ANTICANCER RESEARCH *38*: 4139-4143 (2018)
doi:10.21873/anticanres.12705

^{18}F-Fluorocholine PET/MRI in Restaging of Prostatic Carcinoma in Relation to PSA Level and Detection of Active Disease

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Abstract. *Aim: To evaluate our own experience with ^{18}F- fluoromethylcholine-(FCH)-positron-emission tomography combined with magnetic resonance imaging (PET/MRI) in restaging of patients with prostatic carcinoma and elevated serum prostate-specific antigen (PSA) level. Patients and Methods: The analysis was performed on a sample of 100 male patients who underwent ^{18}F-FCH-PET/MRI, with a mean age of 63.2 years (range=47-78 years). The imaging was performed using an integrated PET/MRI hybrid system after intravenous application of ^{18}F-FCH at a dose of 1.25 MBq/kg. The number and sites of pathological accumulation of FCH related to local recurrence, nodal spread and skeletal metastases were compared to corresponding MRI findings; furthermore, the relation of PSA level and presence of FCH accumulation in tumorous tissue was assessed; finally we correlated the findings of different sites of metastatic involvement. Results: In patients with a PSA level up to 2 ng/ml, accumulation in tumorous tissue of local recurrence or metastases was found in 83.33% in cases of biochemical relapse, and in patients with PSA level above 5 ng/ml in 100% of cases. In general, we found any finding explained rise of PSA level in 94% of patients. Conclusion: ^{18}F-FCH-PET/MRI using an integrated system with 1,25 MBq/kg dosing of FCH is a valuable tool in evaluation of restaging in patients with prostatic carcinoma, with high detection rate even in those with a low serum PSA level.*

Prostate cancer is the most commonly diagnosed malignant disease in the adult male population of the European Union and North America. The most commonly performed methods for early detection of prostate cancer are determination of serum prostate-specific antigen (PSA) levels and digital rectal examination. Recently, magnetic resonance imaging has also been used for early diagnosis of prostate cancer, which includes not only morphological imaging, but also analysis of water molecule diffusivity, pharmacological distribution of the contrast medium in tissues, as well as assessment of choline content in the spectrum obtained during magnetic resonance spectroscopy. Choline is involved in lipid metabolism primarily as one of the main building blocks of phospholipid within biomembranes. In addition to assessing the presence and content of choline in ^{1}H spectroscopy, hybrid imaging positron-emission tomography combined with computed tomography (PET/CT) or magnetic resonance imaging (PET/MRI) can also be used to evaluate the presence of choline in tissue by administering choline products labeled with a beta-plus emitter. At present in PET, the most widely used choline analog is ^{18}F-fluoromethylcholine (^{18}F-FCH) (1-3), although other molecules, ligands of to prostatic surface membrane antigen (PSMA) labeled with ^{68}Ga can be used (4, 5). We evaluated our 2-year experience with ^{18}F- ^{18}F-FCH-PET/MRI with respect to the indication for imaging in patients with suspected biochemical relapse of prostate cancer (3, 6). The study is particularly relevant to clinical practice because ^{18}F-FCH is the only radiopharmaceutical registered for PET imaging of prostate carcinoma in the European Union.

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Key Words: Prostatic carcinoma, fluoromethylcholine, PET/MRI, restaging, PSA.

Patients and Methods

^{18}F-FCH-PET/MRI was performed in 100 men ranging from 47 to 78 years, with a mean age of 63.2 years. The indication for imaging was the restaging of treated prostate cancer. Informed consent was obtained from all patients prior to imaging. All examinations were performed after intravenous administration of ^{18}F-FCH (IasoCholine; Iason GmBh, Graz, Austria) at 1.25 MBq/kg. Patients were prepared by fasting for 4 hours but they were allowed to receive fluids. After 30 to 90 minutes, imaging was performed using an integrated hybrid PET/MRI scanner (Biograph mMRI; Siemens, Knoxville/Erlangen, USA/Germany) with an orthosilicate five-row

Table I. *Findings related to localization of disease recurrence according to serum prostate-specific antigen (PSA) level.*

PSA level (ng/l)	Number of patients	Local (L) only, n	Nodes (N) only, n	Bones (B) only, n	L+N, n	L+B, n	N+B, n	L+N+B, n	Positive, n (%)
<0.2	3	0	1	0	0	0	0	0	1 (33.33)
0.2 to 2.0	27	2	3	6	3	1	6	3	24 (88.89)
2.1 to 5.0	49	3	2	16	3	2	13	9	48 (97.96)
5.1 to 10.0	12	0	0	8	1	0	2	1	12 (100.00)
≥10.1	9	0	0	2	0	0	5	2	9 (100.00)
Total	100	5	6	32	7	3	26	15	94 (94.00)

