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Unenhanced whole-body MRI versus PET-CT for the detection of prostate cancer metastases after primary treatment

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Abstract. – OBJECTIVE: The aim of this study was to evaluate the accuracy of unenhanced whole-body MRI, including whole-body Diffusion Weighted Imaging (DWI), used as a diagnostic modality to detect pathologic lymph nodes and skeletal metastases in patients with prostate cancer (PCa) undergoing restaging after primary treatment.

PATIENTS AND METHODS: 152 male patients with biochemical recurrence after radical prostatectomy (RP) or external beam radiation therapy (EBRT) underwent MRI at a 1.5 Tesla magnet with whole spinal sagittal T2-weighted, sagittal T1-weighted, sagittal STIR images, axial T1 and T2-weighted and STIR images of the pelvis and whole-body. ^{18}Fcholine-PET/CT exam was used as the reference standard.

RESULTS: MRI protocol including whole-body combined T1-weighted+T2-weighted+STIR+DWI showed a sensitivity (Se) of 99%, a specificity (Spe) of 98%, a positive predictive value (PPV) of 98%, a negative predictive value (NPV) of 96%, an accuracy of 98% and an area under the receiver operating characteristic curve (AUC) of 0.971 for identification of bone metastatic lesion. The same protocol, displayed a Se of 98%, a Spe of 99%, a PPV of 97%, a NPV of 98%, an accuracy of 98 % and an AUC of 0.960 in the detection of pathologic lymph nodes.

CONCLUSIONS: Unenhanced whole-body MRI, including whole-body-DWI, is an accurate and cost-effective diagnostic tool which is able to detect lymph node involvement and bone metastases in patients with biochemically recurrent PCa after RP or EBRT. Thanks to its lack of ionizing radiation, excellent soft tissue contrast, high spatial resolution, no need of contrast agent, high Se and Spe, it could play a role in the restaging procedure of such patients.

Key Words:

Diffusion magnetic resonance imaging, Prostate cancer, Restaging, ^{11}C-choline, ^{18}F-fluorocholine, Positron emission tomography/computed tomography (PET/CT).

Introduction

Prostate cancer (PCa) is second only to lung cancer as a cause of cancer mortality among men in western countries[1] and accounts for one-third of all deaths from cancer[2,3]. Relapse after primary treatment, radical prostatectomy (RP) or radiation treatment (RT), is still a significant due to its relatively high frequency[4]. At present, the diagnosis of PCa recurrence is based mainly on rising prostate-specific antigen (PSA) serum values and it is named biochemical recurrence (BR)[5]. Once BR is discovered, the next step is to distinguish local recurrence from systemic disease in order to plan the most appropriate treatment. In this setting, diagnostic imaging plays an important role in differentiating local relapse from metastatic disease. Currently, an increasing number of studies have been proposing multiparametric-MRI as the most useful tool in the diagnostic process of locally recurrent PCa after RP or RT. On the other hand choline-PET/CT is the most accurate diagnostic technique for the identification of pathologic lymph nodes and bone metastases[6,7].

Nowadays, there is an increasingly growing interest in the use of unenhanced MRI because there are compelling clinical and pharmaceutical needs to move towards an ideal whole-body imaging evaluation by using techniques that avoid radiation exposure.

In this contest, the aim of this study was to evaluate the accuracy of an unenhanced whole-body MRI protocol, including whole-body DWI, in the detection of lymph node involvement and skeletal metastases in patients with PCa undergoing restaging after primary treatment, using ^{18}F-choline PET/CT as the standard of reference.

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Patients and Methods

Patient

This prospective study was approved by the local Ethics Committee, and all patients gave written informed consent for inclusion in the study.

From September 2011 to January 2014, 152 consecutive male patients (age range 53-88 years) affected by PCa and treated with RP or external-beam RT (EBRT) were referred to our Institution for unenhanced whole-body MRI.

