Detection of the Prostate Cancer Bone Metastases: Is It Feasible to Compare 18F-fluorocholine PET/CT, 18F-fluorodeoxyglucose PET/CT and 99mTc–methyl Diphosphonate Bone Scintigraphy?

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Purpose: The objective was to compare the efficacy of 99mTc-MDP-BS, 18F-FDG-PET/CT and 18F-FCH-PET/CT in detecting bone metastases in prostate cancer patients.

Materials and methods: 56 patients diagnosed with prostate cancer underwent 99mTc-methylendiphosphonates bone scintigraphy (99mTc-MDP-BS) and fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG-PET/CT) or fluorine-18-fluorocholine PET/CT (18F-FCH-PET/CT) within six weeks. There were 27 patients examined with 99mTc-MDP-BS + 18F-FDG (mean age 67.96 ± 9.04 years) and 29 patients examined with 99mTc-MDP-BS + 18F-FCH (mean age 73.93 ± 8.75 years). The R factor in scintigraphy and semi - quantitative analysis with Standardized Uptake Value (SUV) in the PET/CT were used using semi - automatic methods of bone lesions' contouring. The R factor was calculated as the total count rate in bone metastasis and the total count rate in contralateral area ratio. For further analysis, the mean pixel and the total surface of lesion product in scintigraphy, the Total Lesion Glycolysis (TLG) in the 18F-FDG-PET/CT and the Total Lesion Activity (TLA) in the 18F-FCH-PET/CT were evaluated.

Results: The average maximal SUV (SUVmax) value was significantly higher in patients who underwent 18F-FCH-PET/CT than in 18F-FDG-PET/CT (5.17 ± 2.24, 3.71 ± 1.56, $P < .05$). The R factor differences in both groups (patients who underwent BS and 18F-FDG-PET/CT, BS and 18F-FCH-PET/CT) were insignificant (1.92 ± 0.87, 2.03 ± 0.57, respectively, $P > .05$). There was no statistically significant correlation (Pearsons' correlation coefficient - Rp) between the R factor and the SUVmax within examined groups (Rp = .42; $P = .31$) and between the R factor and the SUVmean (Rp = .43; $P = .28$). A high Rp between measured total surface in the BS and volume in the PET/CT of the metastatic lesion was found. In patients who underwent BS + 18F-FDG-PET/CT and BS + 18F-FCH-PET/CT, Rp equaled .95 and .70.

Conclusion: 99mTc-MDP-BS, 18F-FDG-PET/CT and 18F-FCH-PET/CT occurred as comparable imaging methods in bone metastases detection in the prostate cancer patients and provide complementary clinical conclusions.

Keywords: bone scintigraphy; computed tomography; fluorine-18-fluorocholine; fluorine-18-fluorodeoxyglucose; positron emission tomography; prostate cancer.

INTRODUCTION

Prostate cancer is one of the most common cancer diseases in elder men, especially over age 65 years. The important issue in prostate cancer staging, restaging and response to treatment evaluation is to diagnose and monitor the bone metastases. The probability of bone metastatic lesion occurrence and their incidence depends on many factors, i.e: age, general health condition, Gleason score value (higher than 6) and prostate –specific antigen (PSA) level (higher than 20 ng/mL) [(1)] or metastatic bone microenvironment[(2)]. Metastatic bone disease is associated with several health ailments and affects mortality, thus their management seems to be critical[(3-5)]. Jeong et al. claim that main cause of tumor bone metastases is the high stromal cells activity within bone tissue, resulting in physiologic imbalance between number of osteoblasts and osteoclasts in skeleton. Osteolytic bone metastases are connected with bone resorption and osteoblastic - with tumor growth[(2,6)]. Osteoblastic bone metastases developing with prostate cancer progression are the less aggressive and slow - growing in comparison to mixed or osteolytic metastases from breast cancer[(6)].

