Evaluation of Prostate Cancer with [11]C- and ^{18}F-Choline PET/CT: Diagnosis and Initial Staging

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Early diagnosis and adequate staging are crucial for the choice of adequate treatment in prostate cancer (PC). Morphologic and functional imaging modalities, such as CT and MRI, have had limited accuracy in the diagnosis and nodal staging of PC. Molecular PET/CT imaging with [11]C- or ^{18}F-choline–labeled derivatives is increasingly being used, but its role in the diagnosis and initial staging of PC is controversial because of limitations in sensitivity and specificity for the detection of primary PC. For T staging, functional MRI is superior to [11]C- or ^{18}F-choline PET/CT. For N staging, [11]C- or ^{18}F-choline PET/CT can provide potentially useful information that may influence treatment planning. For the detection of bone metastases, [11]C- or ^{18}F-choline PET/CT has had promising results; however, in terms of cost-effectiveness, the routine use of [11]C- or ^{18}F-choline PET/CT is still debatable. [11]C- or ^{18}F-choline PET/CT might be used in high-risk PC before radiation treatment planning, potentially affecting this planning (e.g., regarding dose escalation). This review provides an overview of the diagnostic accuracy and limitations of [11]C- or ^{18}F-choline PET/CT in the diagnosis and staging of PC.

Key Words: prostate cancer; diagnosis; staging; choline; PET/CT

Prostate cancer (PC) is currently the most frequent malignant cancer of men in the United States (1). Early diagnosis and adequate staging are crucial for an optimal choice of treatment. Routinely used standard procedures in the diagnosis of PC are digital rectal palpation, prostate-specific antigen evaluation, and transrectal biopsy (2). Additionally, morphologic imaging, such as CT or MRI, is performed. However, these imaging modalities have had limited accuracy in the diagnosis and staging of PC. Besides morphologic imaging, molecular imaging such as PET/CT is increasingly being used. ^{18}F-FDG has limited sensitivity for the detection of slowly growing and well-differentiated tumors; additionally, its value is limited because of the confounding influence of bladder activity (3). A high level of ^{18}F-FDG uptake is regularly found only in undifferentiated, aggressive, and metastasized prostate tumors (4). Therefore, PET/CT with [11]C- or ^{18}F-choline–labeled derivatives is more commonly used. This review provides an overview of the diagnostic accuracy and limitations of [11]C- or ^{18}F-choline PET/CT in the diagnosis and initial staging of PC.

DIAGNOSIS OF PC

The use of [11]C- or ^{18}F-choline PET/CT in the pretherapeutic setting for the detection of untreated PC has been discussed in many studies; results with respect to its sensitivity and specificity have been controversial (Fig. 1).

Earlier studies on the usefulness of [11]C- and ^{18}F-choline PET/CT showed promising results, with a high sensitivity (up to 100%) (5–12). However, a high level of ^{11}C-choline uptake was also shown in benign prostatic hyperplasia, resulting in a limited specificity of ^{11}C-choline PET/CT (11–13). Additionally, in more recent studies, sensitivities of 66%–86.5% were reported for [11]C- and ^{18}F-choline in the diagnosis of primary PC (14–21). Farsad et al. described an overall sensitivity of 66% and a specificity of 81% for the detection of local PC (14). Martorana et al. demonstrated that lesion size had the most important influence on sensitivity (sensitivities of 83% for the localization of lesions larger than 5 mm, 66% for all lesions, and only 4% for lesions smaller than 5 mm) (16). There was no significant difference between false-positive and correctly positive findings (16). Scher et al. (17) and Giovacchini et al. (15) confirmed those results, showing limited sensitivities of 86.5% and 72% and specificities of 61.9% and 43%, respectively. Beheshti et al. could not distinguish PC from prostatitis using ^{18}F-choline PET/CT because of a high focal level of ^{18}F-choline uptake in inflammatory tissue (19). Souvatzoglou et al. compared ^{11}C-choline PET/CT and histopathologic findings in 43 PC patients using a segment model (18). The affected segments could not be identified correctly in 21% of the patients. The authors found the large number of microcarcinomas and the influence of the partial-volume effect to be the main reasons for the limited sensitivity (18). The only factor significantly influencing tumor detection was tumor configuration; small tumors and tumors with an "onion" form of growth were detected at a significantly lower rate ($P < 0.001$). There was no significant difference between the SUV_{max} of malignant changes and the SUV_{max} of benign prostatic changes (18). Bundschuh et al. correlated ^{11}C-choline uptake in the prostate gland with histopathologic findings after radical prostatectomy (20). Only 46% of histopathologically positive lesions had increased ^{11}C-choline uptake. The authors could not determine a specific SUV threshold
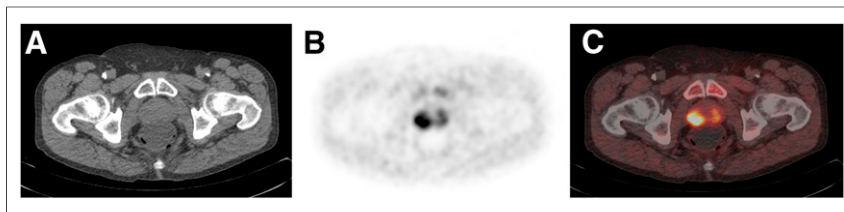
FIGURE 1. 71-y-old patient who had suspected PC (prostate-specific antigen level, 11.4 ng/mL) and was referred for ^{18}F-choline PET/CT. ^{18}F-choline PET/CT showed right-side focal uptake in prostate, indicating PC. Biopsy proved PC (Gleason score, 4 + 5 = 9). (A) Transaxial CT. (B) Transaxial PET. (C) Transaxial PET/CT.