Patients treated with RP were included if they had:

1. Positive ^{18}FCholine-PET/CT for skeletal and/or lymph node metastases
2. Post-RP PSA increase ≥ 1.2 ng/mL
4. No adjuvant or neoadjuvant hormonal therapies
5. Gleason score ≥ 7

Patients treated with EBRT were included if they had:

1. Positive ^{18}FCholine-PET/CT for skeletal and/or lymph node metastases
2. Serum PSA ≥ 2 ng/mL and at least three PSA measurements in the last 6 months
3. Gleason score ≥ 7
4. No adjuvant hormonal therapies

Within one week after a ^{18}FCholine-PET/CT, a whole-body unenhanced MRI exam was performed. The patient population was divided into two groups on the basis of treatment delivered. Group A included 82 patients who underwent RP and Group B included 70 patients treated with EBRT.

Unenhanced Whole-body MRI

All 152 patients were examined using a commercially available 1.5-Tesla scanner (Magnetom Avanto, Siemens Medical Solutions, Erlangen, Germany), equipped with phased-array head-neck and an eight-channel surface coils. The whole-body MRI protocol included the following sequences.

Whole-spine sagittal T1-weighted turbo spin-echo images (repetition time [TR]: 180 ms; echo time [TE]: 10 ms; slice thickness: 4 mm; matrix: 177 × 256).

Whole spine sagittal T2-weighted turbo spin-echo images (TR: 4500 ms; TE: 101 ms; slice thickness: 5 mm; matrix: 256 × 256).

Whole body sagittal T2-weighted STIR images (TR: 4500 ms; TE: 55 ms; inversion time: 170 ms; slice thickness: 5 mm; matrix, 384 × 265).

Axial T1-weighted turbo spin-echo (TR: 400 ms; TE: 10 ms; slice thickness: 5 mm; matrix: 320 × 224), axial T2-weighted turbo spin-echo (TR: 4000 ms; TE: 122 ms; slice thickness: 5 mm; matrix: 320 × 256) and axial T2-weighted STIR (TR: 3000 ms; TE: 97 ms; inversion time: 180 ms; slice thickness: 5 mm; matrix: 320 × 192) of the pelvis.

Whole-body DWI was acquired with free breathing and inversion recovery single-shot spin-echo echo-planar sequences in four imaging stations (TR: 9000 ms; TE: 68 ms; matrix 128 × 128; number of signals averaged: 6, section thickness/gap: 5 mm/0 mm; b values/mm^2 50, 500 and 800 or 1000).

The total imaging time was 40 minutes.

^{18}F-choline PET/CT Study

All patients underwent whole-body ^{18}F-choline PET–CT in 3 different institutions, each exam being acquired with the same PET–CT scan (16-slice computed tomography scanner) and the same equipment. PET/CT studies were performed using the same protocol for every patient, using a hybrid PET/CT tomograph (Discovery ST unit, General Electric Medical Systems, Waukesha, WI, USA). The acquisition protocol begins 60 min after intravenous injection of the choline solution (IASOcholine ®, Graz-Seiersberg, Austria, mean 212.4± 9.6 MBq, range 123–272MBq, median 194 MBq).

Image Interpretation

PET/CT and MR images (Figure 1) were reviewed during four reading sessions by two specialists. The first specialist had 5 years of expertise in MRI interpretation and 1 month of expertise in PET/CT exams; the second specialist had 15 years of expertise in interpretation of MRI and 10 years of expertise in PET/CT exams interpretation.

In the first evaluation session the specialists assessed conventional T1-weighted (T1W), T2-weighted (T2W) and STIR sequences independently and blinded to clinical data. A bone lesion was deemed to be a metastasis if it was of low signal intensity on T1W images and of high or intermediate signal intensity on T2W and STIR images compared with the surrounding bone marrow. Lymph nodes were assumed as malig-

