Detection of Bone Metastases Using ^{11}C-Acetate PET in Patients with Prostate Cancer with Biochemical Recurrence

CLAUDIO SPICK[1], STEPHAN H. POLANEC[1], MARKUS MITTERHAUSER[2], WOLFGANG WADSAK[2], PHILIP ANNER[2], BETTINA REITERITS[2], ALEXANDER R. HAUG[2], MARCUS HACKER[2], MOHSEN BEHESHTI[3] and GEORGIOS KARANIKAS[2]

Divisions of [1]General and Pediatric Radiology and [2]Nuclear Medicine, Department of Biomedical Imaging and Image-guided Therapy, Medical University of Vienna, Vienna, Austria; [3]PET-CT Center Linz, Department of Nuclear Medicine and Endocrinology, St. Vincent's Hospital, Linz, Austria

Abstract. *Aim: To evaluate the diagnostic accuracy of ^{11}C-acetate positron-emission tomography (PET) in the detection of bone metastasis in patients with prostate cancer with biochemical recurrence. Patients and Methods: Ninety patients (100%) with rising prostate-specific antigen (PSA) levels (>0.2 ng/ml) after radical prostatectomy, who had both ^{11}C-acetate PET and bone scan performed and who had clinical follow-up/imaging follow-up for bone metastasis, considered a gold standard, were included. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for ^{11}C-acetate PET were calculated on a per-patient basis. Results: ^{11}C-Acetate PET and ^{99m}Tc-dicarboxypropane-diphosphonate findings were concordant in 84 (93.3%) patients [35 (38.9%) true-positive, 49 (54.4%) true-negative]. Discordant findings were observed in six patients (6.7%). ^{11}C-Acetate PET presented two (2.2%) false-positive and four (4.4%) false-negative findings. The sensitivity, specificity, PPV, and NPV for ^{11}C-acetate PET were 89.7%, 96.1%, 94.6%, and 92.2%, respectively. The median PSA of patients with multiple skeletal metastases (median=23.64 ng/ml, range=3.16-551.1 ng/ml) differed significantly (p=0.018) from that of patients with focal metastases (median=6.7 ng/ml, range=0.31-12.8 ng/ml). Conclusion: ^{11}C-Acetate PET is a useful tool for patients with prostate cancer with biochemical recurrence, as it can depict multiple sites of recurrence and in particularly shows a high diagnostic value equivalent to that of bone scan for the detection of bone metastases.*

Correspondence to: Professor Dr. Georgios Karanikas, Division of Nuclear Medicine, Department of Biomedical Imaging and Image-guided Therapy, Medical University of Vienna, Waehringer-Guertel 18-20, 1090 Vienna, Austria. E-mail: georgios.karanikas@meduniwien.ac.at

Key Words: Bone metastases, PET, acelate, prostate cancer.

Prostate cancer is the most common malignancy and the second leading cause of death in men in Western countries (1). Recurrent disease may occur in up to 50% of patients within 10 years after prostatectomy. Therefore, early and accurate detection of the site of recurrence is of the utmost importance for patient management, selection of therapy, and estimation of patient prognosis. Prostate-specific antigen (PSA) is an established biochemical marker for the assessment of recurrent disease (2, 3). However, it cannot reveal the site of disease, which is of key value in the determination of the treatment. Local therapeutic approaches can be performed in cases of recurrent disease in the locoregional pelvic lymph nodes and prostatic bed, while systemic therapy is required for distant metastatic spread. Approximately 90% of patients who die of prostate cancer present with bone metastases (4). Furthermore, the extent of metastatic bone disease is an independent prognostic factor (5).

In clinical practice, bone scintigraphy (BS) is a widely used, low-cost clinical examination that can demonstrate skeletal involvement due to osteoblastic bone remodeling. BS has high sensitivity but suffers from limited specificity due to non-specific tracer uptake in regions of inflammation, degeneration, and trauma. Its specificity has, however, been improved with the introduction of SPECT/CT imaging (6, 7).

Currently, several tracers for positron-emission tomography (PET) are in use for the assessment of prostate cancer (8-11). These various metabolic and receptor-based PET probes showed promising results in the detection of recurrent disease, as well as in the early detection of bone marrow metastases (8-11). However, their value in the detection of osteoblastic bone metastases, especially in dense sclerotic lesions, is still controversial (12).

