difficult.\(^10\) Other radiotracers have, therefore, been developed for PET such as \(^11\)C or \(^18\)F-choline and \(^11\)C-acetate, with the main objective of localizing biochemical relapse.\(^11–13\) In Europe, choline is the tracer most frequently used. Its mechanism of uptake is based on an increase in cellular proliferation in the tumors and upregulation of choline-kinase by cancerous cells, both of which are produced in prostate cancer cells.\(^14,15\) Along this line Beheshti et al. reported a sensitivity and specificity of 79% and 97%, respectively for \(^18\)F-choline in the detection of bone metastasis in patients with prostate cancer.\(^16\)

The aim of this study was to compare the diagnostic accuracy of bone scintigraphy with \(^99m\)Tc-hydroxymethyl-diphosphonates (\(^99m\)Tc-HMDP) and \(^11\)C-choline PET/CT in the detection of bone metastasis in prostate cancer patients with biochemical relapse.

**Materials and methods**

**Patients**

This study was approved by the Ethical Committee of the center. Informed consent was obtained from all the patients prior to performing bone scintigraphy and \(^11\)C-choline PET/CT.

From February 2007 to February 2013 we included 169 patients (65 ± 11 years) referred for both studies due to biochemical relapse (PSA: range 2.4–58 ng/ml; mean 4.8) of prostate cancer. The primary therapy was surgery in 67 patients and radiotherapy in 102, with the time between radical treatment and biochemical relapse being 20 months (range 8–72 months).

The maximum time between bone scintigraphy and \(^11\)C-choline PET/CT was 15 days (range 0–15 days, mean 5 days).

Patients with more than four metastatic bone lesions were excluded from the study since correct final evaluation of all the lesions is not possible as reported in the study by Even Sapir.\(^6\)

**Bone scintigraphy with \(^99m\)Tc-MDP**

Whole body bone scintigraphy was carried out 2 h after the intravenous administration of 740 MBq of \(^99m\)Tc-HMDP. Additionally, according to the decision of the medical specialist, selective planar and/or SPECT/CT were obtained (Figs. 1 and 2).

**\(^11\)C-choline PET/CT**

\(^11\)C-choline PET/CT was carried out after 8 h of fasting. Five minutes after the intravenous injection of 296 MBq \(^11\)C-choline images of the upper third of the femurs to the skull were obtained at 3 min per bed. The CT was performed with diagnostic characteristics (140 kV, 160 mAs) but without intravenous contrast.

**Image interpretation**

Interpretation of the bone scintigraphy study was made with the consensus of two specialists in nuclear medicine while the \(^11\)C-choline PET/CT was interpreted by consensus of one specialist in...
nuclear medicine and one radiologist. Each study was evaluated separately and blind to the other.

We analyzed the rates of detection by bone scintigraphy and $^{11}$C-choline PET/CT by lesions and patients.

**Bone scintigraphy**

All the lesions demonstrating a focal increase of $^{99m}$Tc-MDP in the bone scintigraphy were visually evaluated analyzing their intensity, localization and pattern of uptake according to a 4-point scale (1 definitively benign; 2 probably benign; 3 probably metastatic and 4 definitively metastatic). All the lesions with scores of 3 or 4 were interpreted as positive and those scored as 1 or 2 were considered negative.\textsuperscript{17}

Vertebral lesions were considered as benign if localized in articular zones or if they corresponded with osteophytes, while those considered as malignant were localized in the posterior part of the vertebral bodies or in pedicules. This latter localization is better...
evaluated in cases undergoing SPECT/CT. Rib lesions were considered to be benign or traumatic because of their focal nature and multiple linear pattern, while those deemed to be malignant showed linear extension along the rib or morphologic abnormalities in the SPECT/CT study.  

\[^{11}\text{C}-\text{choline PET/CT}^\text{11}\]

In \[^{11}\text{C}-\text{choline PET/CT},\] focal uptake with greater activity than physiologic bone activity was considered to be positive. Focal uptake of \[^{11}\text{C}-\text{choline}\] corresponding with degenerative or traumatic changes or other lesions with benign characteristics in the CT component was considered negative.

The lesions were considered to be metastatic if presenting blastic, mixed, or lytic CT pattern on calculating the Hounsfield units (HU) using a standard spheric ROI (maximum diameter 6.5 mm). If they did not have alterations in the CT component they were considered metastatic in the follow-up.

**Final diagnosis**

**True positive results**

Bone lesions were considered as metastatic lesions according to the following criteria: positive bone biopsy (5 cases), confirmation by CT or MR, bone progression at 6-month follow-up using imaging techniques, including bone scintigraphy, \[^{18}\text{F-fluoride PET/CT}\] and \[^{11}\text{C}-\text{choline PET/CT}\] (mean 10 ± 3, range 6–15 months). After diagnosis all the patients were treated according to the restaging of the prostate cancer.