for distinguishing tumor tissue from nontumor tissue (*20*). Those results were confirmed by Grosu et al., who showed that correct differentiation of malignant from normal prostate tissue with ^{11}C-choline PET/CT was not feasible (*21*).

Comparing ^{11}C-choline PET/CT and MRI for the detection of primary PC, Watanabe et al. showed that MRI was superior to PET/CT (sensitivities of 88% vs. 73%) (*22*). Combining these modalities, Hartenbach et al. showed a very high sensitivity of ^{18}F-choline PET/MRI for the detection of dominant malignant lesions of the prostate (*23*).

In summary, [11]C- or ^{18}F-choline PET/CT has had limited value for the detection of primary PC because of limited sensitivity and specificity for the differentiation of benign from malignant prostatic changes. Additionally, the value of ^{18}F-choline PET/CT especially is limited because of the confounding influence of bladder activity. [11]C- or ^{18}F-choline PET/CT cannot be recommended as a routine imaging modality in this scenario. MRI seems to be superior for the detection of primary PC; in the future, combined PET/MRI might improve diagnostic accuracy for the detection of malignant prostatic lesions.

T STAGING

The choice of treatment for PC depends on various factors, such as local tumor stage, presence of metastases, patient's age, and coexisting comorbidities. Initial staging takes into account the results of systematic biopsy, prostate-specific antigen level, and findings of digital rectal examination (*24*). Depending on these factors, the likelihood of locally advanced or metastatic disease is determined, and additional staging procedures may be needed. Several studies have shown a limited sensitivity of ^{11}C-choline PET/CT for the detection of extracapsular extension (e.g., 22% and 27% reported by Martorana et al. and Rinnab et al., respectively (*16,25*)). Those results were confirmed by Pinaquy et al., who recently reported a higher sensitivity of diffusion-weighted (DW) MRI than of ^{18}F-choline PET/CT (73% vs. 36%) for the detection of seminal vesicle invasion (*26*). In a recently published review, De Bari et al. concluded that MRI is superior to [11]C- or ^{18}F-choline PET/CT in terms of sensitivity and specificity for the local assessment of PC (*27*).

In summary, less detailed anatomic information from CT (compared with MRI), the influence of the partial-volume effect, and especially the well-known limited resolution of PET seem to be the most important drawbacks for correct T staging with [11]C- or ^{18}F-choline PET/CT (*28*). Therefore, [11]C- or ^{18}F-choline PET/CT does not play a significant role in T staging of PC. For local staging in the prostate, MRI (with or without the use of endorectal coils) is the method of choice.

N STAGING

Because treatment strategies will differ for PC with and PC without nodal metastases or distant metastases, discriminating nonmetastatic PC from metastatic PC is important. As discussed by Farsad et al., the best staging method for the detection of nodal metastases is pelvic lymph node dissection (PLND) (*28*). Patients who have intermediate- or high-risk tumor stages and a higher incidence of lymph node metastases are likely to benefit from PLND. However, PLND may be associated with postsurgical complications, such as lymphocele and impairment of wound healing (*28*). Therefore, a sensitive and specific imaging modality for the accurate detection of lymph node metastases is needed. Both CT and MRI have limitations for the detection of nodal metastases (*29*), related to the fact that both modalities rely on lymph node size as the only criterion for metastatic involvement. However, at the present time, PC is often detected at an initial stage with lymph nodes of a normal size. Besides morphologic imaging, [11]C- and ^{18}F-choline PET/CT is used for nodal staging. The rate of detection of lymph node metastases with [11]C- and ^{18}F-choline PET/CT was recently examined in several metaanalyses.

