

# When to perform positron emission tomography/computed tomography or radionuclide bone scan in patients with recently diagnosed prostate cancer

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**Abstract:** Skeletal metastases are very common in prostate cancer and represent the main metastatic site in about 80% of prostate cancer patients, with a significant impact in patients' prognosis. Early detection of bone metastases is critical in the management of patients with recently diagnosed high-risk prostate cancer: radical treatment is recommended in case of localized disease; systemic therapy should be preferred in patients with distant secondary disease. Bone scintigraphy using radiolabeled bisphosphonates is of great importance in the management of these patients; however, its main drawback is its low overall accuracy, due to the nonspecific uptake in sites of increased bone turnover. Positron-emitting radiopharmaceuticals, such as fluorine-18-fluorodeoxyglucose, choline-derived drugs (fluorine-18-fluorocholine and carbon-11-choline) and sodium fluorine-18-fluoride, are increasingly used in clinical practice to detect metastatic spread, and particularly bone involvement, in patients with prostate cancer, to reinforce or substitute information provided by bone scan. Each radiopharmaceutical has a specific mechanism of uptake; therefore, diagnostic performances may differ from one radiopharmaceutical to another on the same lesions, as demonstrated in the literature, with variable sensitivity, specificity, and overall accuracy values in the same patients. Whether bone scintigraphy can be substituted by these new methods is a matter of debate. However, greater radiobiological burden, higher costs, and the necessity of an in-site cyclotron limit the use of these positron emission tomography methods as first-line investigations in patients with prostate cancer: bone scintigraphy remains the mainstay for the detection of bone metastases in current clinical practice.

**Keywords:** bone metastases, prostate cancer, bisphosphonates, positron emission tomography

## Introduction

Prostate cancer is the most common malignancy in men, especially in the elderly: this condition is more frequently diagnosed over age 65 years, although extensive screening programs through widespread availability of prostate-specific antigen (PSA) assay have increased the possibility of diagnosis at an earlier age (40–50 years).<sup>1–3</sup> Skeletal metastases are very common in prostate cancer, with an 84% prevalence on autoptic series, and represent the initial and main metastatic site in about 80% of prostate cancer patients.<sup>4</sup> Bone involvement significantly affects the prognosis of these patients; particularly, the rate of increase in the number of bone metastases, as detected on bone scintigraphy, is associated with lower survival rates after the detection of bone involvement itself.<sup>5</sup> Several studies have demonstrated that the

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extent of bone involvement from prostate cancer is an independent negative prognostic factor.<sup>6-8</sup> The incidence of bone metastases depends on many factors: it is reasonably low in patients with Gleason score (GS) of the primary tumor lower than 6 and PSA lower than 20 ng/mL;<sup>9</sup> however, Moslehi et al<sup>10</sup> found that a combination of elevated PSA (>20 ng/mL) and serum alkaline phosphatase, regardless of GS, best predicts the risk of bone metastases in asymptomatic patients with newly diagnosed prostate cancer, with 98.2% sensitivity.

Common sites of bone metastases from prostate cancer are vertebral bodies, sternum, pelvic bones, ribs, and proximal femurs; skull base and orbital and extremity involvement is fairly uncommon.<sup>11,12</sup> However, pathological fractures are unusual, because metastases from prostate cancer usually show a marked osteoblastic reaction of the surrounding bone. Bone pain and spinal cord compression are more frequently seen; most cases are asymptomatic.

Early detection of metastatic bone involvement is critical in the management of patients with high-risk prostate cancer, since radical treatment with curative intent (surgery, radiation therapy, or both) is recommended only in patients presenting with localized disease; patients with metastatic disease should be treated with systemic therapy (androgen-deprivation therapy, bisphosphonates).<sup>13-15</sup> Moreover, accurate staging could be helpful in identifying patients with single-bone metastasis susceptible to radiation therapy, particularly when painful.

Radionuclide bone scintigraphy is the most widely used nuclear medicine diagnostic technique in evaluating patients with high-risk prostate cancer and suspicion of skeletal metastases: it is highly accurate, available in almost all nuclear medicine units, and is simple to execute. However, new diagnostic methods such as positron emission tomography (PET)/computed tomography (CT) are increasingly used for this purpose, in order to make the identification of bone metastases easier and to overcome the limitations of bone scintigraphy (low specificity). This notwithstanding, whether and when these PET/CT techniques should be performed in these patients, or even whether they could substitute bone scintigraphy in the future, is still a matter of debate.