PET detector subsystem equipped with avalanche photodiodes and a 3-T MRI subsystem. The acquisition of MRI data was performed with the use of gadobutrol (Gadovist at a dose of 4 ml; Bayer HealthCare, Berlin, Germany) all imaging was performed after administration of the contrast agent. T1-Weighted gradient echo sequences with Dixon volume interpolated breath-hold examination (VIBE) in transversal orientation with creation of the in-phase, opposed-phase, water and fat images, followed by T2 turbo inversion recovery images using short inversion time (T2 TIRM STIR) in transversal orientation. The PET data were reconstructed using the iterative reconstruction – ordered subset expectation maximization (OSEM) algorithm, with an attenuation correction using tissue modeling based on Dixon VIBE T1. Soft tissues and bone were evaluated independently using T1 water images and T2 STIR images, PET image and their PET/MRI fusions.

The endpoint of the study was to assess the effectivity of the ^{18}F-FCH-PET/MRI in the detection of viable tumorous tissues in patients with biochemical relapse of prostatic carcinoma. In patients after radical prostatectomy or radical prostatic irradiation, the examinations included the detection of tumorous tissue with increased accumulation of ^{18}F-FCH within local recurrence, lymph node metastases, bone metastases or other systemic spread of the disease. The region interest to assess the metabolic activity of FCH uptake was placed into the accumulating tissue and the maximum standardized uptake value exceeding 2.5 was considered as sign of increased choline turn-over. The results were compared with indications by serum prostate-specific antigen (PSA) levels.

Table II. *General detection rate of recurrent disease according to serum prostate-specific antigen (PSA) level.*

PSA level (ng/ml)	Positive finding of recurrent disease (%)
<0.2	33.33
0.2 to 2.0	83.89
2.1 to 5.0	92.41
>2	98.57
>5	100.00
Any	94.00

Table III. *Findings related to localization of recurrent disease.*

FCH-positive site	N (%)
Local	30
Nodes	54
Bones	76
Lungs	2
Liver	1
Any	94

Results

A total of 100 examinations were performed in patients with elevated or rising PSA level for restaging of their disease after radical prostatectomy, radical prostate irradiation, during complete androgen blockade or advanced chemotherapy. In this group, there were 30 cases of local recurrence, while distal or nodal metastasis was confirmed in 89 cases (including three cases with metastatic involvement of lung or liver). Table I summarizes the results of ^{18}F-FCH-PET/MRI in relation to the PSA level, local, nodal and bone findings, including their combination. The ratio of recurrent disease increased with PSA level; above the level of 5.0 ng/ml, the detection rate was 100%. Table II summarizes the rate of detection of relapse of disease with the respect to cut-off values, the cut-off 5.0 ng/ml represents again the value for positive findings of ^{18}F-FCH-PET in 100%. Table III details the cases (and the rate) of site of recurrence without respect to their combinations – the most frequent type of recurrence was skeletal spread of disease (example is documented in Figure 1), followed by nodal disease. Other malignancies were found in three patients – one patient had colorectal carcinoma, one patient had pulmonary metastasis of colorectal carcinoma, and one patient had lung carcinoma.

Discussion

It is possible for prostate cancer to be detected incidentally in Western men with increased use of PSA to detect high-risk individuals, but the shift in morbidity and mortality indicates that the disease is occurring more often than in the past (7).

