First results of hybrid 18F-fluorocholine PET/MRI for the prostate cancer

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Authors: M. Lord, T. De Perrot, M. Pusztaszeri, S. Heinzer, C. Iselin, O. Ratib, J.-P. Vallee; Geneva/CH
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Purpose

One in six men will be diagnosed with a prostate cancer during their lifetime, most of them after 65 years of age. The 5-year survival is almost 100% for localized and regional (lymph nodes) disease, but falls to only 30% when distant metastases are present (1). $^{18}$F-fluorocholine is a radiotracer which has been used successfully for re-evaluation of a rising PSA post-prostatectomy (2), and for initial staging, before surgery, as well (3,4,5). MRI remains a modality of choice to evaluate prostate cancer. T2-weighted MRI has shown high sensitivity (97%) in prostate cancer localization. However, performance varies with the patient population studied (6) and MRI is known to be less sensitive in detecting cancer in regions other than the peripheral zone of the prostate (7). Functional MRI imaging techniques, such as MR spectroscopy (MRS), diffusion-weighted MRI (DWI), and dynamic contrast-enhanced MRI (DCE-MRI), have gained acceptance to complement T2-weighted MRI in improving prostate cancer localization (8). Positron emission tomography (PET)/magnetic resonance imaging (MRI) is a new hybrid imaging modality, used mainly for animal research (9) and human brain imaging (10,11). It has the potential to improve prostate cancer evaluation over PET/CT or MRI alone. MRI has the ability to give excellent soft-tissue contrast and has the great advantage, over computed tomography (CT), to not submit the patient to ionizing radiations (12). The first PET/MRI in Europe was installed in our center at the beginning of year 2010 (Figure 1), and the first patient scan was performed in April 2010. In this study, we present patients who underwent a PET/IRM at initial staging of prostate cancer from which pathological specimens from prostatectomy were available. We will discuss the first results of integrated $^{18}$F-fluorocholine positron emission tomography (PET)/magnetic resonance imaging (MRI) for the detection of prostate cancer at initial staging.
Fig. 1: Combined 3 Tesla PET-MRI Philips system as installed in the Geneva University Hospitals at the beginning of the year 2010. The two scanners are placed in tandem, the first system in the foreground corresponding to the gamma camera and the second one corresponding to the MRI gantry.

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Methods and Materials

Patients

This was a retrospective study of fifteen patients with a history of prostate cancer presenting at initial staging. All patients were referred by urologists working in our center. The study protocol was approved by the Ethics Committee of the University Hospitals of Geneva and was performed in conformance with Swiss legislation regarding patient confidentiality and data protection. All patients provided their written informed consent to the use of $^{18}$F-fluorocholine as an unregistered radiopharmaceutical that was authorized for each patient by the Swiss federal authorities (Swissmedic and Federal Office of Public Health, Section of Radioprotection). To be included in this study, main indication was a biopsy-proven prostate cancer at initial diagnosis.

The PET/MRI hybrid camera

Philips Medical Imaging have developed, in collaboration with the Translational and Molecular Imaging Institute, Department of Radiology, Mount Sinai School of Medicine, New York, a new hybrid scanner (figure 1) which resolved some of previously described technical issues. The PET part of the hybrid imaging system is a Philips Gemini TOF PET, known to use time-of-flight to improve resolution and sensibility. The MRI machine is a Philips Achieva 3.0T X-series whole-body scanner. This 3-tesla MRI serves for both coregistration and attenuation correction. The TOF PET and 3.0T MRI scanners are operated in the same scanning room. A rotating bed placed between the scanners is used to move patient inside each scanner.

$^{18}$F-fluorocholine PET

The radiotracer doses were obtained from a company (Advanced Accelerator Applications, France), which guarantees quality control. Patients were requested to void before onset of imaging. Acquisitions protocols were the same developed in our institution by Steiner (2), consisting of 10 minutes list-mode PET done over the prostate bed after antecubital vein injection of 300 MBq of $^{18}$F-fluorocholine, from which three time frames of 3 minutes each were reconstructed for analysis, followed by a whole-body PET (figure 3), from mid-thigh to the skull, consisting of sequential 7 to 8 bed positions of 4 minutes each. An additional 5 minutes delayed pelvic imaging was then obtained (around 40 minutes after tracer injection, figure 2). The sinogram data were corrected for dead time, decay, and photon attenuation and reconstructed in a 256x256 matrix. Image reconstruction followed a fully 3-dimensional maximum-likelihood ordered-subsets expectation maximum algorithm incorporating random and scatter correction with 2 iterations and 28 subsets. The final in-plane full width at half maximum of the
The whole-body MRI was segmented and used to create an attenuation map, to correct PET images.