In prostate neoplasms, prostate epithelial cells undergo a metabolic transformation from being citrate-producing normal cells to citrate-oxidizing malignant cells. Malignant cells overexpress the enzyme fatty acid synthase, which carries out the rate-limiting step in the metabolic conversion

of acetate into (membrane) lipid pools (13, 14). Thus, ^{11}C-acetate PET has been introduced to assess prostate cancer in primary staging, restaging, and localization of recurrent disease, and serves as a valid alternative to choline imaging (14-19). However, the diagnostic accuracy of ^{11}C-acetate PET specifically for the detection of skeletal involvement, by means of metastatic prostate cancer cells, has not been studied extensively.

The purpose of the study was to evaluate the diagnostic accuracy of ^{11}C-acetate PET in the detection of bone metastases in patients with prostate cancer with biochemical recurrence, and compare it to results of ^{99m}Tc-biphosphonate bone imaging.

Patients and Methods

Patient selection. This retrospective study was approved by the local institutional Review Board (2022/2013) and informed consent was waived. Overall, 90 patients with prostate cancer were included for data analysis based on medical reports. The inclusion criteria were: (i) rising PSA levels (>0.2 ng/ml) after radical prostatectomy; (ii) both ^{11}C-acetate PET and BS performed within a maximum interval of 3 months (range=0-96±29 days); (iii) clinical follow-up and imaging follow-up, which was considered the gold standard, including magnetic resonance imaging (MRI), computed tomography (CT), BS, and PET for at least 6 months in order to validate concordant or discordant findings between the two imaging modalities.

Image acquisition protocol. PET: ^{11}C-Acetate was prepared as described in detail by Mitterhauser *et al*. (20). ^{11}C-Acetate PET scans were obtained with a dedicated PET system (GE Advance; General Electric, Milwaukee, WI, USA), and covered an axial field of view of 15.2 cm. For the attenuation correction, a transmission scan was performed with standard source of 11Ge. Whole-body emission scans were acquired after intravenous injection of 740 MBq ^{11}C-acetate (five bed positions, 5 minutes per bed position) from the mid-thigh to the head at approximately 15 minutes after tracer injection.

Attenuation-corrected scan data were reconstructed as filtered back-projection images using a Hanning filter with a cut-off of 12, as well as iterative algorithms, and were reformatted in the coronal, transaxial, and sagittal planes for interpretation of the data.

Normal ^{11}C-acetate distribution is defined by physiological tracer uptake in the upper abdominal parenchymatous organs (liver, spleen, and pancreas) and by minor uptake in muscles, intestines, and renal parenchyma. Increased tracer uptake higher than physiological background activity was interpreted as being pathologic. Pathological lesions on ^{11}C-acetate PET were classified as local recurrence (LR), lymph node metastases (LNM), and distant metastases (*i.e*. organ or bone).

Whole-body bone scan: Whole-body BS was performed in all patients 3 hours after the intravenous administration of 740 MBq ^{99m}Technetium-dicarboxypropane diphosphonate (^{99m}Tc DPD). Anterior and posterior whole-body images were obtained using a double-headed, large-field-of-view gamma camera (GCA 901A; Toshiba Corp., New York, NY, USA) equipped with low-energy, parallel Id-hole, and high-resolution collimators at a scan speed of 15 cm/min, such that approximately 1000 k counts were accumulated per image and stored in a 256×1024 matrix. Malignant lesions were defined based on standard criteria, using the pattern and localization of tracer uptake.

Data analysis. During the study period, imaging was performed by clinical routine and reported by several nuclear medicine physicians. Data were obtained from these reports. No imaging review was performed. According to the gold standard (clinical follow-up and imaging follow-up, cf. inclusion criteria), all ^{11}C-acetate PET and BS findings – on perpatient-based analysis - could be definitively categorized as either positively concordant (true positive, TP), negatively concordant (false positive, FP), positively discordant (false negative, FN), or negatively discordant (true negative, TN) for skeletal involvement.