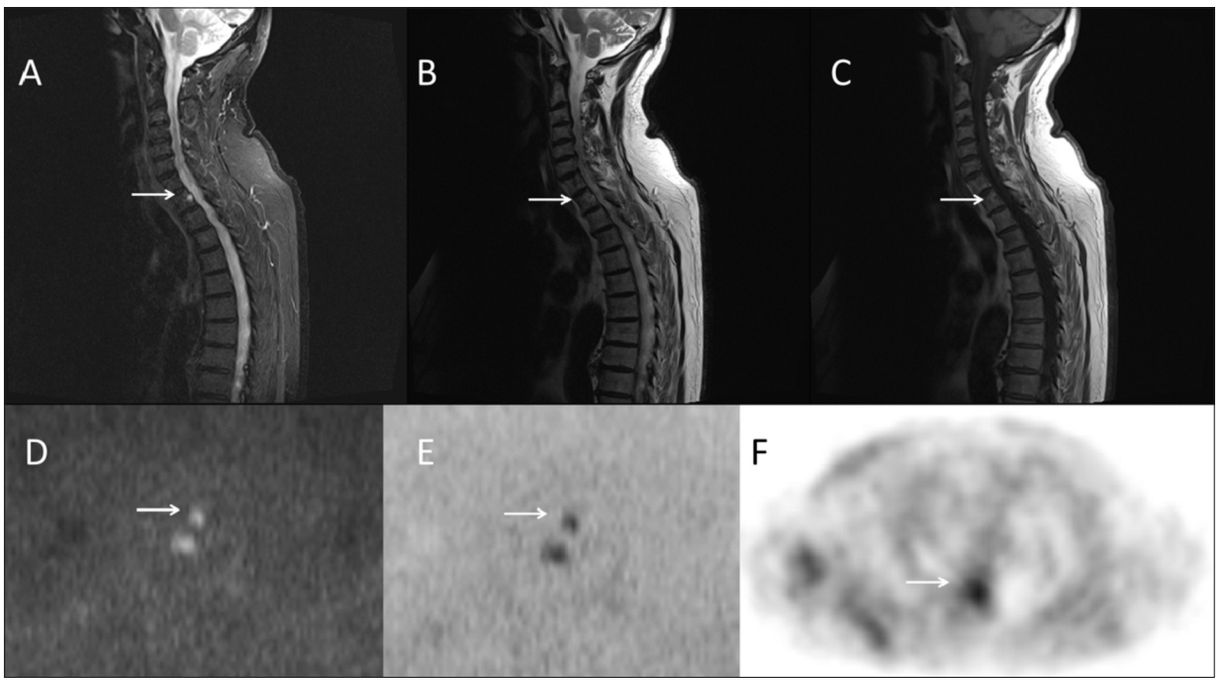

Figure 1. MR and 18Fcholine-PET images of a 68-year-old patient with biochemical failure (PSA serum value 2.6 ng/mL) after radical prostatectomy for prostate cancer. Sagittal STIR ***(A)***, sagittal T2-weighted ***(B)*** and sagittal T1-weighted ***(C)*** images showing a metastatic lesion (*white arrow*) located at posterior aspect of T1 vertebral body which appears of high signal intensity on STIR image, slightly hyperintense on T2-weighted image and of low signal intensity on T1-weighted image. Axial DW image ***(D)***, axial PET-like DW image ***(E)*** obtained with reversal window and PET image ***(F)*** display the bone lesion (*white arrow*) which appears of high signal intensity on DW images and shows avid choline uptake at PET scan.

nant if the short-axis diameter was elongated and exceeded 10 mm or if they were rounded and the diameter exceeded 8 mm. The readers disagreed in only 3% (4 out of 152) of the MR scans. The final diagnoses were reached by consensus.

In the second reading session the specialists reviewed DW images independently, blinded to clinical data and unaware of conventional MRI results. A suspicious skeletal metastatic lesion was defined, by a qualitative image analyses, as a focal or patchy area with signal intensity higher than that of the surrounding bone marrow on native DW images and dark on ADC map. A pelvic lymph node was considered to be pathologic if it was bright on native DW images compared to the background and appeared of low signal intensity on ADC map. The quantitative image analyses were not performed. Therefore, ADC values were not measured for both bone lesions and suspicious lymph nodes because an accurate cut-off value has not yet been established to distinguish between benign and malignant disease. The readers disagreed in only 4% (5 out of 152) of the DWI-MR scans. The final diagnoses were reached by consensus and by the consultation of a third reader.