The aim of this review was to investigate the state of the art of published literature about PET/CT and radionuclide bone scans to define what the contribution of each of these techniques is in the management of patients with recent diagnosis of prostate cancer, and therefore when they should be performed.

## Radionuclide bone scintigraphy

Radionuclide bone scintigraphy using radiolabeled bisphosphonates is the mainstay for the detection of skeletal metastases in patients with various tumoral entities. Bisphosphonates are organic phosphate compounds currently used as therapeutic agents for osteoporosis, due to their ability to reduce bone resorption by inhibiting human osteoblast secretion and proliferation.<sup>16</sup> The rationale of using bisphosphonates for the detection of bone malignancies is that the presence of neoplastic cells usually induces increased turnover by the surrounding bone tissue; therefore, bisphosphonates primarily accumulate on the surface of crystals of hydroxyapatite around neoplastic tissue, rather than in the healthy bone. Technetium-99m methylene bisphosphonate (MDP) and technetium-99m hydroxymethylene bisphosphonate (HMDP) are the radiopharmaceuticals of choice to detect skeletal metastases in patients with high-risk prostate cancer at either first diagnosis or suspicion of relapse due to doubtful imaging findings and/or increased PSA value.

Bone scintigraphy can be performed by using either a planar or a tomographic (single-photon emission computed tomography [SPECT]) acquisition protocol: a non-contrast-enhanced CT scan can be performed in addition to tomographic SPECT acquisition (SPECT/CT) for anatomical correlation and attenuation-correction purposes. A slight increase in sensitivity, yet without significant changes in specificity, when SPECT is performed as a completion of planar scan, has been reported.<sup>17</sup> Since osteoblastic reaction occurs much earlier than anatomical changes in cortical bone, bone scintigraphy using MDP or HMDP is much more sensitive than such morphological modalities as CT or magnetic resonance imaging (MRI) and detects bone metastases long before anatomical changes appear. Since marked osteoblastic reaction is common in bone metastases from prostate cancer, bone scintigraphy is the most sensitive, widely available, and easy-to-perform diagnostic method in this setting, currently.

Although very sensitive, bone scintigraphy has low specificity, since both MDP and HMDP accumulate in the surrounding bone reaction, not inside the neoplastic cells, thus a higher uptake of radiopharmaceutical in a skeletal site could be ascribed to each event able to produce an increased bone apposition in that site.<sup>15,18</sup> In a very recent prospective study, Damle et al<sup>19</sup> evaluated 151 patients with suspected bone metastases from either lung, breast, or prostate cancers by using bone scan and PET/CT: overall specificity of bone scintigraphy (in both patients at first diagnosis and patients with suspected recurrent disease) was 54% in lung cancer

patients, 63% in breast cancer patients, and 41% in prostate cancer patients. Sclerotic lesions were more commonly detected than mixed lytic ones (70 vs eleven and eight, respectively). False-positive findings on bone scintigraphy are more commonly consequent to traumatic/microtraumatic injury (accidental or iatrogenic), joint degenerative or inflammatory disease (arthrosis, osteoarthritis), metabolic disorders (eg, hyperparathyroidism), or benign bone diseases (eg, benign neoplasms, Paget's disease).<sup>15,18</sup> Moreover, as described by Withofs et al,<sup>20</sup> the overall accuracy of bone scintigraphy varies depending on the location of findings in the skeleton, being as low as 42% and 51% for pelvis and lumbar spine, respectively; conversely, higher accuracy values are shown for skull and long-bone lesions (83% and 75%, respectively).

Therefore, a careful collection of clinical history, paying particular attention to recent traumatic injuries and previous surgical interventions, is mandatory to reduce the risk of misinterpretation of benign findings.

## Positron emission tomography

PET is a nuclear medicine diagnostic technique that uses molecules labeled with positron-emitting radionuclides, such as fluorine-18 or carbon-11, to trace physiological or pathological aspects and processes within the human body. Due to the lack of anatomical landmarks, PET is usually performed in coregistration with contrast-enhanced or more frequently non-contrast-enhanced CT: this hybrid morphological and functional technique is called PET/CT.