Umbehr et al. reported pooled patient-based sensitivity of 84% and specificity of 79% (*30*). In a lesion-based analysis, they described a lower sensitivity (66%) and a higher specificity (92%) (*30*). Von Eyben and Kairemo reported a sensitivity of 59%, a specificity of 92%, a positive predictive value of 70%, and a negative predictive value of 85% on a patient basis (*31*). [11]C- or ^{18}F-choline PET/CT led to a change in therapy in 41% of patients (*31*). In another systematic review, including 10 studies with 441 patients, Evangelista et al. reported a sensitivity of 49% and a specificity of 95% on a patient basis (*32*). The sensitivity of ^{11}C-choline PET/CT was significantly higher than that of ^{18}F-choline PET/CT (58% vs. 40%) (*32*).

Schiavina et al. evaluated the use of ^{11}C-choline PET/CT for nodal staging in 57 patients with biopsy-proven intermediate- or high-risk PC (*33*). In a patient-based analysis, a sensitivity of 60%, a specificity of 98%, a positive predictive value of 90%, and a negative predictive value of 87% were shown. In a lesion-based analysis, the sensitivity was lower (41%) (*33*). Beheshti et al. correlated histopathologic findings after radical prostatectomy and extended PLND with preoperative ^{18}F-choline PET/CT results in 111 patients with intermediate- or high-risk PC (*19*). They reported a sensitivity of 45%, a specificity of 96%, and a negative predictive value of 83% for the detection of nodal metastases in a patient-based analysis. They found higher sensitivity and negative predictive value (66% and 92%, respectively) for lymph nodes larger than 5 mm. As in other studies, ^{18}F-choline PET failed to detect micrometastases. In 20% of patients with high-risk PC, ^{18}F-choline PET/CT led to a change in treatment (*19*). In a lymph node–based analysis, Contractor et al. reported a sensitivity of 40.7% and a high specificity (98.4%) for N staging with ^{11}C-choline PET/CT (*34*). Comparing preoperative ^{18}F-choline PET/CT results from 210 patients with intermediate- or high-risk PC with histopathologic findings after PLND, Poulsen et al. reported patient-based sensitivity and specificity of 73.2% and 87.6%, respectively (*35*). On a lymph node basis, sensitivity was 56.2% and specificity was 94.0%. ^{18}F-choline PET/CT failed to detect

nodal metastases smaller than 5 mm (35). In line with these results, Evangelista et al. recently reported overall accuracies of ^{18}F-choline PET/CT for lymph node involvement of 83.3% for high-risk PC and only 33.3% for intermediate-risk PC (36); these findings may have been due to a larger number of small metastases and micrometastases in intermediate-risk PC.

Besides [11]C- or ^{18}F-choline PET/CT, functional MRI techniques are used for N staging of primary PC. Pinaquy et al. compared ^{18}F-choline PET/CT with diffusion-weighted MRI for initial staging in patients with high-risk PC and correlated the results with histopathologic findings (26). On a region basis, they reported a higher sensitivity (56%) and a higher positive predictive value (98%) for ^{18}F-choline PET/CT than for DW MRI (17% and 97%, respectively). On a patient basis, higher sensitivities were reported for both ^{18}F-choline PET/CT and MRI (78% and 33%, respectively). The authors concluded that ^{18}F-choline PET/CT could detect nodal metastases with higher sensitivity and specificity than DW MRI (26). Vag et al. compared ^{11}C-choline PET/CT and DW MRI for N staging in 33 patients with biopsy-proven intermediate- or high-risk PC (37). They reported overall sensitivity and specificity of 69.72% and 90.48%, respectively, for ^{11}C-choline PET/CT. The sensitivity of DW MRI was similar, but the specificity was lower (69.70% and 78.57%, respectively). The authors concluded that both imaging modalities might provide complementary information on tumor biology (37). In a patient-based analysis, Heck et al. showed that—because of higher specificity—[11]C-choline PET/CT performed better than CT and DW MRI in 33 patients with intermediate- or high-risk PC (90% vs. 68% and 79%) (38). In contrast to those promising results, van den Bergh showed very low region-based sensitivities—8.2% and 9.5%—for ^{11}C-choline PET/CT and DW MRI, respectively, in a prospective trial comparing imaging results with histopathologic findings for 1,665 resected lymph nodes, of which 1,065 were malignant (39). Patient-based sensitivities were 18.9% and 36.1% for ^{11}C-choline PET/CT and DW MRI, respectively.