**MRI acquisitions**

The MR acquisition was a two steps process (figure 2). First, pelvic T2 turbo spin echo (T2 TSE) sequences are acquired with an endorectal coil combined with an external cardiac 6 array coil in a sagittal and axial plane in a 2D method with the following parameters: TR 4000 ms - TE 120 ms - number of scan average (NSA) 2 - slice thickness 3 mm - echo train length (ETL) 20 - matrix 328/290 for the sagittal acquisition and 432/386 for the axial acquisition - FOV 22 cm. Then, the endorectal coil was removed and the acquisitions were continued with only the external cardiac 6 array coil in place. Using the body coil, the whole-body attenuation correction MR sequence (figure 3) was performed from the head to the thighs by an axial fast field echo (FFE) with the following parameters: TR 4.1 ms - TE 2.3 ms - slice thickness 6 mm - matrix 200/200 - FOV 600 mm. A MR diffusion was acquired on the prostate (TR 3644 - TE 66 - slice thickness 3 mm - number of scan average (NSA) 4 - FOV 200 mm - matrix 88/79) with 4 b values (0,500,1000, 1500). A 3D pelvic acquisition is performed with a 3D fast spin echo MR sequence with: TR 2000 ms - TE 243 ms - number of scan average (NSA) 1 - slice thickness 1 mm - matrix 392/448/125 - FOV 390 mm. At this time a bolus of an intravenous injection of paramagnetic gadolinium-containing contrast agent is administered using gadoterate dimeglumine (Dotarem®) 0.01 mmol/kg. The perfusion consists of a multiframe 3D T1 Fat Sat gradient echo MR sequence with: TR 6.9 - TE 3.4 - matrix 192/189 - FOV 210 mm - slice thickness 3 mm - acquisition time 5 min. Finally, the entire abdomen was examined for lymph nodes in 5 batches of a 3D gradient echo T1 Fat Sat MR sequence: TR 3 ms - TE 1.4 ms - matrix 228/227 - FOV 375 mm - 30 slices - 6 mm slice thickness.

**18F-fluorocholine PET/MRI analysis**

All PET and MRI images were analyzed with dedicated software (Osirix, Osirix Medical Systems) using a 12 segments model of the prostate. The MRI were interpreted in a blinded fashion by a radiologist and the PET-MRI restricted to T2 images and PET data by a nuclear medicine physician. In a second time, the radiologist and the nuclear medicine physician performed a common and consensual interpretation of the complete MRI and PET exams. The radiologist and nuclear medicine physician were blindly asked to rate their index of suspicion for neoplasia for each segment of the prostate, according to the following scale: 0 (no evidence of cancer); 1 (equivocal); 2 (suspect); 3 (positive for cancer); 4 (uninterpretable). The regional nodes were also assessed using, for the MRI, a longest short-axis of at least 1 centimeter and, on PET, a SUVmax over the vascular metabolic activity.

**Processing of radical prostatectomy specimens**
After radical prostatectomy, each specimen was fixed in 4% buffered formalin for at least 24 h. The prostate glands were cut into axial sections from base to apex, in a plane perpendicular to the long axis of the prostate (similar to the MRI plane). Sections were approximately 0.4 cm thick (the number of sections varied between 4 and 7 depending on the dimension of the prostatectomy specimen). Macroscopic pictures of each section were taken. Whole mount sections were then completely embedded in paraffin blocks. The blocks were cut and extra large glass slides were prepared and stained with standard Hematoxylin-Eosin. The slides were evaluated for the presence and grade (Gleason scoring system (13), (14)) of invasive prostatic adenocarcinoma by a pathologist who was kept unaware of the imaging findings. Foci of cancer were marked on each slide using a fine indelible marker pen. Standard morphological criteria (e.g.: small infiltrative glands; absence of basal cells; perineural invasion; cells with large nucleoli) were used to diagnose prostatic adenocarcinoma. Isolated high grade prostatic intraepithelial neoplasia (retaining a basal cell layer by definition) without associated invasive adenocarcinoma was not included. Histomorphometry for the assessment of total and relative tumor volume was performed using computerized image analysis. For exact correlation of histopathology with imaging findings, the slides from whole-mount step sections were digitized using a commercially available scanner; each slide was oriented from the base to the apex according to the radiological images.
Fig. 1: Combined 3 Tesla PET-MRI Philips system as installed in the Geneva University Hospitals at the beginning of the year 2010. The two scanners are placed in tandem, the first system in the foreground corresponding to the gamma camera and the second one corresponding to the MRI gantry.