In the third reading session the specialists analyzed PET/CT images independently and blinded to MRI results. PET images were first assessed visually using transaxial, sagittal and coronal planes. Visual interpretation was used as the main criterion to reach the final diagnosis. Any uptake higher than background was considered as tissue suspicious of malignancy. The SUVmax (maximum standardized uptake values) was measured for each lesion, but it was not used as the main criterion to reach the final diagnosis because an accurate cut-off value has not yet been established. A bone lesion was counted as metastasis if it showed radiotracer accumulation and if it could not be rated as a benign process. Corresponding morphology data from low-dose CT were analyzed in the evaluation of focal tracer accumulation in the PET/CT examination. Lymph node involvement was considered pathologic if a lymph node showed a higher than background uptake of the radiotracer. The readers disagreed in only 7% (10 out of 152) of the choline PET/CT scans. The final diagnoses were reached by consensus and by the opinion of a third reader.

In the last evaluating session the readers compared, in consensus, PET/CT scans, conventional MR images and DW images of each patient, being aware of clinical data.

Statistical Analysis

Statistical data analysis was performed using software MedCalc for Windows. Sensitivity (Se), specificity (Spe), positive predictive value (PPV), negative predictive value (NPV) and accuracy of whole-body unenhanced MRI were calculated on a per-lesion basis analyses. Receiver operating characteristic (ROC) curves were generated to compare the ability of various MR protocols to detect skeletal metastases and pathologic lymph nodes. ^{18}Fcholine-PET/CT was considered the reference standard for both pathologic bone lesions and suspicious nodes. Statistically significative difference between different MRI protocols and the standard of reference was assessed by means of the chi-square test (the significance was set at $p \leq 0.05$).

Results

The results of bone metastases identification are summarized in Table I and Figure 2. There was no statistically significant discordance between T1W+T2W+STIR+DWI and T1W+T2W+DWI imaging protocols compared with each other or with the standard of reference (T1W+T2W+STIR+DWI *vs*. T1W+T2W+DWI, $p = 0.27$; T1W+T2W+STIR+DWI *vs*. reference, $p = 0.25$; T1W+T2W+DWI *vs*. reference, $p = 0.23$). A statistically significant discordance was observed between T1W+T2W+STIR *vs*. T1W+T2W+STIR+DWI $p = 0.0469$, T1W+T2W+STIR *vs*. T1W+T2W+DWI $p = 0.0436$, T1W+T2W+STIR *vs*. reference $p = 0.0326$, STIR+DWI *vs*. T1W+T2W+STIR+DWI $p = 0.0395$, STIR+DWI *vs*. T1W+T2W+DWI $p = 0.0274$, STIR+DWI *vs*. reference $p = 0.0256$, DWI *vs*. T1W+T2W+STIR+DWI $p = 0.0349$, DWI *vs*. T1W+T2W+DWI $p = 0.0346$ and DWI *vs*. reference $p = 0.0196$.

The results of pathologic lymph nodes identification are summarized in Table II and Figure 2. A statistically significant discordance was observed between T1W+T2W+STIR *vs*. T1W+T2W+STIR+DWI $p = 0.0412$, T1W+T2W+STIR *vs*. T1W+T2W+DWI $p = 0.0358$, T1W+T2W+STIR *vs*. STIR+DWI $p = 0.0468$, T1W+T2W+STIR *vs*. DWI $p = 0.0417$, T1W+T2W+STIR *vs*. reference $p = 0.0264$.

Discussion

Recently, multiparametric-MRI has been proposed as the most useful tool in the diagnostic process of local relapse of PCa after RP and after RT.

PET/CT using ^{11}C or ^{18}F-labeled choline compounds, on the other hand, is the most promising whole-body imaging modality for detection of lymph node involvement and bone metastases during restaging of biochemically recurrent PCa after RP or EBRT, with a high Se, Spe and accuracy[8,9].

Currently, there are compelling clinical and pharmaceutical needs to move towards an ideal whole-body evaluation of cancer burden by using imaging techniques that avoid radiation exposure and fulfill, at the same time, some essential prerequisites such as accuracy, availability, reproducibility, cost effectiveness and efficiency[10]. DW-MRI seems to fulfill these requirements, because no ionizing radiation is administered and no intravenous injection of isotopes or any contrast medium is necessary. DWI is based on an echo-planar sequence and depicts the diffusivity of water molecules along the three space direc-

Table I. MRI results in detecting bone metastases.