According to the study results described so far, the use of [11]C- or ^{18}F-choline PET/CT for primary nodal staging remains unclear. The range of patient-based sensitivity of [11]C- or ^{18}F-choline PET/CT is wide, and lesion-based sensitivity is even more limited. In patients with high-risk PC, [11]C- or ^{18}F-choline PET/CT might provide useful information on the presence of nodal metastases, potentially influencing treatment planning (Fig. 2); however, the detection of single lymph node metastases is not feasible. Most studies showed that [11]C- or ^{18}F-choline PET/CT might perform better than MRI, especially because of its high specificity, as also discussed by Evangelista et al. (40).

In summary, the use of [11]C- or ^{18}F-choline PET/CT for N staging of high-risk PC is under debate; its use in clinical routine practice for PC patients (irrespective of risk group) cannot be recommended because of limited sensitivity, especially for the detection of small metastases and micrometastases.

M STAGING

Bone metastases are the second most common manifestation of metastases in PC (80% osteoblastic, 15% osteolytic, and 5% of mixed type). The existence of bone metastases results in a poor prognosis and significantly higher morbidity and mortality. Therefore, the detection of bone metastases in primary staging is crucial. Bone scintigraphy (BS) is the imaging tool routinely used to detect bone metastases. The value of [11]C- or ^{18}F-choline PET/CT for M staging of primary PC (also in comparison with other imaging modalities) has been evaluated in several studies (for a review, see Bombardieri et al. (41)).

Beheshti et al. preoperatively compared ^{18}F-choline PET/CT and ^{18}F-fluoride PET/CT for M staging in 17 PC patients (42). They reported overall sensitivity of 74% and specificity of 99% for ^{18}F-choline PET/CT and 81% and 93%, respectively, for ^{18}F-fluoride PET/CT. They found that ^{18}F-choline PET/CT might allow for earlier detection of bone marrow metastases than ^{18}F-fluoride PET/CT (42).

The sensitivity and specificity of ^{18}F-choline PET/CT in another study by Beheshti et al. were similar (79% and 97%, respectively) (43). With ^{18}F-choline PET/CT, no increased uptake was observed in sclerotic lesions; those lesions were detected mainly in patients receiving antiandrogen therapy. The authors suggested that missing ^{18}F-choline uptake may have been due to missing viability after therapy (43). Kjölhede et al. examined 90 patients with biopsy-proven PC before treatment with ^{18}F-choline PET/CT and ^{18}F-fluoride PET/CT after BS (the results of which were negative) (44). Both modalities detected malignant bone lesions not revealed by BS. Not all bone metastases detected by ^{18}F-fluoride PET/CT could be found by ^{18}F-choline PET/CT. In 20% of the patients, treatment was changed on the basis of PET/CT results. The authors concluded that ^{18}F-choline PET/CT could provide additional information for staging in patients with negative BS results; however, the rate of detection with ^{18}F-choline PET/CT was lower than that with ^{18}F-fluoride PET/CT (44). Those results are in accordance with the results of the aforementioned studies (42,43). Evangelista et al. compared ^{18}F-choline PET/CT and BS and reported that both sensitivity and specificity were higher for PET/CT (100% vs. 90% and 86.4% vs. 77.2%, respectively) (36). ^{18}F-choline PET/CT changed the stage in 33.3% of the patients (36). In a prospective study on the accuracy of various imaging modalities for the detection of spine metastases, Poulsen et al. reported that ^{18}F-choline PET/CT had a higher specificity than BS and ^{18}F-fluoride PET/CT (91% vs. 82% and 54%) and that the sensitivity of ^{18}F-choline PET/CT was higher than that of BS but lower than that of ^{18}F-fluoride PET/CT (85% vs. 51% and 93%) (45).