The methods of first choice in the metastatic bone lesions monitoring are most often the bone scintigraphy (BS), using 99mTc – diphosphonates (99mTc-MDP BS) or positron emission tomography/computed tomography with the fluorine -18- fluorodeoxyglucose (18F-FDG PET/CT). Although the 18F-FDG is not a tumor – specific agent, the 18F-FDG PET/CT is commonly recognized as sensitive, specific and accurate imaging method in detecting bone metastases as a consequence of advanced stage of various cancer diseases[(7-10)]. The growing knowledge about the prostate cancer cells resulted in extraction of several highly spe-

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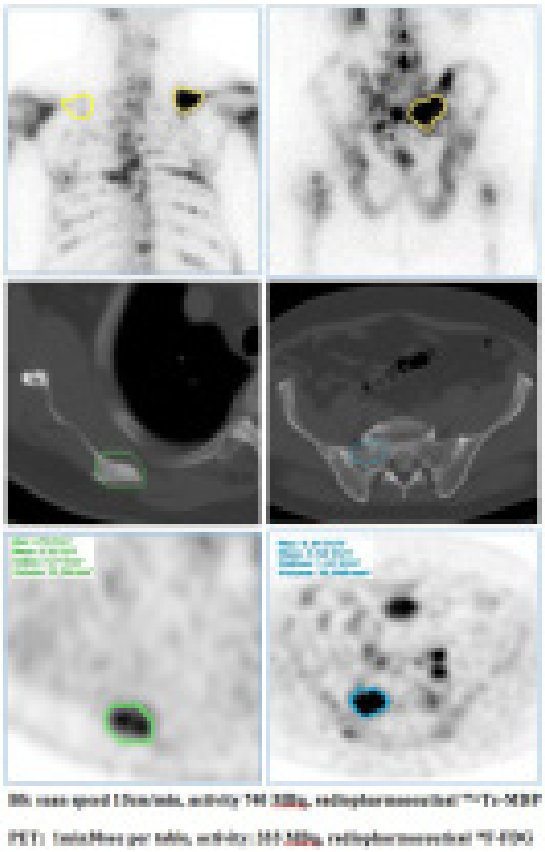

Figure 1. 99mTc-MDP BS and 18F-FDG PET/CT scans in prostate cancer patient.

cific tracers, i.e. fluorine-18-fluorocholine (18F-FCH). 18F-FCH seems to be superior to 18F-FDG according to relatively high specificity in prostate cancer cells uptake(11). Multiply nuclear medicine departments worldwide constantly perform 18F-FDG PET/CT as a standard protocol in prostate cancer patients due to its availability and advantages in comparison to other imaging techniques, such as single computed tomography (CT). The main difference between 18F-FDG and 18F-FCH is that choline accumulates mostly in prostate tumors. The uptake is regulated by choline kinase capture of lecithin (phosphatidylcholine) and the tracer's utilization is not connected with cells proliferation (the uptake does not depend on proliferative activity while increasing choline utilization reflects the cells division intensity due to membrane lipid synthesis estimation). As a result, the 18F-FCH PET/CT reveals relatively higher than 18F-FDG specificity in detecting prostate cancer tumors and metastases[5,12].

Prostate cancer is diagnosed also with the biomolecular markers, i.e. PSA.

The role of PSA depends on few factors such as age, body mass index (BMI) and prostate gland size. It is used to detect and to monitor the prostate cancer but it has some limitations: dependency on multiply factors and decreased specificity in low from high grade tumors differentiation. However, it has been proven that PSA serum level significantly increases with either prostate cancer, prostatitis or benign prostatic hyperplasia (BPH), thus the PSA cannot be used as a single cancerous marker[12-17].

Evaluation of prostate cancer bone metastases is the crucial clinical issue and needs complex and fast management with imaging and biomolecular methods.

The aim of this research article was to compare the planar bone scintigraphy with technetium-99m methyl diphosphonate bone scintigraphy (99mTc-MDP BS), fluorine-18-fluorodeoxyglucose PET/CT (18F-FDG PET/CT) and fluorine-18-fluorocholine PET/CT (18F-FCH PET/CT) in detecting prostate cancer bone metastases.

MATERIALS AND METHODS

Dataset characteristics

The study was performed upon receiving of the patients' informed consent in writing and all requirement of local bioethical committee were fulfilled.

We diagnosed 56 male prostate cancer patients with 99mTc-MDP BS and PET/CT scans (18F-FDG PET/CT or 18F-FCH PET/CT) within six weeks. There were 27 patients examined with 99mTc-MDP BS + 18F-FDG (mean age 67.96 ± 9.04 years, age range: 52-80 years) and 29 with 99mTc-MDP BS + 18F-FCH (mean age 73.93 ± 8.75 years, age range: 57-85 years). The differences between age, number of patients and number of lesions occurred as statistically insignificant, thus groups were homogenic and comparable. We compared one metastatic bone lesion with bone scintigraphy and the PET/CT technique. We used the semi - automatic method of the metastatic bone lesions contouring in the BS and semi - automatic with 50% background cut-off to delineate malignant findings in the PET/CT. We evaluated the R factor in the 99mTc-MDP BS and the SUVmax and SUVmean values to characterize bone metastases.