MRI sequences	Se	Spe	PPV	NPV	Accuracy	AUC
T1W+T2W+STIR+DWI	99%	98%	98%	96%	98%	0.971
T1W+T2W+DWI	99%	97%	96%	95%	96%	0.943
T1W+T2W+STIR	86%	98%	95%	84%	89%	0.871
STIR+DWI	83%	96%	93%	82%	87%	0.771
DWI	98%	82%	83%	93%	84%	0.700

Se: sensitivity; Spe: specificity; PPV: positive predictive value; NPV: negative predictive value; AUC: area under the receiver operating characteristic curves.

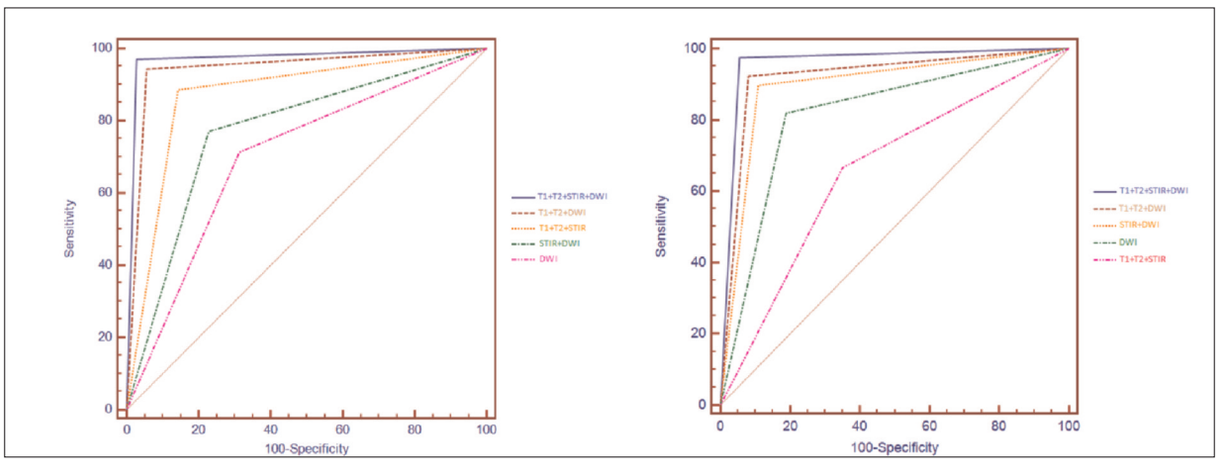

Figure 2. Receiver operating characteristic (ROC) curve comparison for each technique in the detection of bone metastatic lesions (*left ROC curves*) and pathologic lymph nodes (*right ROC curves*). ROC curves for bone metastases show area under the curve (AUC) for combined whole-body T1W+T2W+STIR+DWI, T1W+T2W+DWI, T1W+T2W+STIR, STIR+DWI and DWI. ROC curves for pathologic lymph nodes show AUC for combined whole body T1W+T2W+STIR+DWI, T1W+T2W+DWI, STIR+DWI, DWI and T1W+T2W+STIR.

tions within the tissue. It provides qualitative and quantitative information reflecting tissue cellularity and cell membrane integrity and, thus, complements morphologic information obtained with conventional MRI[11].

Recent technologic advances have enabled the development of whole-body examinations with DWI. Most modern 1.5- or 3-Tesla MRI units with echo-planar and parallel imaging capabilities and with high-performance gradients and phased-array multichannel surface coils can be used to perform whole-body DWI in reasonably short data-acquisition times[12].

With this background, the purpose of this work was to evaluate the accuracy of a whole-body unenhanced MRI protocol including whole-body DWI in the detection of pathologic lymph nodes and skeletal metastases in patients with PCa who undergo restaging after RP or RT. MRI was compared to ^{18}F-choline PET/CT, used as the standard of reference. From September 2011 to January 2014, we studied a large number of patients (152 consecutive male patients) with BR. Unenhanced whole-body MRI protocol including T1W+T2W+STIR+DWI showed a high Se, Spe and accuracy in detecting bone metastases and lymph node involvement, almost comparable to ^{18}F-choline PET/CT in both group A and group B patients. We hypothesized that the overall accuracy of ^{18}F-choline PET/CT imaging is moderately superior to that of whole-body MRI because DWI can suffer several artifacts, such as: intrinsic distortion artifacts, distortion artifacts in the pelvic region, gas pockets, magnetic susceptibility artifacts due to hip replacements and motion artifacts. We noticed that whole-body DWI, used as single imaging modality, seemed to be a very sensitive but rather unspecific modality for the detection of bone metastases; this should be related to the false-positive findings that could be encountered with this technique. Causes of falsely-positive high bone marrow signal intensity on

Table II. MRI results in detecting pathologic lymph nodes.