**True negative results**

Patients were defined as not having bone metastasis when neither the bone scintigraphy nor \[^{11}\text{C}-\text{choline PET/CT}\] showed bone lesions. These patients were not followed up. In addition, lesions which were positive in the bone scintigraphy or \[^{11}\text{C}-\text{choline PET/CT}\] with benign characteristics in the CT component were considered as true negative lesions.

**False positive lesions**

These were lesions which were positive in the bone scintigraphy or \[^{11}\text{C}-\text{choline PET/CT}\] but were finally determined to be benign.

**False negative lesions**

These were lesions presenting a characteristic pattern in the CT or were positive in only one of the two studies on follow-up.

**Statistical analysis**

The quantitative data are expressed as mean and range. In the analysis by lesion in each method (bone scintigraphy and \[^{11}\text{C}-\text{choline PET/CT}\]) the sensitivity and specificity were calculated to differentiate between benign and malignant lesions. We compared the detection of bone metastases by bone scintigraphy and \[^{11}\text{C}-\text{choline PET/CT}\] using the \(\chi^2\) test. The Kappa test (K) was used to determine concordance between the two studies in the analysis by patients.

All the analyses were done using the Statistical Package for the Social Sciences (SPSS®) statistical software system (SPSS® Inc., Chicago, IL, USA). A p value <0.05 was considered statistically significant.

**Results**

**Analysis by patients**

In 118 patients (69.8%) both studies were negative. They were considered as true negative results and were excluded from the follow-up.

In 51 patients (30.2%) bone scintigraphy and/or \[^{11}\text{C}-\text{choline PET/CT}\] showed uptake in bone lesions. In 30 of these 51 patients the results of the two studies were considered concordant (true positive results in both studies). In 21 of these 51 patients the results of the two studies did not agree. These results did not obtain a good grade of concordance between the two tests in the K test (K=0.712), with the difference being statistically significant (p=0.00). In 10 of these 21 patients the discordance was complete (Table 1): 5 patients had false negative results by bone scintigraphy, 2 false positive results with bone scintigraphy (degenerative disease and bone dysplasia), 1 false negative result with \[^{11}\text{C}-\text{choline PET/CT}\] (blastic lesions), 2 false positive results with \[^{11}\text{C}-\text{choline PET/CT}\] (degenerative vertebral changes), and 1 was outside the field with \[^{11}\text{C}-\text{choline PET/CT}\] (single tibial metastatic lesion).

**Extraosseous disease**

In addition, \[^{11}\text{C}-\text{choline PET/CT}\] allowed the diagnosis of extraosseous disease in 26 of the 51 patients (51%) with metastatic bone lesions: local recurrence in 9, infradiaphragmatic adenopathies in 5, supradiaphragmatic adenopathies in 2, local recurrence and infradiaphragmatic involvement in 5, infra- and supradiaphragmatic adenopathies in 4, and supradiaphragmatic adenopathies and pulmonary metastases in 1.

**Analysis by lesions**

We analyzed a total of 91 lesions with uptake in bone scintigraphy and/or \[^{11}\text{C}-\text{choline PET/CT}\] (corresponding to 40 patients). Of these, 78 lesions were finally considered to be metastatic.

The most frequent localizations of the lesions with uptake were: lumbar spine (22 lesions) followed by the pelvis (20 lesions) and the dorsal spine (17 lesions). The remaining localizations included: ribcage (10), sacrum (6), cervical spine (3), scapula (4), sternum (3), zygomatic arch (2) femur (1), clavicle (1), humerus (1), and tibia (1).

The CT study only detected 48 of the 78 metastatic lesions (61.5%): 44 with a blastic and/or mixed pattern and 4 with a lytic pattern. Twenty-nine lesions finally considered as metastatic did not demonstrate morphologic alterations, and one was outside the study field in the CT (localized in the tibia). In addition, CT diagnosed 11 benign lesions: 5 degenerative, 3 traumatic, 2 dysplasias, and 1 bone islet.

Bone scintigraphy detected 51 true positive results: 5 true negative results, 8 false positive results and 27 false negative results. \[^{11}\text{C}-\text{choline PET/CT}\] allowed the diagnosis of 44 lesions (86.3%), with a sensitivity and specificity of 96.1% and 65.4%, respectively while the specificity was 92.3% and 38.5%, respectively. The diagnostic yield of \[^{11}\text{C}-\text{choline PET/CT}\] was significantly greater than that of bone scintigraphy in the \(\chi^2\) test (8.27; p<0.04).