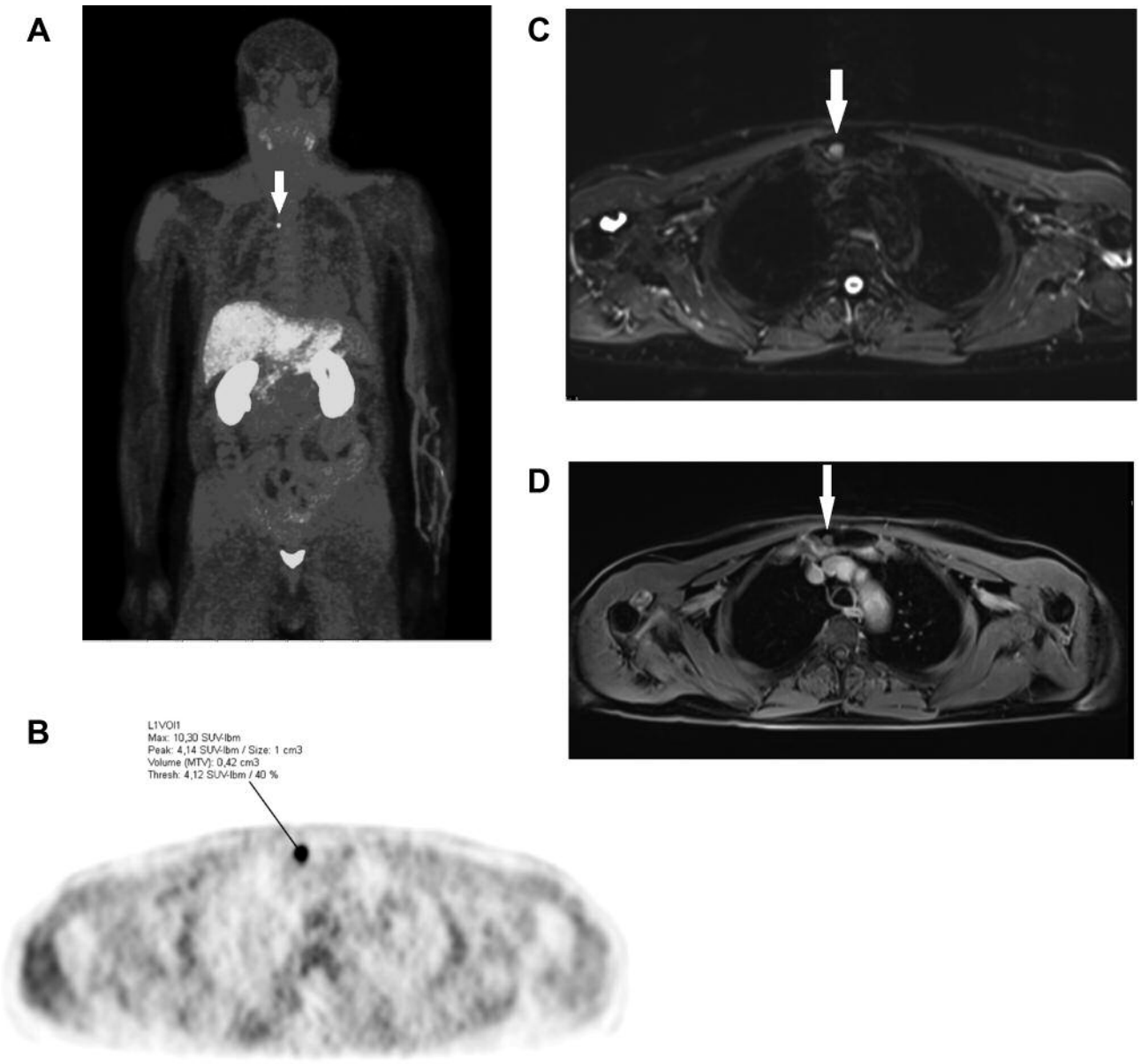

Figure 1. *Solitary metastasis (arrows) found in the sternum in a patient with serum prostate-specific antigen level rising over 6 months from 0.001 ng/ml to 0.296 ng/ ml. A: Whole-body maximum intensity projection positron emission tomography (PET) image. B: Transaxial PET image. C: T2 STIR image. D: T1 CRE water image.*

Prostate cancer requires multiple lines of treatment, starting with radical prostatectomy or radical irradiation. Radical prostatectomy is indicated in patients with locally operable tumors and also in the absence of distant metastases and metastases outside the pelvic lymph nodes. Biopsy and tumor classification using Gleason score play a key role in determining the prognosis of the disease and further treatment. However, since some tumors, including clinically evident ones, escape diagnosis through biopsy sampling, even several times in a row, FCH-PET/CT leads to more accurate biopsy targeting and increases the success of biopsy (7). A significantly higher incidence of distant metastases, especially of bone, but also more frequent involvement of lymph nodes is expected in patients with a Gleason score of 8 or more (1, 7, 8). When comparing PET/CT with findings of subsequent lymphadenectomy, it was found that the sensitivity for detecting lymph node metastases was only about 33%, although with high specificity of 92% (5-8). It appears that

increased accumulation of ^{18}F-FCH can be considered as a highly suspicious sign of metastasis, although not all metastases accumulate FCH (9). Lower sensitivity can be attributed to frequent metastatic infiltration of lymph nodes much smaller than 10 mm, as only about 10% of patients had metastases in the lymph nodes exceeding this size (2).