^{11}C-Acetate PET findings were considered TP when both modalities revealed skeletal involvement and were confirmed by follow-up. FP results were those presenting positive findings on ^{11}C-acetate PET without confirmation on BS and follow-up. FN results occurred when lesions undetected by ^{11}C-acetate PET were documented as neoplastic at BS and follow-up. Findings of negative ^{11}C-acetate PET were considered TN when the absence of skeletal metastasis at BS and follow-up were documented.

Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for ^{11}C-acetate PET were calculated on a per-patient basis using the standard of reference. In order to compare the PSA of patients with multiple and focal bone metastases, the exact version of the Mann-Whitney *U*-test was used.

Results

Between January 2001 and January 2013, 90 (100%) consecutive patients (mean age=64±12 years) fulfilled the criteria for inclusion in this retrospective single-center study. All patients presented with biochemical recurrence (PSA relapse >0.2 ng/ml) after radical prostatectomy. Exact serum PSA levels were available for 48 (53.3%) patients (mean=41.8 ng/ml, range=0.3-551.1 ng/ml).

^{11}C-Acetate uptake was considered positive for bone metastasis in 37 (41.1%) patients. There were 25 (27.8%) patients with multifocal and 12 (13.3%) with single-focal ^{11}C-acetate bone uptake.

With regard to BS, 39 (43.3%) patients were considered positive for skeletal metastasis. Of 39 patients, 15 (16.7%) had a single focus of bone uptake, whereas 24 (30%) exhibited multifocal bone uptake. The remaining 51 (56.7%) patients were considered negative for bone metastasis. Sensitivity and specificity were 100% for BS.

^{11}C-Acetate and BS findings were concordant in 84 (93.3%) patients [35 (38.9%) TP and 49 (54.4%) TN] (Figures 1 and 2).

Discordant findings were observed in six patients (6.7%). Based on the standard of reference, ^{11}C-Acetate presented two (2.2%) FP and four (4.4%) FN findings. As a consequence, the sensitivity, specificity, PPV and NPV for ^{11}C-acetate PET were 89.7%, 96.1%, 94.6%, and 92.2%, respectively.

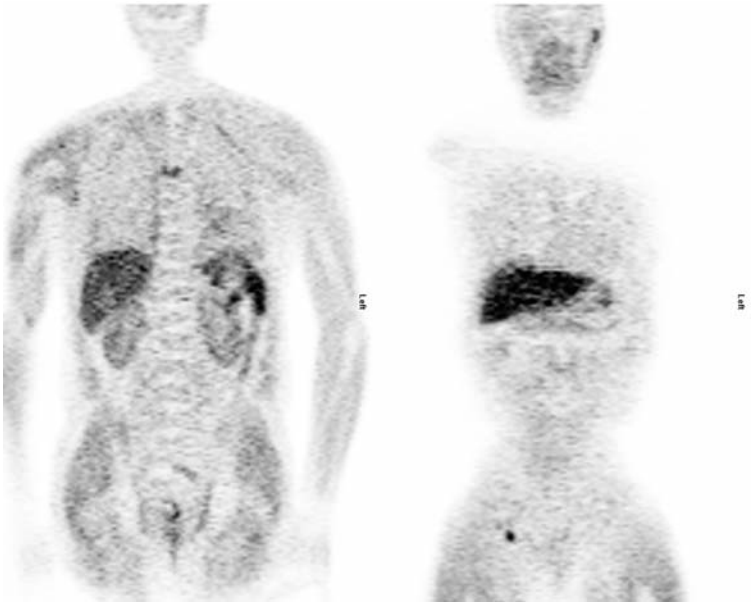

Figure 1. *^{11}C-Acetate positron-emission tomographic images (coronal A, sagittal B) show, in addition to the physiological accumulation in the liver and spleen, abnormal radiotracer uptake in multiple vertebrae.*

The median PSA of patients with multiple skeletal metastases (median=23.64 ng/ml, range=3.16-551.1 ng/ml) differed significantly (p=0.018) from that of patients with focal metastases (median=6.7 ng/ml, range=0.31-12.8 ng/ml).

Finally, in our study population, uptake of ^{11}C-acetate was positive in 55 (61.1%) patients. In addition to their bone metastases, 21 (23.3%) patients presented positive tracer uptake in the lymph nodes and 13 (14.4%) in the prostatic bed, thus depicting lymph node metastases and local recurrence, respectively. Thirteen (14.4%) patients with lymph nodes metastases and seven (7.8%) patients with recurrence in the prostatic bed did not have any bone metastasis (TN and concordant with BS).