On evaluating the lesions detected by bone scintigraphy according to their morphologic behavior this study detected 38 blastic, 2 lytic and 10 normal lesions (Table 2). Those detected on
**Table 1**
Patients with total disagreement between the detection of bone metastasis with bone scintigraphy and $^{11}$C-choline PET/CT.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Lesion localization</th>
<th>Gamma scale 0–4</th>
<th>Scintigraphy</th>
<th>$^{11}$C-choline PET/CT</th>
<th>CT Confirmation</th>
<th>Extraosseous disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 S</td>
<td>D7</td>
<td>2</td>
<td>FN</td>
<td>TP</td>
<td>Normal</td>
<td>$^{18}$F-fluoride PET Local</td>
</tr>
<tr>
<td>2 S</td>
<td>Left ischium</td>
<td>0</td>
<td>FN</td>
<td>TP</td>
<td>Normal</td>
<td>$^{18}$F-fluoride PET Local</td>
</tr>
<tr>
<td>3 RT</td>
<td>Right acetabulum</td>
<td>3</td>
<td>TP</td>
<td>FN</td>
<td>Blastic CT</td>
<td></td>
</tr>
<tr>
<td>4 RT</td>
<td>Zygomatic arch</td>
<td>0</td>
<td>FN</td>
<td>TP</td>
<td>Normal MR Infra CT Supra</td>
<td></td>
</tr>
<tr>
<td>5 S</td>
<td>Right ribs cage</td>
<td>0</td>
<td>FN</td>
<td>TP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 S</td>
<td>L4</td>
<td>3</td>
<td>FP</td>
<td>TN</td>
<td>Degenerative CT</td>
<td></td>
</tr>
<tr>
<td>7 S</td>
<td>Left tibia</td>
<td>3</td>
<td>TP</td>
<td>FN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8 S</td>
<td>Right femur</td>
<td>4</td>
<td>FP</td>
<td>TN</td>
<td>Dysplasia CT</td>
<td>Local Infra</td>
</tr>
<tr>
<td>9 S</td>
<td>Left scapula</td>
<td>2</td>
<td>FN</td>
<td>TP</td>
<td>Normal MR Infra</td>
<td></td>
</tr>
<tr>
<td>10 S</td>
<td>D3</td>
<td>0</td>
<td>TN</td>
<td>FP</td>
<td>Normal MR Infra</td>
<td></td>
</tr>
</tbody>
</table>

**S:** surgery; **RT:** radiotherapy; **FN:** false negative; **FP:** false positive; **TN:** true negative; **TP:** true positive.

$^{11}$C-choline PET/CT were: 41 blastic, 4 lytic and 29 normal lesions (Table 3).

**Discussion**

Of the 91 lesions detected, 78 were considered to be definitively metastatic. CT detected 48 true positive results while bone scintigraphy found 51 and $^{11}$C-choline PET/CT, 74. Thus, the latter technique showed greater sensitivity than bone scintigraphy while the sensitivity of CT is already known to be low.

These findings are probably related to the different mechanism of $^{99m}$Tc-HMDP and $^{11}$C-choline uptake. Disphosphonates are based on the detection of osteoblastic resection of the metastatic lesions. $^{11}$C-choline can directly detect malignant cells in the bone and bone medulla.

Bone metastases in prostate cancer are mainly of osteoblastic origin in which neoformed bone tissue is deposited without reabsorption (osteoblastic proliferation and apoptosis of the osteoclast precursors). The results of our study agree with these series with the most frequent pattern being (44/78, 56.4%) of metastatic lesions with a blastic or mixed nature with osteolysis and osteosclerosis. Nonetheless, albeit infrequent, lytic lesions were detected (4/78, 5%), similar to other reports.

However, the detection of 37.2% (29/78) of metastatic lesions with normal CT was of note. Beheshti et al. hypothesized that this pattern is due to the development of metastatic bone lesions from the bone medulla. Thus, the detection of lesions with this behavior allows their early diagnosis when the metastases have a medullar or microsclerotic nature, with most being localized in the middle region of the vertebral body or the medullar region of the long bones.

Another reason which may explain this greater sensitivity of $^{11}$C-choline is related to the greater resolution of the PET systems compared to scintigraphic studies and even SPECT. This is important in the spine which is frequently affected by degenerative changes in elderly patients as well as in the pelvic region due to physiological urinary elimination of the tracer.