We have calculated the R factor with the following equation:

$$\text{R factor} = \frac{\text{total count rate in a metastatic bone lesion}}{\text{total count rate in a contralateral area}}$$

The semiquantitative assessment of tracer uptake in the PET/CT was based on the Standardized Uptake Value (SUV) calculation. The SUVmax value of the metastatic bone lesion was based on the equation[18-19]:

$$\text{R factor} = \frac{\text{total count rate in a metastatic bone lesion}}{\text{total count rate in a contralateral area}}$$

For further analysis, we evaluated the mean pixel and the lesions' total surface product in the bone scintigraphy, the Total Lesion Glycolysis (TLG) in the 18F-FDG PET/CT and the Total Lesion Activity (TLA) in the 18F-FCH PET/CT. The mean pixel, TLG and TLA were calculated with following equations:

$$\text{Mean Pixel} = \frac{\text{total count rate in metastatic bone lesion}}{\text{total surface of metastatic bone lesion [mm2]}}$$

$$\text{TLG} = \text{SUVmean} \times \text{Volume [mm3]}$$

$$\text{TLA} = \text{SUVmean} \times \text{Volume [mm3]}$$

Study protocols

We performed bone scans with dual – head Gamma

Table 1. Patients' and lesions' characteristics.

Variables	^{99}mTc-MDP BS + ^{18}F-FDG PET/CT	^{99}mTc-MDP BS + ^{18}F-FCH PET/CT	*P*-value
Age, year; mean ± SD (range)	67.96 ± 9.04 (52-80)	71.93 ± 8.75 (57-85)	.10
PSA level before BS, ng/mL; mean ± SD (range)	25.86 ± 36.31 (5.16-146.50)	195.69 ± 301.19 (1.49-934.60)	.34
PSA level before PET/CT, ng/mL; mean ± SD (range)	37.42 ± 62.76 (5.16-320.90)	230.07 ± 308.74 (6.07-934.60)	.26
R factor, mean ± SD	1.92 ± 0.87	2.03 ± 0.57	.58
Max Pixel, mean ± SD	103.44 ± 69.84	142.52 ± 57.45	.03
Total surface, mm^2; mean ± SD	1165.78 ± 1267.22	583.16 ± 468.62	.01
SUVmax; mean ± SD	3.71 ± 1.56	5.17 ± 2.24	.01
SUVmean; mean ± SD	2.20 ± 0.97	3.30 ± 1.39	.00
Volume, mm^3; mean ± SD	6966.34 ± 8017.14	5952.55 ± 5442.08	.59

Abbreviations: PSA, Prostate Specific Antigen; BS, Bone Scintigraphy; PET/CT, Positron Emission Tomography/Computed Tomography

Camera (BrightView XCT, Philips, Cleveland) 2.5 - 3h p.i. of the 99mTc–MDP (methylenodiphosphonian) with activity up to 800MBq (range: 650-800MBq). A total body scans were performed in anterior and posterior projections with low–energy and high- resolution collimators (LEHR) with the 256x1024 pixels matrix and table scan speed of 15 cm/min. Special patient preparation was not required.

We performed the whole body 18F-FGD PET/CT scans (Gemini TF 16, Philips, Cleveland) 60 min p.i. of the 18F-FDG with activity up to 400MBq (range: 250-400MBq). As a preparation protocol, patients fasted for 6h before the examination, avoided cold environment and exercises 48h before the tests. The water intake before the examination was required. The patients laid supine on the PET scanner table with arms above the head and neck up to 30min of scanning. CT was performed before PET acquisition with 120 kVp and 100 mAs. Emission images were acquired for 1:30min per table[20-21].

The whole body 18F-FCH PET/CT static scans were performed with Gemini TF 16, Philips, Cleveland, 6-10min p.i. of the 18F-fluorocholine with activity up to 300MBq (range: 200-300MBq). Acquisition was performed in the same position as in above described 18F-FDG PET/CT. Technical conditions were similar in the 18F-FDG PET/CT and the 18F-FCH PET/CT.

Methods of contouring

We used the semi - automatic method of contouring with 50% background cut–off to delineate structures and to calculate the volume of the metastatic bone lesions in the PET/CT scans. We delineated the abnormal findings in the 99mTc-MDP BS semi - automatically (**Figure1,2**).