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**Fig. 2:** Protocol imaging used in our institution to perform the prostatic PET-MRI in a single session. First, we realize the MR acquisition with the T2 spin echo endorectal prostatic sequences. Then, after removal of the endorectal coil, T2 3D Vista, diffusion and post gadolinium perfusion MR sequences are acquired using the external 6 channel cardiac array coil. The whole-body MR attenuation correction is performed before the table rotation and beginning of the PET acquisition.

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**Fig. 3:** Example of the type of acquisition extending from the head to the thighs and corresponding to the whole-body sequence. The whole-body T1 MR sequence is used for the attenuation correction. The fusion with the PET data allows to better define the anatomical location of metabolic uptake.

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Results

Clinical findings and PET/MRI image quality.

Patients had a mean age of 60.9 years old (range, 47-75). Mean PSA was 18.9 mg/l (range, 5.33-67.3). Final Gleason scores ranged from 6 to 10, with 2, 10 and 3 patients belonging, respectively, to the low- (2-6), intermediate- (7), and high-risk (8-10) groups. Obtained PET and MRI examinations were all of diagnostic quality. The registration of PET-MRI images allowed accurate SUV measurement and hypermetabolic focus localization in the prostate or in the regional nodes. No significant artifacts from attenuation correction or interference between the two scanners were observed.

Diagnostic accuracy of $^{18}$F-fluorocholine PET and MRI

In the prostatic bed, most cases were coherent between PET and MRI for the presence of neoplasia (14/15 patients). Among patients with concordant positive PET and MRI examinations, figures 4 to 11 show complete imaging illustrations with MRI and PET images. The examples demonstrate the complementary information between anatomic and functional or metabolic images on PET/MRI and tumor extent. Patient with discordant results, had a history of previous radiotherapy and trans-urethral resection of the prostate (TURP) for a local cancer, but prostate was still in place. In loco-regional nodes somewhat less cases were coherent between PET and MRI for the presence or absence of neoplasia (11/15 patients). On the four discordant results between IRM and PET for nodes status, we could obtain pathology for three patients. Two patients had infracentimetric pelvic lymph nodes depicted on MRI, but clearly avid of $^{18}$F-fluorocholine. Pathology confirmed reactive inflammatory bilateral lymph nodes without evidence of neoplasia. In the third patient, (figure 12) there were infracentimetric right internal iliac lymph nodes on MRI, but these were hypermetabolic on PET. One of these resected right internal iliac lymph nodes was effectively positive for neoplasia.

When neoplastic lesions under 5 mm (which is the limit of resolution of our PET camera) were excluded, sensitivity and accuracy on a per-segment basis for MRI alone was 48.3% and 79.4% using a 12 segments model. These values increased to 58.6% and 82.4%, respectively, for combined PET/MRI. The specificity did not change significantly, rising to 96.3% for MRI alone and 95.3% for both techniques. We observed a high correlation between PET and MRI results but only a poor correlation between both imaging modalities and the pathology results. This was clearly related to a too important number of segments in our model. As a work in progress, using a 6 segments model, the sensitivity and specificity for the detection of prostate cancer in the peripheral zones were 75% and 73% for MRI only and 88% and 77% for combined PET and MRI.
Fig. 4: PET-MRI in a 47-year-old man with prostatic carcinoma, PSA 14 and Gleason score 9. A large tumor infiltrating the right peripheral zone is seen on the images of all the modalities.

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**Fig. 5:** Histological slide from the radical prostatectomy of the patient presented in figure 4. Tumor extension is outlined in the histology section using a blue ink. Note the high correlation between pathology and imaging.

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**Fig. 6:** PET-MRI in a 54-year-old man with prostatic carcinoma, PSA 6.4 and Gleason score 7. The lesion is located in the left peripheral zone of the apex in the prostate. In the T2 sequence the hyposignal may be subtle and the lesion not immediately detectable from an anatomical point of view. In the functional MR and the metabolic PET data, the pathological focus is well demonstrated.