A number of radiopharmaceuticals are currently available for PET/CT evaluation of prostate cancer, for both initial staging and restaging purposes: detection of distant (bone and soft tissue) metastases and nodal sites of disease, rather than the depiction of the primary lesion, are the primary indications to perform a PET/CT examination in patients with recently diagnosed prostate cancer. Particularly, fluorine-18-fluorodeoxyglucose (FDG), fluorine-18-fluorocholine (FCh), or carbon-11-choline (CCh) and sodium fluorine-18-fluoride (NaF) are currently used in PET/CT investigation of bone metastases from prostate cancer.

## Fluorine-18-fluorodeoxyglucose

FDG is a radioactive glucose analogue that is actively trapped into cells by means of transmembrane glucose transporters, whose expression on the cell membrane is physiologically variable in response to the metabolic needs of the cell itself. The rationale of using FDG to detect tumoral sites is that glucose transporters are abnormally overexpressed on the

cell membrane of neoplastic cells due to dysregulation of metabolic pathways; besides, hexokinase II enzymatic activity is dramatically enhanced in tumors, so that phosphorylated FDG (as FDG-6-phosphate) accumulates into neoplastic cells much more often than into normal ones.<sup>21,22</sup> The phenomenon of FDG uptake by prostate cancer cells is variable, mostly depending on the grade of differentiation and aggressiveness: higher FDG uptake can be observed in tumors that are resistant to androgen-deprivation therapy than in androgen-dependent ones.<sup>23</sup>

However, the few studies that have specifically investigated the efficacy of FDG PET/CT using FDG in the detection of skeletal sites from prostate cancer have demonstrated a high risk of false-negative results: low glycolytic activity of prostate cancer cells and physiological urinary excretion account for low sensitivity of PET/CT using FDG in this setting. Therefore, FDG is of little or no interest for detecting skeletal sites from prostate cancer in current clinical practice. Shreve et al<sup>24</sup> observed that PET/CT using FDG identified only 131 out of 202 untreated skeletal metastases in 22 patients, with a sensitivity of 65%, lower than that of conventional bone scintigraphy in the same population; moreover, in six patients undergoing hormonal treatment, FDG identified merely four out of 131 skeletal sites on bone scan. Yeh et al<sup>25</sup> reported that only about 18% of skeletal sites of disease on conventional bone scan showed a corresponding increase of FDG uptake; this finding was independent of duration of illness, entity of PSA increase, previous hormone therapy, and overall extent of disease. More recently, Morris et al<sup>26</sup> observed that despite its low sensitivity, PET/CT using FDG could be helpful in distinguishing progressive from quiescent bone metastatic disease in patients with prostate cancer: although PET/CT was falsely negative in 31 out of 126 metastatic sites seen on bone scintigraphy (sensitivity 77%), all but one lesion seen on bone scan alone (FDG-negative) showed no progression on follow-up when compared with the baseline bone scan; on the contrary, all 95 FDG-positive lesions reflected progressive disease on subsequent studies. Therefore, FDG uptake should predict further progression of skeletal disease.

In support of these observations, it has been supposed that glucose metabolism is not important in providing prostate cancer with a source of energy. Moreover, sclerotic prostate cancer metastases may be relatively hypocellular, so that viable tumor volume is under the detection limit of the PET/CT technique; conversely, these lesions are typically positive on conventional bone scan, since the radiopharmaceutical is actively bound by osseous matrix. Osteolytic metastases,

instead, reveal a particularly aggressive behavior of the tumor, which results in reduced blood flow, hypoxia, and enhanced glycolysis (FDG-positive lesions).

## Fluorine-18-fluorocholine and carbon-11-choline

Choline is an essential nutrient that acts as a substrate for the synthesis of phosphatidylcholine and sphingomyelin, two classes of cell membrane phospholipids. Their synthesis by choline kinase is upregulated in tumor cells.<sup>27,28</sup> Ackerstaff et al<sup>27</sup> observed that malignant prostate cells exhibit significantly higher levels of choline-derived compound compared with normal prostate epithelial and stromal cells; such behavior is attributable to an alteration of phospholipid metabolism rather than increased cell density. Therefore, choline-derived radiopharmaceuticals, such as FCh and CCh, are currently the most commonly used tracers for PET/CT evaluation of prostate cancer.<sup>29</sup> The short half-life of carbon-11 (20 minutes) requires an in-site cyclotron, and this limits the use of CCh in clinical practice. FCh was developed as a more versatile alternative, thanks to the longer half-life of nuclide fluorine-18 (about 110 minutes).