Discussion

Previous studies have reported the ability of various metabolic and receptor-based PET probes, such as choline (^{11}C, ^{18}F), ^{11}C-acetate and ^{68}G-prostate-specific membrane antigen, to detect morphological correlates of PSA progression in patients with prostate cancer recurrence (2, 11).

In general, only a small number of studies in the past had shown that ^{11}C-acetate PET is able to detect local recurrence and bone metastases in patients with PSA progression (15, 16). Consequently, no definitive strategy is available, and it is unclear which tracer is preferable for the evaluation of recurrent disease that includes bone involvement. Therefore, the motivation for our study was to provide results for the clinical

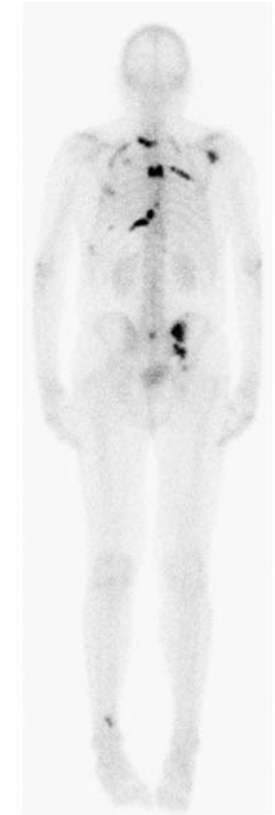

Figure 2. *Concordant abnormal accumulation of ^{99m}Tc-DPD in the posterior image of bone scan in the same patient as Figure 1.*

usefulness of ^{11}C-acetate in patients with prostate cancer with biochemical recurrence that includes skeletal involvement.

Previously, Oyama *et al*. studied 22 patients with prostate cancer using ^{11}C-acetate PET for the initial staging. Seven out of 22 patients presented with bone metastases confirmed by conventional imaging. Findings for six of these patients were positive on the ^{11}C-acetate PET scan (15). Fricke *et al*. investigated 25 patients in the follow-up of primary prostate cancer, revealing eight patients with distant metastases. ^{11}C-Acetate PET detected the metastases in half of these patients (14). Kotzerke *et al*. investigated 31 patients who had increasing PSA levels, or a suspicious transrectal ultrasound following complete prostatectomy, with ^{11}C-acetate PET. In five patients, ^{11}C-acetate uptake within the bone was detected, and conventional BS confirmed the focal acetate uptake in the skeleton to be typical metastases (16). For the detection of bone metastasis by ^{11}C-acetate PET, the results mentioned above are insufficient for a final conclusion due to the small number of studies available, the types of patients investigated, the patients who presented with bone metastasis, as well as the heterogeneity of the reference standard.

Our study included 90 patients with prostate cancer with biochemical recurrence in whom ^{11}C-acetate PET revealed a very high sensitivity, specificity, PPV and NPV for the detection of skeletal involvement. Due to the fact that prostate cancer cells have an increased turnover of acetate, ^{11}C -acetate accumulation in bones reflects primarily metastases. However, in our study, we had two FP results, both showing uptake in multiple vertebrae on the acetate scans but which were negative on BS. Follow-up did not reveal any metastasis in these patients. However, major degenerative changes were observed. This observation is in accordance with the recently published bio-distribution pattern of ^{11}C-acetate (21).

Furthermore, there were four negative discordant results where ^{11}C-acetate PET did not reveal any tracer uptake. Each of these patients had a focal lesion on BS that was also present in the follow-up. For two of these patients (focal sternal and femoral lesion, respectively), accurate PSA levels were available, which were low (4.8 and 5.6 ng/ml). Nevertheless, ^{11}C-acetate PET revealed findings that were concordant with bone scintigraphy in 35 (38.9%) TP and 49 (54.4%) TN cases.

With regard to the recurrence of prostate cancer, most patients initially demonstrate a serum PSA relapse. Therefore, it is important to detect the morphological correlates of biochemical recurrence. It has been shown that sensitivity is dependent on the level of serum PSA. Previous studies reported a detection rate, by means of positive tracer-uptake, of 59-68% for ^{11}C-acetate PET scans (14, 19). These numbers are similar to our findings in demonstrating (the potential site of) recurrence in 61.1% (55 out of 90) patients.