The absence of $^{11}$C-choline uptake in the degenerative changes represents an increase in the specificity of the technique over bone scintigraphy (8 false positive vs. 1 false positive result, respectively) which presents uptake in nonspecific localizations of bone

**Table 2**
Morphological characteristics of the metastatic bone lesions detected on bone scintigraphy.

<table>
<thead>
<tr>
<th>Lesions $^{99m}$Tc-HMDP</th>
<th>CT</th>
<th>No. of lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>False negative</td>
<td>Blastic</td>
<td>6</td>
</tr>
<tr>
<td>Lytic</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>False positive</td>
<td>Dysplasia</td>
<td>2</td>
</tr>
<tr>
<td>Deegenenerative</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Islet</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Traumatic</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>True negative</td>
<td>Deegenenerative</td>
<td>2</td>
</tr>
<tr>
<td>Normal</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Traumatic</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>True positive</td>
<td>Blastic</td>
<td>39</td>
</tr>
<tr>
<td>Lytic</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>No. of lesions</td>
<td>91</td>
<td></td>
</tr>
</tbody>
</table>

CT: computed tomography.

**Table 3**
Morphologic characteristics of the metastatic bone lesions detected on $^{11}$C-choline PET/CT.

<table>
<thead>
<tr>
<th>Lesions $^{11}$C-choline</th>
<th>CT</th>
<th>No. of lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outside field</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>False negative</td>
<td>Blastic</td>
<td>3</td>
</tr>
<tr>
<td>False positive</td>
<td>Normal</td>
<td>1</td>
</tr>
<tr>
<td>True negative</td>
<td>Dysplasia</td>
<td>2</td>
</tr>
<tr>
<td>Deegenervative</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Islet</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Traumatic</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>True positive</td>
<td>Blastic</td>
<td>41</td>
</tr>
<tr>
<td>Lytic</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>No. of lesions</td>
<td>91</td>
<td></td>
</tr>
</tbody>
</table>

CT: computed tomography.
remodeling or turn-over. In this sense, CT provides additional diagnostic information with its incorporation as SPECT/CT or PET/CT.

In our series, the most frequent localizations of bone metastases were the pelvis, sacrum and lumbar spine (52.7%), which may be explained by the hematogenous dissemination of prostate cancer through the venous system, mainly of the Baston venous plexus. However, Dodd et al. have described connections with other venous systems that extend the vascular network involved in the dissemination of bone metastases.23

It is of note that the acquisition of PET/CT includes the skull and the upper third of both femurs. In this sense, in our series only one lesion was outside the study field of the PET/CT, being localized in the tibia, while two lesions were localized in zygomatic arches. These data seem to validate the need to not include the extremities in the study field of PET, especially with 11C-choline, taking into account the short half life of this radiotracer (20 min).

In 21/51 patients the results of bone scintigraphy and 11C-choline PET/CT did not agree. This correlation is not clinically relevant since both studies detected the presence of metastatic bone lesions. What is of therapeutic importance was the 10/51 patients in whom pathological accumulation of 11C-choline was observed in the bone structures of patients without lesions in the bone scintigraphy study. Therefore, in 19.6% of our patients in whom one of the two studies was positive, the 11C-choline PET/CT allowed early detection of bone metastases, thereby avoiding unnecessary therapies in the cases of false positive results and leading to the implementation of directed therapies in oligometastatic patients.

Despite bone scintigraphy being more accessible and less expensive than PET, some authors have proposed the development of a feasible and cost-effective strategy using bone scintigraphy, SPECT, PET/CT and MR. These studies advocate the use of a PET/CT first and bone scintigraphy in the case of uncertain lesions in which a direct SPECT study or MR has already been performed.24

Finally, it is of note that 11C-choline PET/CT allows the diagnosis of local or adenaenocarcinogenic recurrence or distant metastasis. Thus, our study detected extrasosseous disease in 26 patients (15.4%), with an impact on the therapeutic planning of patients with biochemical relapse of prostate cancer.

Our study has several limitations due to the selection of the patients included, the differences in the diagnostic techniques compared and the validation of the results.

Firstly, we did not follow the 118 patients with negative results undergoing bone scintigraphy and 11C-choline PET/CT. Follow-up could have verified the presence of bone metastases, and thus, this group may have had some false negative results.

Secondly, we compared a planar study with a whole body tomographic study. It should be noted that in the literature this same methodology is described since whole body SPECT is not used in clinical practice.25,26

Lastly, the validation of the positive results was performed by follow-up in most of the cases. Histological confirmation would have been desirable but was not possible due to practical and ethical questions. Thus, few of the metastatic lesions were histologically confirmed. This is common in most studies and is related to the difficulty in its practice and ethical questions.27,28

In conclusion, 11C-choline PET/CT has a better sensitivity and specificity than bone scintigraphy for early detection of metastatic lesions in patients with biochemical relapse of prostate cancer. In addition, a single study allows extrasosseous restaging. The better diagnostic accuracy of 11C-choline PET/CT also has an impact on patient management. Taking these results into account further studies are required to determine the best diagnostic algorithm in these patients.

Conflict of interests

The authors declare no conflict of interest.

References