Currently, the primary indication for PET/CT using FCh or CCh is the detection of eventual sites of recurrent disease in patients with biochemical relapse (namely, a rise in PSA values regardless of concurrent hormone therapy). A recent meta-analysis by Evangelista et al<sup>30</sup> reported high sensitivity and specificity of PET/CT using choline-derived radiopharmaceuticals (85.6% and 92.6%, respectively) in detecting sites of prostate cancer recurrence after radical prostatectomy or external beam radiation therapy.

Several studies have investigated the reliability of PET/CT using choline-derived radiopharmaceuticals in the detection of bone metastases from prostate cancer. Beheshti et al<sup>31</sup> studied 38 men with biopsy-proven prostate cancer, either preoperatively or postoperatively, and evaluated both patient-based and lesion-based accuracy of PET/CT using FCh in 321 bone lesions, comparing imaging findings with histopathology and/or clinical follow-up, considered as gold-standard references: sensitivity, specificity, and overall accuracy were 74%, 99%, and 85%, respectively. Moreover, they found that FCh uptake negatively correlates with bone lesion density, expressed as Hounsfield unit (HU) level: bone marrow metastases without significant bone reaction and remodeling and lytic lesions tend to be more frequently FCh-positive, while highly sclerotic lesions with predominant osteoblastic reaction do not show significant FCh uptake. In their study, no lesions with CT density more

than 825 HU were FCh-positive. Smaller numbers of cancer cells, eventually with low metabolic activity, and lower blood supply in sclerotic lesions are possible explanations of poor FCh uptake, similar to the lower FDG uptake observed in sclerotic metastases.

These encouraging results were confirmed in a wider study on 70 patients:<sup>32</sup> sensitivity, specificity and overall accuracy values were 79%, 97%, and 84%, respectively, on a lesion-based analysis. A significant correlation was found between FCh uptake, expressed as maximum standardized uptake value ( $SUV_{max}$ ), and lesion density, expressed as HU level. Low FCh uptake was observed in highly sclerotic lesions, even in cases with biochemical evidence of progressive disease and in two patients undergoing hormone therapy, although there were multiple FCh-positive metastases in other skeletal sites. Moreover, PET/CT using FCh is helpful in detecting early bone marrow infiltration without evidence of morphological alterations: such FCh-positive findings lead to significant changes in the management of high-risk patients in preoperative staging.<sup>32,33</sup> Tuncel et al<sup>34</sup> observed in a population of 45 advanced prostate cancer patients that bone lesions with high uptake of CCh showed an average density of 458 HU, in comparison with CCh-negative lesions, which showed an average density of 787 HU (sclerotic).

Finally, clinical follow-up of patients with progressive prostate cancer has revealed that bone lesions from prostate cancer usually evolve from FCh-positive/CT-negative, low-density, high-cellularity metastases (substantially, expression of bone marrow involvement) to usually slightly osteoblastic alterations, with mild-to-moderate positivity on FCh and positivity on CT, and finally progress to high-density, sclerotic FCh-negative lesions, with a limited amount of viable cancer cells.<sup>32</sup> Furthermore, as reported by Beheshti et al,<sup>32</sup> hormone therapy tends to increase average density of bone lesions (713 HU in previously treated vs 542 HU in untreated patients), despite no significant changes on average  $SUV_{max}$  (8.2 vs 7.9), presumably as a consequence of posttreatment apoptotic phenomena.

Lastly, a recent meta-analytic paper by Umbehr et al<sup>35</sup> investigated the role of both FCh and CCh in staging patients with proven but untreated prostate cancer: sensitivity, specificity and diagnostic odds ratio were 84%, 79%, and 20%, respectively, on a per-patient basis, and 66%, 92%, and 23%, respectively, on a per-lesion basis. The authors underlined that there is limited but promising evidence that PET/CT using FCh or CCh performs well in this setting, warranting further studies.