In patients with recurrent PSA elevation after radical therapy, the increased PSA level (as ng/ml) is a sign of the presence of viable tumor tissue of prostate cancer. In several studies, the authors documented a value of about 4 ng/ml as the critical value for detecting a pathological focus of FCH accumulation (3, 6, 10-13); our own results showed that the rate of detection of recurrence is improved even at a serum PSA level of 2.0 ng/ml. An improved detection rate was documented in patients when ^{68}Ga-labeled ligand of PSMA (^{68}Ga-PSMA-HBED) was used (4, 5). Our own experience has shown that the most significant thresholds for the detection of recurrence are 2 ng/ml, above which tumor tissue manifests FCH accumulation in more than 98% of all cases, and 5 ng/ml, above which accumulation in tumor tissue is detected in all cases. In addition to these findings, a very satisfactory detection rate was found in the group of patients with PSA levels below 2 ng/ml. We were also able to detect solitary metastasis in a patient with a PSA level rapidly rising within half a year from 0.01 to 0.296 ng/ml (11), that finding documented that PET/MRI can help to detect recurrence very early in selected cases. The onset of skeletal findings, and its load, predicts the development of skeletal events in patients with metastatic skeletal spread of the disease (14).

When evaluating prostate tissue, lymph nodes and the skeleton, FCH-PET faces several problems. Choline distribution to the tissues through blood flow is relatively rapid depending on the perfusion level, and in some tissues, accelerated FCH extraction from the bloodstream occurs in proportion to their perfusion. The primary points of interest are activated lymph nodes and also activated bone marrow. When detecting bone metastases, our experience showed that it is necessary to search for local bone findings, and if FCH accumulation is focally associated with focal osteosclerosis or focal osteolysis, the findings should be evaluated as metastasis when concordant MRI findings are present – typically increased intensity on T2 STIR or T1-weighted water MRI after application of contrast agent obtained using the Dixon method of T1-weighted gradient echo MRI. Conversely, diffuse accumulation in vertebral bodies accompanied by increased signal on T2 STIR could be the consequence of chemotherapy or the therapeutic androgen blockage. The decline of FCH accumulation was observed after erythropoetin application (15), similar observations were documented also in our own sample of patients.

The relationship between *de novo* bone formation due to osteoblastic stimulation by prostate cancer metastasis and FCH accumulation has not yet been fully elucidated. Apparently, a proportional relationship is present between the population of active prostate cancer cells and the level of FCH accumulation. In some bone metastases with NaF accumulation, FCH accumulation may not be present and *vice versa*. Bisphosphonates may play a role in bone tissue behavior, such as the most commonly used zolendronate, which suppresses the activity of osteoclasts and indirectly stimulates osteoblastic activity and the increase of the NaF accumulation. Therefore, some authors indicate the possibility of dual imaging of bone involvement in prostate cancer, first with FCH imaging (9, 10), and thereafter also with NaF imaging in patients with negative or ambiguous findings and positive biochemical results (16). Further studies are needed to show whether these imaging techniques are complementary. Our own experience has shown that the MRI part of PET/MRI improved the discrimination between bone metastases and bone turnover due to other reasons.

Regarding PET imaging with choline derivatives, ^{11}C-labeled products are unusable in conventional clinical practice, except for centers equipped with a cyclotron, due to their very short half-life of only 20 minutes. In the European Union, ^{18}F-labeled FCH is dominant among radiopharmaceutical labeled with ^{18}F; it seems to be capable of being incorporated into the phosphatidylcholine precursor. Increased choline turnover is typical for tissues with high proliferation activity dependent on lipid metabolism (1, 2). Imaging with PSMA ligands has been increasing in recent years (4, 5). These substances are more selective in their binding to prostatic carcinoma tissue in metastases: studies using PSMA ligands and PET/CT in the evaluation of restaging in prostate carcinoma showed an increased number of detected lesions in comparison to PET/CT with FCH in patients with raised PSA (4, 5). But, our results demonstrated a satisfactory detection rate. The reason is the high tissue contrast within bone marrow when magnetic resonance is used in the evaluation of the correlation between morphological and metabolic images. Thus, the improved detection rate of the pathologies is related to the use of integrated PET/MRI system in those patients who have low-level raised PSA value.

With rare exceptions (such as small cell prostate carcinoma), fluorodeoxyglucose PET imaging is irrelevant in prostate cancer, since typical acinar prostate carcinoma does not accumulate ^{18}F-fluorodeoxyglucose, irrespective of Gleason score. In some studies, early dynamic imaging is combined with early scan complemented by late PET scan, but this combination currently does not produce better results, and even early imaging fails to provide better results than late imaging (12).

Conclusion

Our experience with the use of FCH in PET/MRI imaging shows that this technique is sufficient to detect the spread of

the disease in men treated for acinar prostate cancer. The presence of viable prostate cancer tissue can be detected depending on the development of the PSA level and its absolute value. The development of metastatic disease can also be monitored by FCH-PET/MRI, especially when the advantages of MRI are exploited in the evaluation of the skeletal FCH accumulation.

Acknowledgements

This study was supported by the project of the conceptual development of the Czech Ministry of Health - University Hospital Plzen 00669806 and the project of Charles University - Progress Q39.

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Received April 17, 2018
Revised May 14, 2018
Accepted May 16, 2018