The limitations of our study were its retrospective study design and the fact that exact PSA values were unavailable for almost half of the patients. This was due to the fact that most of our study patients were outpatients referred to our Department for further evaluation. However, we were able establish that the median PSA of patients with multiple skeletal metastases differed significantly from that of patients with focal metastases. Furthermore, like most previous studies, we were unable to provide data on the diagnostic accuracy for lymph node metastasis and local recurrence due to a lack of a standard of reference. Nevertheless, to our knowledge, our study presents the highest number of patients with prostate cancer with biochemical recurrence in whom ^{11}C-acetate PET revealed a very high sensitivity, specificity, PPV and NPV for the detection of skeletal involvement. The retrospective design of the study did not allow a per-lesion-based analysis, which would in fact not influence the suitable therapeutical approaches of these patients. The fact that pelvic recurrence (lymph nodes/local recurrence) without bone metastases were detected by ^{11}C-acetate in 20 patients highlights the usefulness of this tracer for the therapeutical management of patients with prostate cancer with biochemical recurrence.

In summary, our study provides data that ^{11}C-acetate PET has a high diagnostic value for the detection of bone metastasis in patients with prostate cancer with biochemical recurrence; nevertheless, ^{11}C-acetate was, in essence, equivalent to BS on a per-patient analysis. Consequently, while ^{99m}Tc-biphosphonate BS remains the first-line clinical imaging protocol following biochemical evidence of prostate cancer recurrence, our study suggests that the same results could be achieved with ^{11}C-acetate PET, where this modality is available. Since ^{11}C-acetate will also detect regional and distant soft-tissue metastases, ^{99m}Tc-biphosphonate BS might be unnecessary.

In conclusion, ^{11}C-acetate PET is a useful tool for patients with prostate cancer with biochemical recurrence, as it depicts multiple sites of recurrence.

Acknowledgements

Study design: CS and GK. Study conduct: CS and GK. Data collection: CS, SHP, MM, WW, PA, BR, MH and GK. Data analysis: CS, MM, WW and GK. Data interpretation: CS, MM, WW, ARH, MH, MB, and GK. Drafting manuscript: CS, SHP, MM, WW and GK Revising manuscript content: CS, MB and GK. Approving final version of manuscript: CS, SHP, MM, WW, PA, BR, ARH, MH, MB and GK. GK takes responsibility for the integrity of the data analysis.

References

1 Jemal A, Siegel R, Xu J and Ward E: Cancer statistics, 2010. CA Cancer J Clin *60*: 277-300, 2010.

2 Brogsitter C, Zöphel K and Kotzerke J: ^{18}F-Choline, ^{11}C-choline and ^{11}C-acetate PET/CT: comparative analysis for imaging prostate cancer patients. Eur J Nucl Med Mol Imaging *40(Suppl 1)*: S18-27, 2013.