MRI sequences	Se	Spe	PPV	NPV	Accuracy	AUC
TT1W+T2W+STIR+DWI	98%	99%	97%	98%	98%	0.960
T1W+T2W+DWI	97%	95%	94%	88%	97%	0.921
STIR+DWI	95%	92%	93%	91%	92%	0.895
DWI	93%	85%	89%	80%	87%	0.816
T1W+T2W+STIR	81%	87%	82%	89%	81%	0.658

Se: sensitivity; Spe: specificity; PPV: positive predictive value; NPV: negative predictive value; AUC: area under the receiver operating characteristic curves.

DW images include bone marrow edema caused by fracture, degenerative disease, bone infarction, infection, hemangioma, isolated islands of red bone marrow within yellow marrow and T2 shine-through effect. Nevertheless, many of these false-positive rises in signal intensity on DWI images can be overcome by performing image interpretations with ADC maps and conventional images. Therefore, conventional imaging including T1W, T2W and STIR sequences may improve the specificity of DWI in detecting bone metastases. In our study, the quantitative image analyses was not performed; therefore, ADC values were not estimated for both bone lesions and suspicious lymph nodes, because a) there is an overlap in ADC values of benign and malignant disease, b) the inconsistency of ADC cutoff values among different studies, and c) high observer variability in defining regions of interest for measurement of ADCs of small lesions[13,14].

The main limitation of our study might seem to be the imperfect reference standard used, as we could not verify any of the metastases by biopsy for ethical and logistic reasons. Nevertheless, this is not of primary concern because the aim of our study was not to survey the effective Se and Spe of unenhanced whole-body-MRI in detecting pathologic lymph nodes and skeletal metastases in patients with biochemically recurrent PCa after RP or EBRT. Our goal was to assess if MRI could be considered comparable to ^{18}F-choline PET/CT which is up to now widely considered to be the "state of the art" in the restaging procedure of such patients.

Our latest practice highlights the diagnostic power of unenhanced whole-body MRI including whole-body DWI that can be considered to be almost comparable to ^{18}F-choline PET/CT, which has been assumed to be, up to now, the most reliable diagnostic modality in restaging patients with PCa. Therefore, our data could pave the way to the possibility of using unenhanced whole-body MRI including whole-body DWI as an alternative to ^{18}F-choline PET/CT for follow up after RP and RT, with a high Se, Spe and accuracy in detecting bone metastases and lymph node involvement. Besides, there are other reasons that foster the possibility of using unenhanced whole-body MRI including whole-body DWI as an alternative to ^{18}F-choline PET/CT: its acceptable acquisition time, its repeatability which is absolutely superior to that of a PET/CT exam, and the absence of complications due to intravenous administration of contrast medium. Our findings show the potential of unenhanced whole-body MRI including whole-body DWI as a feasible and very useful tool in detecting bone and lymph node metastases, owing to its diagnostic accuracy. Unenhanced whole-body MRI including whole-body DWI can be, therefore, proposed either as a further imaging study or as a reliable alternative to ^{18}F-choline PET/CT in restaging PCa patients.

Conclusions

Unenhanced whole-body MRI including whole-body DWI could play a role as part of restaging of patients with biochemically recurrent PCa after RP or EBRT.

MRI has several advantages such as the lack of ionizing radiation, excellent soft tissue contrast, high spatial resolution, and no need of contrast agent. Lastly, its high Se and Spe, which are similar to that of ^{18}F-choline PET/CT, make it a promising accurate and cost-effective diagnostic tool for detection of pathologic lymph nodes and bone metastases in such patients.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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