Statistical analysis

We compared several factors in two groups of patients in the interval scale (values were comparable, the differences between them were crucial for analysis).

We assumed there is none known direction of values fluctuation; the basic hypothesis was there are no significant differences between compared groups in every single condition of the analysis. We compared groups of dependent (two factors in same patients, for example in patients who underwent 99mTc-MDP BS and 18F-FDG PET/CT) and the independent variables (i.e.: SUVmax value in patients who underwent 18F-FDG PET/CT and 18F-FCH PET/CT). All measured parameters had the Gaussian distribution according to the Shapiro – Wilk test's results, thus we used the t-test to evaluate statistical significance. The variances in every analysis were equal (the tendency was unpredictable). The investigators calculated the Pearsons' correlation coefficient an used the materiality level of $P < .05$.

The authors used STATISTICA (StatSoft) commercial software for the statistical analysis.

RESULTS

The dataset characteristics

We have analyzed 56 prostate cancer patients who underwent 99mTc-MDP BS and 18F-FDG PET/CT with several factors. The PSA marker data (**Table 1**) were included. The differences between the PSA level before the BS and the PET/CT were statistically insignificant ($P = .09$).

Analysis

The average R factor, SUVmax and SUVmean values in patients who underwent

99mTc-MDP BS + 18F-FDG PET/CT were 1.92 ±

Table 2. Statistics for correlation between studied diagnostic methods.

Variables	BS + ^{18}F-FDG PET/CT	BS + ^{18}F-FCH PET/CT
	P-value	
R factor and SUVmax value	.42	.43
R factor and SUVmean value	.31	.28
	Rp	
R factor and SUVmax value	.42	.43
R factor and SUVmean value	.31	.28
TLGa, TLAb and 'Mean pixel x Total surface'	.37	.46

Abbreviations: TLG, Total Lesion Glycolysis; TLA, Total Lesion Activity

[a] TLG for the 18F-FDG PET/CT

[b] TLA for the 18F-FCH PET/CT

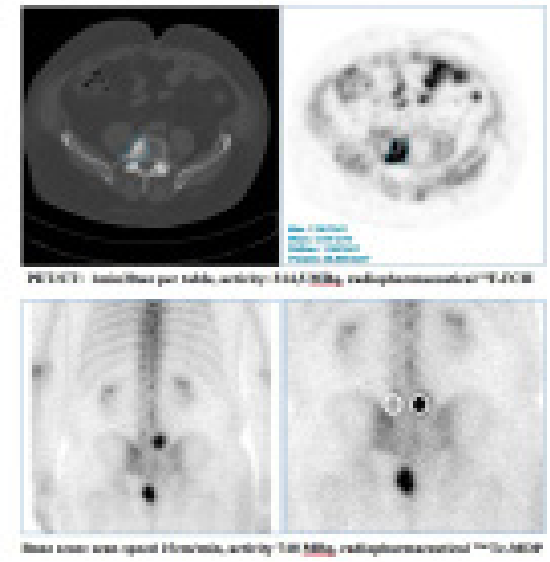

Figure 2. 99mTc-MDP BS and 18F-FCH PET/CT scans in prostate cancer patient.

0.87, 3.71 ± 1.56 and 2.20 ± 0.97, respectively and in the 99mTc-MDP BS + 18F-FCH PET/CT: 2.03 ± 0.57, 5.17 ± 2.24, 3.30 ± 1.39, respectively (**Table 1**).

According to the t – test's results the differences between SUVmax and SUVmean were statistically significant ($P < .05$). The SUVmax value in the 18F-FDG PET/CT and the 18F-FCH PET/CT: $P = .01$, SUVmean value in 18F-FDG PET/CT and 18F-FCH PET/CT: $P < .001$.

The differences between the R factors obtained with 99mTc-MDP BS in both groups were insignificant ($P = .58$).

According to the Pearsons' correlation coefficient (Rp) analysis, we found no significant correlation between the R factor and the SUVmax value within examined groups (Rp = .42; $P = .31$) or between the R factor and the SUVmean value (Rp = .43; $P = .28$) (**Table 2**).