3 Han M, Partin AW, Zahurak M, Piantadosi S, Epstein JI and Walsh PC: Biochemical (prostate specific antigen) recurrence probability following radical prostatectomy for clinically localized prostate cancer. J Urol *169*: 517-523, 2003.
4 Gomez P, Manoharan M, Kim SS and Soloway MS: Radionuclide bone scintigraphy in patients with biochemical recurrence after radical prostatectomy: when is it indicated? BJU Int *94*: 299-302, 2004.
5 Rigaud J, Tiguert R, Le Normand L, Karam G, Glemain P, Buzelin J-M and Bouchot O: Prognostic value of bone scan in patients with metastatic prostate cancer treated initially with androgen deprivation therapy. J Urol *168*: 1423-1426, 2002.
6 Keidar Z, Israel O and Krausz Y: SPECT/CT in tumor imaging: technical aspects and clinical applications. Semin Nucl Med *33*: 205-218, 2003.
7 Ben-Haim S and Israel O: Breast cancer: role of SPECT and PET in imaging bone metastases. Semin Nucl Med *39*: 408-415, 2009.
8 Effert PJ, Bares R, Handt S, Wolff JM, Büll U and Jakse G: Metabolic imaging of untreated prostate cancer by positron emission tomography with ^{18}fluorine-labeled deoxyglucose. J Urol *155*: 994-998, 1996.
9 Beheshti M, Haim S, Zakavi R, Steinmair M, Waldenberger P, Kunit T, Nader M, Langsteger W and Loidl W: Impact of 18F-choline PET/CT in prostate cancer patients with biochemical recurrence: influence of androgen deprivation therapy and correlation with PSA kinetics. J Nucl Med Off Publ Soc Nucl Med *54*: 833-840, 2013.
10 Picchio M, Spinapolice EG, Fallanca F, Crivellaro C, Giovacchini G, Gianolli L and Messa C: [^{11}C]Choline PET/CT detection of bone metastases in patients with PSA progression after primary treatment for prostate cancer: comparison with bone scintigraphy. Eur J Nucl Med Mol Imaging *39*: 13-26, 2012.
11 Eiber M, Maurer T, Souvatzoglou M, Beer AJ, Ruffani A, Haller B, Graner F-P, Kübler H, Haberhorn U, Eisenhut M, Wester H-J, Gschwend JE and Schwaiger M: Evaluation of Hybrid 68Ga-PSMA Ligand PET/CT in 248 Patients with Biochemical Recurrence After Radical Prostatectomy. J Nucl Med Off Publ Soc Nucl Med *56*: 668-674, 2015.
12 Beheshti M, Langsteger W and Fogelman I: Prostate cancer: role of SPECT and PET in imaging bone metastases. Semin Nucl Med *39*: 396-407, 2009.
13 Costello LC and Franklin RB: Citrate metabolism of normal and malignant prostate epithelial cells. Urology *50*: 3-12, 1997.
14 Fricke E, Machtens S, Hofmann M, van den Hoff J, Bergh S, Brunkhorst T, Meyer GJ, Karstens JH, Knapp WH and Boerner AR: Positron emission tomography with ^{11}C-acetate and ^{18}F-FDG in prostate cancer patients. Eur J Nucl Med Mol Imaging *30*: 607-611, 2003.
15 Oyama N, Akino H, Kanamaru H, Suzuki Y, Muramoto S, Yonekura Y, Sadato N, Yamamoto K and Okada K: ^{11}C-acetate PET imaging of prostate cancer. J Nucl Med Off Publ Soc Nucl Med *43*: 181-186, 2002.
16 Kotzerke J, Volkmer BG, Neumaier B, Gschwend JE, Hautmann RE and Reske SN: Carbon-11 acetate positron emission tomography can detect local recurrence of prostate cancer. Eur J Nucl Med Mol Imaging *29*: 1380-1384, 2002.
17 Wachter S, Tomek S, Kurtaran A, Wachter-Gerstner N, Djavan B, Becherer A, Mitterhauser M, Dobrozemsky G, Li S, Pötter R, Dudczak R and Kletter K: ^{11}C-acetate positron emission tomography imaging and image fusion with computed tomography and magnetic resonance imaging in patients with recurrent prostate cancer. J Clin Oncol Off J Am Soc Clin Oncol *24*: 2513-2519, 2006.
18 Sandblom G, Sörensen J, Lundin N, Häggman M and Malmström P-U: Positron emission tomography with C11-acetate for tumor detection and localization in patients with prostate-specific antigen relapse after radical prostatectomy. Urology *67*: 996-1000, 2006.
19 Vees H, Buchegger F, Albrecht S, Khan H, Husarik D, Zaidi H, Soloviev D, Hany TF and Miralbell R: 18F-choline and/or ^{11}C-acetate positron emission tomography: detection of residual or progressive subclinical disease at very low prostate-specific antigen values (<1 ng/mL) after radical prostatectomy. BJU Int *99*: 1415-1420, 2007.
20 Mitterhauser M, Wadsak W, Krcal A, Schmaljohann J, Bartosch E, Eidherr H, Viernstein H and Kletter K: New aspects on the preparation of [^{11}C]acetate--a simple and fast approach *via* distillation. Appl Radiat Isot Data Instrum Methods Use Agric Ind Med *61*: 1147-1150, 2004.
21 Karanikas G and Beheshti M: (11)C-Acetate PET/CT Imaging: Physiologic Uptake, Variants, and Pitfalls. PET Clin *9*: 339-344, 2014.

Received August 21, 2015
Revised September 21, 2015
Accepted September 25, 2015