Rare variants of prostate carcinoma, such as small-cell subtype, should be considered as a possible source of false-negative findings on PET/CT using choline-derived radiopharmaceuticals.<sup>36</sup> False-positive findings are usually related to nonspecific uptake of FCh or CCh by inflammatory cells; this could result in significant uptake by both actively remodeling pagetic bone and coexisting skeletal metastases from prostate cancer, as reported by Giovacchini et al.<sup>37</sup>

## Sodium fluoride-18-fluoride

NaF is a sodium salt of fluorine-18 that binds to calcium ions in hydroxyapatite crystals in bone. Therefore, it is successfully used as a PET/CT bone-seeking tracer to detect skeletal abnormalities, mainly for oncological purposes (detection of distant bone metastases): uptake of NaF reflects blood flow and bone remodeling, which are increased in sites of metastatic spread to the bone. Greater accuracy values than those observed in radionuclide bone scintigraphy using technetium-99m-labeled samples have been reported in the detection of skeletal metastases from different primary tumors.<sup>20,38-40</sup> It has been demonstrated not only that PET/CT using NaF is highly reliable in detecting both sclerotic and osteolytic lesions and in differentiating malignant from benign lesions but also that it is more accurate than bone scintigraphy, especially in spine and pelvic lesions.<sup>38-41</sup> A meta-analysis by Tateishi et al<sup>42</sup> confirmed sensitivity and specificity values of 96.2% and 98.5%, respectively, on a patient basis, and 96.9% and 98.0%, respectively, on a lesion basis.

Many studies have investigated the role of PET/CT using NaF in patients with prostate cancer. Even-Sapir et al<sup>17</sup> found that PET using NaF is a very sensitive tool for the detection of bone metastases in patients with high-risk prostate cancer, with reported sensitivity, specificity, and positive and negative predictive values of 100%, 62%, 74%, and 100%, respectively. In particular, 21 patients with negative NaF PET/CT had no clinical or imaging evidence of metastatic spread for at least a 6-month follow-up period. The specificity of NaF is greater than that of bone scintigraphy, especially in depicting malignant lesions rather than benign ones; besides, the addition of CT scan to PET alone contributed to an increase in diagnostic accuracy and specificity, due to a possible correlation of function changes with morphological alterations.

Beheshti et al<sup>31</sup> evaluated 321 bone lesions from prostate cancer and found that NaF is more sensitive than FCh (81% vs 74%); however, a significant change in patients' management was not observed in comparison with FCh.

Furthermore, osteoblastic lesions usually showed intense NaF uptake due to increased apposition of mineralized matrix; conversely, possible negative findings have been reported in highly sclerotic dense lesions in patients undergoing antiandrogenic therapy, as a consequence of effective treatment.

More recently, Damle et al<sup>19</sup> prospectively studied 49 prostate cancer patients (25 for initial staging and 24 for restaging purposes) without known bone metastases but with high risk/clinical suspicion (eg, bone pain). The authors found that PET/CT using NaF had the highest possible sensitivity and negative predictive value (100%) and 90% overall accuracy, when compared with FDG and bone scintigraphy. Particularly, PET/CT using NaF detected the greatest number of lesions, followed by bone scintigraphy, followed in turn by FDG. Therefore, they inferred that PET/CT using NaF is of the greatest importance in patients with high risk or high clinical suspicion for bone metastases from either prostate or breast and lung cancers (the authors also studied 72 and 30 patients with breast and lung carcinomas, respectively).

Withofs et al<sup>20</sup> prospectively investigated the accuracy of PET/CT using NaF in ten patients with prostate cancer and at high risk of bone metastases, using MRI or thin-slice CT as gold-standard imaging methods. All patients were also studied with both planar and SPECT bone scintigraphy using technetium-99m-labeled bisphosphonates. PET/CT using NaF was confirmed to be more accurate than bone scintigraphy in detecting skeletal metastases from prostate cancer: sensitivity, specificity, accuracy, and positive and negative predictive values were 100%, 95%, 96%, 86%, and 100%, respectively (vs 67%, 84%, 80%, 57%, and 89% for bone scintigraphy), for lesions confirmed as malignant, and 100%, 89%, 92%, 75%, and 100%, respectively (vs 67%, 82%, 78%, 53% and 89% for bone scintigraphy), for benign findings. False-positive findings were mostly due to posttrauma osteoblastic activity for both NaF and bone scintigraphy. Tomographic acquisition did not significantly contribute to overall accuracy of planar bone scintigraphy. The accuracy of NaF was significantly higher than bone scintigraphy for pelvic and lumbar spine malignant lesions (73% vs 42% and 78% vs 51%, respectively), rather than for lesions located in other skeletal sites. The sensitivity of NaF and bone scintigraphy were related to heterogeneity of presentation of bone metastases, with greater accuracy in osteoblastic lesions.