The high correlation coefficient between total surface obtained with 99mTc-MDP BS and volume in PET/CT of the metastatic bone lesions was found. In patients who underwent 99mTc-MDP BS + 18F-FDG PET/CT and 99mTc-MDP BS + 18F-FCH PET/CT correlation coefficients were .95 and .70, respectively ($P < .05$). The volume differences between 18F-FDG PET/CT and 18F-FCH PET/CT were statistically insignificant, $P = .57$,

however 18F-FCH seems to be more precise in the lesion edge detection in prostate cancer bone metastases. Furthermore, there was no correlation between PSA level and R factor or SUVmax values in both groups.

The analysis of TLG within metastatic bone lesions in comparison with contralateral in 99mTc-MDP BS mean pixel multiplied by the total surface showed no significant correlation in both groups (99mTc-MDP BS + 18F-FDG PET/CT, Rp = .37; 99mTc-MDP BS+18F-FCH PET/CT, Rp = .46).

There was no significant correlation between measured indices within analysed groups (TLG and the mean pixel multiplied by the total surface in the 99mTc-MDP BS + 18F-FDG PET/CT

and TLG, TLA and the mean pixel multiplied by the total surface in the 99mTc-MDP BS + 18F-FCH PET/CT; .37, .43, respectively).

DISCUSSION

18F-FDG is a commonly used radiopharmaceutical in the oncology, however several studies have shown its limitations in the prostate cancer lesions assessment because

of relatively low metabolic activity of prostate cancer cells. According to some authors[22-24], the 18F-FDG will most likely be useful in the prostate cancer patients with hormone-resistant low-differentiated cell types and can be promising in the bone metastases detection and monitoring. 18F-FCH occurred as highly lesion-specific radiotracer: useful in every stage of the prostate cancer, especially in detecting the disease cells regardless localization, however metastatic bone lesions can be reliably monitored with both tracers. Moreover, commonly performed in metastatic bone lesions assessment sodium fluoride 18F-NaF PET/CT does not significantly increase the specificity of the prostate cancer bone metastases detection. The sensitivity, specificity and the accuracy of each method: 99mTc-MDP BS, 18F-FDG PET/CT, 18F-FCH PET/CT, 18F-NaF PET/CT, is high and exceeds 90% [25-27]. 18F-NaF seems to be superior to 99mTc-MDP BS in detection osteoblastic metastases because of, i.e., higher affinity of 18F-NaF for bone tissue than diphosphonates[27].

Several imaging methods are useful in the prostate cancer metastatic bone lesions monitoring as planar bone scintigraphy and single photon emission tomography/computed tomography (SPET/CT) technique. SPET/CT is predictively more meaningful in particular bone findings monitoring of known localization, while in many conditions, patients who underwent bone scintigraphy are suspected of having metastatic disease or have numerous bone metastases. The sensitivity of the 99mTc-MDP BS and the SPET/CT was recognized as 79%, 89%; specificity 91%, 94%; accuracy 87%, 93%, respectively[28].

The TLG or the TLA are the volume-based prognostic markers, used for, i.e., preoperative assessment and metastatic bone disease treatment monitoring in various types of cancers. TLG emerged from 18F-FDG PET/CT as a prognostic factor in pre- and posttreatment monitoring of the cancer patients. TLA as a corresponding to TLG parameter might be used in PET/CT technique as an additional volume and SUV-based clinical index[28,29]. In this paper, we compared imaging methods with several factors. To find the connection between obtained using each technique indices, we multiplied the mean pixel multiplied by the total surface of the metastatic bone lesions in the 99mTc-MDP BS. We evaluated the TLG or the TLA in the PET/CT methods and the Rp, however no significant correlation have been found, what leads to conclusion that the bone scintigraphy and the PET/CT provide valuable and complementary clinical informations.

In this research article, we have found cognitively interesting to evaluate

and to compare described groups of patients with the 99mTc-MDP BS + 18F-FDG PET/CT and the 99mTc-MDP BS + 18F-FCH PET/CT and did not focus on the sensitivity, specificity and accuracy of the methods as it had been widely investigated before but on the feasibility to compare metabolic and osteoblastic activity of the

metastatic bone lesions assessed with three molecular imaging techniques within two groups of patients. Research has been limited by number of patients who underwent the 99mTc-MDP BS and the PET/CT in short period of time, thus sample could be too small to find significant correlation between measured parameters.

CONCLUSIONS

In conclusion, 99mTc-MDP BS, 18F-FDG PET/CT and 18F-FCH PET/CT reveal complementarity in metastatic bone disease. It provides information that it is highly valuable to use all these methods to diagnose bone metastases in the prostate cancer patients.

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CONFLICT OF INTEREST

The authors report no conflict of interest.

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