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**Fig. 7:** Histological slide corresponding to the patient presented in figure 6. Tumor extension is seen in the prostatic left apex in the form of two adjacent foci, outlined in the histology section using a blue ink.

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**Fig. 8:** PET-MRI in a 64-year-old man with prostatic carcinoma, PSA 6.8 and Gleason score 7. In this example, the prostate showed a prominent adenomatous hyperplasia in the central gland. The slices are at the basal level of the prostate. In the peripheral left zone, a strong hypointense signal T2 is present suspicious for prostate cancer. Diffusion MRI and PET, but not perfusion MRI, were able to clearly detect the abnormal area. The PET sequence clearly showed an asymmetric uptake separated from the central gland in the tumor area. Note also the normal metabolic activity in the transitional hyperplasic zone.

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**Fig. 9:** Histological slide corresponding to the patient presented in figure 8. The tumor focus, outlined in blue, is present in the prostatic left base.

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**Fig. 10:** PET-MRI in a 75-year-old man with prostatic carcinoma, PSA 11 and Gleason score 7. The T2 sequences showed a focal alteration in the right peripheral zone at the mid level of the prostate. In the diffusion, the restriction was not strong and the ADC map did not demonstrate easily the tumor. In the perfusion, the suspected region showed a slight hyperperfusion but not demarcated from the rest of the peripheral zone and not conspicuous. In this case, the PET allowed to confirm the suspected lesion, demonstrating a clear hypermetabolic focus.

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**Fig. 11:** Histological slide corresponding to the patient presented in figure 10. The pathology confirmed the tumor location in the right mid level of the prostate with three adjacent foci of carcinoma (outlined in blue).

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**Fig. 12:** PET-MRI in a 47-year-old man with prostatic carcinoma (illustrated in figure 4), PSA 14 and Gleason score 9. The MR and PET images correspond to pelvic axial section, at the level just above the prostate. In this case, a right internal iliac node was not diagnosed as cancer in the MR examination due to its infra-centimetric size. In the PET acquisition, an uptake was clearly demonstrated coming from this node by the images fusion. After surgery, pathology confirmed the presence of tumor in the node.

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Conclusion

Imaging evaluation of prostate cancer remains a challenging endeavor. MRI has the potential to yield more information about the prostate gland than any other imaging modality. Because of its parametric capabilities, MRI in a single exam can produce high-resolution anatomic imaging with excellent soft-tissue contrast (6). During the last years, $^{18}$F-fluorocholine PET has been studied as a tracer in patients with newly diagnosed prostate cancer and in patients with biochemical recurrence and rising PSA (2-5, 13, 15, 16-19). In this study, we demonstrate the feasibility of the integrated prostate PET-MRI in a single session without any loss in image quality for both imaging. The examinations were well tolerated by all patients. The whole-body MR appeared to be excellent for the correction attenuation with PET images of diagnostic quality by all patients. In the pelvic analysis of the prostatic bed or the regional nodes, the co-registration (fusion) between the MR and PET acquisition allowed the anatomical location of hyper-metabolic areas in the prostatic gland or in pelvic nodes with adequate precision. We did not observe significant anatomical deformation between the PET or MR images, limitations due to the bladder filling or time delay between sequential acquisition of the PET or MR (e.g. motion artifact). As a preliminary result, there was a general agreement between the PET, MR and pathologic images, especially in high-grade tumor (as shown in Figure 4). This is in agreement with the results obtained with choline-avid lesions on PET and neoplastic foci on pathological specimens (20, 21). For more difficult tumors, our preliminary experience suggests a complementary value of PET in addition to MRI. For the nodal status, the co-registered PET/MRI data was of help in interpreting tracer uptake in the lymph nodes (Figure 12). The ureteral or urinary activity did not interfere with image interpretation of tracer uptake.

In conclusion, the combination of MRI and $^{18}$F-fluorocholine PET examinations in a single session appears to be a promising imaging modality for newly diagnosed prostate cancer. The exquisite resolution of MRI permits adequate anatomical localization of $^{18}$F-fluorocholine abnormal prostatic uptakes. The fusion of PET data with MRI allows to clearly distinguish between both peripheral and transitional zones for an accurate SUV$_{\text{max}}$ measurement. The better confidence in the tumor localization on the PET images has the potential to improve tumor detection and staging in prostate cancer justifying further clinical studies.
References