The detection of bone metastases by using NaF and FCh in 42 patients with prostate cancer complaining of osteoarthritic pain was evaluated prospectively by Langsteger et al.<sup>43</sup> Despite overall similar sensitivity between NaF and FCh in

360 skeletal lesions (91%), FCh showed greater overall specificity (89% vs 83%) and accuracy (90% vs 88%; however, no statistical significance was reached in this setting). By considering only patients at initial staging, no significant differences were seen between FCh and NaF in site-based performance.

## Clinical recommendations

The role of nuclear medicine imaging tools in evaluating patients with biochemical recurrence of prostate cancer (ie, increase in PSA levels) after radical treatment has been extensively investigated. In particular, PET/CT using FCh has shown high reliability in the detection of both locoregional and distant metastases in patients with biochemical relapse.<sup>30</sup> Conversely, the proper use of imaging techniques in the initial staging of patients with recently diagnosed prostate cancer is more controversial.

Early detection of distant metastases, and particularly skeletal ones, is useful in the correct staging, definition of prognosis, and further treatment decision-making for patients with recently diagnosed prostate cancer; in fact, patients with extensive skeletal disease may benefit from systemic therapies, such as androgen deprivation or bisphosphonates, while those with localized disease may take advantage of surgical and/or radiation therapy.<sup>13,14</sup> However, the routine use of skeletal imaging is not recommended in all patients for staging purposes. The Best Practice Statement edited in 2000 by the American Urological Association and recently updated in 2009 recommended pretreatment staging of prostate cancer only in cases of high-risk disease: PSA level, GS at biopsy, and clinical stage of disease could be used to predict the yield of imaging in patients' further management.<sup>44-47</sup> Since pretreatment serum PSA level correlates with the risk of extraprostatic extension, routine bone scan is not required for staging asymptomatic patients with clinically localized prostate cancer when PSA level is equal to or less than 20 ng/mL, unless the history or clinical examination suggests skeletal involvement. Abuzallouf et al<sup>47</sup> reported that metastases were found on bone scans in 5.3% of patients with PSA levels lower than 20 ng/mL; conversely, 16.2% of patients with PSA levels higher than 20 ng/mL showed bone metastases. Higher GS (>7) at biopsy significantly correlates with higher risk of bone involvement, as recently reported by De Nunzio et al.<sup>48</sup>

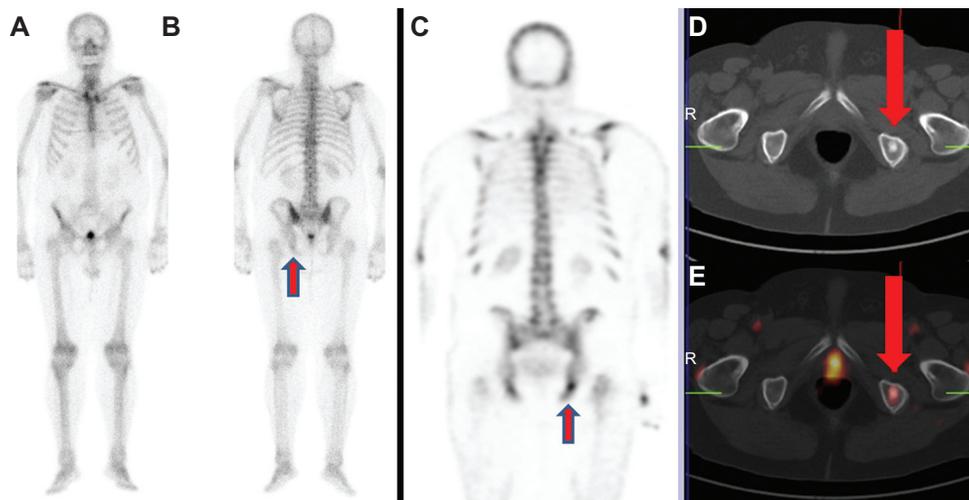
Despite well-defined clinical recommendations, widespread overuse of imaging in low-risk and intermediate-risk prostate cancer patients has been reported. Expensive unnecessary imaging is common in older and less educated

people, and in patients managed with proton-beam or standard radiation therapy rather than in those undergoing radical prostatectomy or active surveillance.<sup>49,50</sup> Anyway, staging procedures that are not expected to affect further treatment decision-making should be avoided.