In their recently published review, De Bari et al. concluded that [11]C- or ^{18}F-choline PET had a better sensitivity during the early progression of bone metastases, when they were still located in the bone marrow (27). In the course of disease progression, [11]C- or ^{18}F-choline PET and BS might perform similarly; later on, [11]C- or ^{18}F-choline PET seems to be more specific, showing increased [11]C- or ^{18}F-choline uptake only in viable metastases.
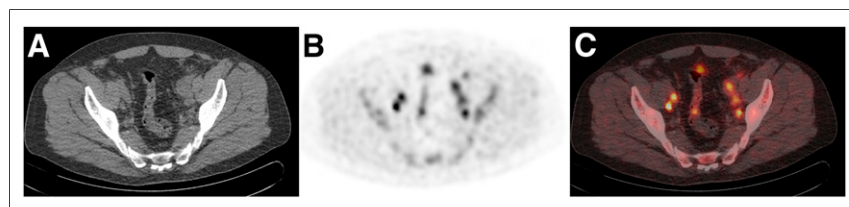
FIGURE 2. 52-y-old patient who had biopsy-proven high-risk PC (Gleason score, 4 + 5 = 9; prostate-specific antigen level, 84.4 ng/mL) and was referred for ^{18}F-choline PET/CT for initial staging before treatment. ^{18}F-choline PET/CT revealed multiple ^{18}F-choline–positive nodal iliac metastases on both sides. (A) Transaxial CT. (B) Transaxial PET. (C) Transaxial PET/CT.
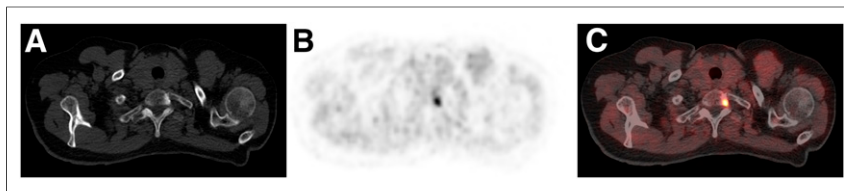
FIGURE 3. 71-y-old patient who had suspected PC and unclear (BS-negative) vertebral bone lesions and was referred for ^{18}F-choline PET/CT for initial staging before treatment. ^{18}F-choline PET/CT revealed high level of focal choline uptake in vertebral bone metastases that was missed by BS. (A) Transaxial CT. (B) Transaxial PET. (C) Transaxial PET/CT.

Therefore, ^{11}C- or ^{18}F-choline PET could be recommended as an alternative to BS in patients with high-risk PC, with a possible impact on treatment. Because of the possibility of detection of bone marrow metastases in the early stage of disease and its higher specificity, ^{11}C- or ^{18}F-choline PET/CT is superior to BS (Fig. 3). However, BS is more cost-effective in clinical settings (*27*).

POSSIBLE IMPACT OF ^{11}C- OR ^{18}F-CHOLINE PET/CT ON RADIATION TREATMENT PLANNING

Because of the limited sensitivity and specificity of ^{11}C- and ^{18}F-choline PET/CT for the diagnosis of primary PC, its routine use for radiation treatment planning is controversial. Target tumor volume delineation for intraprostatic lesions is critical because of the lack of an SUV threshold for the differentiation of benign from malignant tissues (*20,21*). Before radiation treatment planning, ^{11}C- or ^{18}F-choline PET/CT might be used in patients with high-risk PC to detect and encompass lymph node metastases outside the conventional irradiation field (for an overview, see Schwarzenböck et al. (*46*)). In a recent study by López et al., radiation treatment plan was changed on the basis of ^{11}C-choline PET/CT findings in 37.5% of the patients, resulting in good clinical and biochemical control and fewer or no side effects or less toxicity (*47*). Garcia et al. showed the feasibility of dose escalation for nodal metastases in 11 of 61 patients with biopsy-proven intermediate- or high-risk PC on the basis of ^{11}C-choline PET/CT findings (*48*). Further trials are necessary to define the role of ^{11}C- or ^{18}F-choline PET/CT in radiation treatment planning.

CONCLUSION

The role of ^{11}C- or ^{18}F-choline PET/CT in the diagnosis of PC has limitations in terms of sensitivity and specificity. In T staging, functional MRI is superior to ^{11}C- or ^{18}F-choline PET/CT. In nodal staging, ^{11}C- or ^{18}F-choline PET/CT might provide useful information on the presence of nodal metastases, potentially influencing therapy planning; however, the detection of small nodal metastases and micrometastases is limited. Despite promising results for the detection of bone metastases, the clinical routine use of ^{11}C- or ^{18}F-choline PET/CT is under debate. ^{11}C- or ^{18}F-choline PET/CT might be used in patients with high-risk PC, potentially influencing radiation treatment planning.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

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