To date, bone scintigraphy using MDP or HMDP has been the cornerstone in the evaluation of newly diagnosed high-risk prostate cancer patients, since it is a widely available and inexpensive whole-body imaging technique that allows the reliable ruling out of skeletal involvement in a single examination, due to its high sensitivity. However, this technique suffers from low specificity and is not able to exclude osteolytic and soft-tissue metastases. Therefore, PET/CT using choline-derived radiopharmaceuticals is used even more in this setting to detect both soft-tissue and skeletal metastases (Figure 1); indeed, it has been proposed as a "one-stop shop" technique in the evaluation of metastases from prostate cancer, due to its higher specificity. However, there is little agreement in the literature about which method is the best, since discrepancies between PET/CT using FCh or CCh and bone scintigraphy have been described.<sup>51-54</sup> However, as recently reported by Balogova et al,<sup>55</sup> generalized skeletal uptake in patients receiving bone marrow-stimulating factors (like erythropoietin) could reduce the sensitivity of PET/CT using FCh or CCh; such behavior is not seen in bone-seeking radiopharmaceuticals, such as NaF and bisphosphonates. Another well-known drawback of PET/CT using choline-derived radiopharmaceuticals is its low negative predictive value, mainly due to its limited capability to detect micrometastases.<sup>56,57</sup>

PET/CT using NaF should be preferred to PET/CT using FCh or CCh in the evaluation of patients with high-density sclerotic bone metastases, due to the naturally increased uptake of NaF in sites of bone remodeling; moreover, better spatial resolution of PET modality and the advantages deriving from tomographic acquisition and CT-dependent attenuation correction allow NaF to perform better than classic bone scintigraphy in the depiction of small skeletal sites of disease and in mixed-type lesions. Its very high sensitivity and negative predictive value make it very useful in detecting occult skeletal metastases in patients with biochemical relapse, and positivity tends to associate with increasing PSA levels.<sup>58</sup> Higher specificity than diffusion-weighted MRI has recently been reported.<sup>59</sup> However, further studies comparing these techniques and correlating imaging findings with PSA values and PSA velocity are needed.

The role of PET/CT using FDG is not well defined in this setting, since a very low detection rate of bone and soft-tissue



**Figure 1 (A–E)** A 76-year-old patient with recently diagnosed prostate cancer (prostate-specific antigen level, 18 ng/mL) underwent bone scan and positron emission tomography (PET)/computed tomography (CT) using radiolabeled choline for staging purposes. Bone scan in anterior (A) and posterior view (B) shows an area of mild radiopharmaceutical uptake corresponding to the left ischiatic bone (arrow). This finding was more evident by using single-photon emission computed tomography imaging (C).

**Notes:** Axial CT (D) and radiolabeled choline PET/CT (E) images showed the presence of increased radiopharmaceutical uptake corresponding to an osteosclerotic lesion located in the left ischiatic bone (arrows). This finding was highly suspicious for skeletal metastasis. Biopsy confirmed the presence of a bone metastasis by prostate cancer.

metastases is commonly described. As reported by Jadvar in a recent review article,<sup>60</sup> FDG uptake in prostate cancer depends on tumor differentiation, with low accumulation in well-differentiated tumors and high uptake in aggressive poorly differentiated tumors.

## Conclusion

Radionuclide bone scintigraphy using labeled bisphosphonates, either performed with planar, SPECT, or SPECT/CT acquisition, remains the most widely available and simple technique for the early detection of bone metastases in prostate cancer patients at diagnosis. However, PET/CT using different non-FDG radiopharmaceuticals (FCh, CCh, and NaF) is emerging as a possible alternative to bone scintigraphy in this setting. Indeed, choline-derived radiopharmaceuticals are helpful in the detection of small lytic skeletal metastases, nodal and soft-tissue metastases, despite low sensitivity in the evaluation of osteoblastic lesions; on the other hand, NaF shows high sensitivity (due to the detection of even minimal changes in the bone turnover and blood flow in metastatic sites), overcoming the low specificity of bone scintigraphy, thanks to its higher spatial resolution and the anatomical correlate deriving from CT scan. Greater radiobiological burden, higher costs, and the restricted territorial availability of PET/CT methods, however, limit their use as first-line investigations in patients with prostate cancer.

## Disclosure

The authors report no conflicts of interest in this work.

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