Clinical applications

Fusion of transrectal ultrasound with pre-acquired MRI for prostate biopsy guidance

Prostate cancer is highly prevalent in Europe and North America, with an incidence rate of 172/100,000 in the USA (2004). One in six men will be stricken with prostate cancer in their lifetime, and over 230,000 new cases are diagnosed each year in the USA (2004). Although prostate cancer generally progresses slowly, the mortality rate is currently 30,000/year [1].

The first stages of prostate cancer screening and diagnosis involve a digital rectal examination and prostate-specific antigen (PSA) test, followed by a transrectal ultrasound (TRUS) examination and, if necessary, a TRUS-guided biopsy. Since the accuracy of TRUS in depicting prostate cancer is insufficient, biopsies are generally not lesion-targeted. Instead, the vast majority of biopsies are carried out using a sextant approach with 6 - 12 core systematic geometric samples of the prostate being taken [2-4]. Over a million biopsies are performed annually in the USA, with false negative rates of up to 30% reported [5].

Prostate imaging limitations and potential alternatives to TRUS have been studied extensively and continue to be an active area of research. Novel imaging methods are being sought for screening, diagnosis, and staging of prostate cancer, as well as for biopsy and therapy guidance. Advanced magnetic resonance imaging (MRI) methods, such as dynamic contrast enhanced MRI (DCE-MRI), and MR spectroscopy are among the most promising new diagnostic modalities for prostate cancer [6-9].

Improving image guidance for diagnostic and therapeutic prostate interventions is one of the goals of an ongoing collaboration between Philips Research North America and the National Institutes of Health (NIH) in Bethesda, MD. The research aims to utilize existing imaging modalities more effectively for interventional procedures by bringing pre-acquired image information into the real-time ultrasound-based workflow.

At present, thin slice T2 weighted (T2w) MRI obtained with an endorectal coil (ERC) with a small field of view is considered very helpful for the detection and local staging of prostate cancer [10]. On T2w images, prostate cancer in the peripheral zone appears as a focal area of low signal intensity and can be easily differentiated from normal peripheral zone tissue, which appears as high intensity. However, the utility of T2w sequences is limited in the detection of central and/or transitional zone tumors, which have signal characteristics similar to normal prostate tissue. Additionally, various conditions, such as post-biopsy hemorrhage, focal atrophy, inflammation and fibrosis, can show low signal intensity on T2w images [11]. In addition to conventional T2w images, various sequences such as diffusion weighted imaging (DWI), DCE-MRI and MR spectroscopy add up to improve the overall performance of MRI in lesion detection. DWI allows demonstration of restricted diffusion in cancer tissue within the gland and lesions are seen as low signal intensity areas on apparent diffusion coefficient (ADC) maps [12]. DCE-MRI and the quantitative measures based on pharmacokinetic parameters derived from DCE can enable detection of prostate cancer lesions [13]. MR spectroscopy allows metabolic assessment of the prostate gland, which normally has high levels of citrate, but in the presence of tumors citrate values decrease significantly, whereas choline values are found to be elevated [14].

Among the imaging modalities available today, MRI has by far the best spatial resolution, and yields unsurpassed anatomic images of the prostate. Despite this, the findings of prostate
cancer on MR images can be non-specific, and the nature of each lesion must be verified with a directed biopsy. One method of resolving this is to design a biopsy device that is MR compatible and then perform the biopsy while the patient is in the MR scanner. While this approach may be accurate it can be cumbersome and occupies the MR scanner for a long period of time, thus increasing costs. Moreover, the patient must assume an uncomfortable position for an extended period of time to enable the biopsy to be performed inside the magnet. Thus, improved methods of targeting MR lesions would be welcome. The ability to transfer the MR data onto a real time ultrasound image opens many possibilities in developing a more practical method of obtaining biopsies from areas of the prostate that are suspicious on MR images.

Materials and methods

Materials
An image registration and fusion system was developed consisting of a custom visualization and registration workstation [15-18] interfacing with the Aurora electromagnetic tracking system (Northern Digital Inc, Waterloo, ON, Canada). Endorectal biopsy guides (CIVCO; Kalona, IA, USA) were equipped with electromagnetic tracking sensors (Traxtal Inc, Toronto, Canada) compatible with the Aurora system (Figure 1), and were attached to an endorectal ultrasound probe (Philips C9-5ec). Real-time transrectal ultrasound images (iU22, Philips Healthcare, Andover, MA, USA) were transferred to the workstation using video frame-grabbing, enabling spatial localization of each ultrasound frame with the tracking system.

The system was developed using a prostate biopsy phantom (Model M53 A; Computerized Imaging Reference Systems, Norfolk, VA). T2w axial MR scans of the phantom were acquired using a SENSE protocol (TR = 8852 ms, TE = 120 ms, flip angle = 90°) on a 3T Philips Achieva MR scanner (Philips Healthcare, Best, the Netherlands). The MR images were segmented manually using the NIH’s medical image processing analysis and visualization (MIPAV) software. The segmentations were converted automatically into surface meshes on the fusion workstation. A typical setup of the system for phantom studies is shown in Figure 2.

Workflow
The fusion workstation supports a workflow consisting of four steps:

- Read MR image, segmentation, and pre-selected targets
- 3D ultrasound (3D-US) sweep
- Register 3D-US with MRI
- Select target and obtain biopsy based on fused MRI/US feedback

Targets are selected manually in axial, sagittal and coronal views of the MRI. 3D-US sweeps of the prostate are obtained by scanning the
probe manually from base to apex. A rapid reconstruction algorithm [16] converts the series of 2D images into a 3D volume, which is then displayed in axial, sagittal and coronal views jointly with the MRI and MRI-based segmentation. A graphical user interface is provided for rigid manual registration of the ultrasound and MRI volumes (Figure 3).

Upon completion of the registration, a target is selected and the workstation is switched to live fusion mode, which jointly displays the real-time ultrasound image and the spatially corresponding multi-planar reconstruction (MPR) from the MR scan.

**Motion compensation**
A motion compensation algorithm was developed to account for intra-procedural prostate motion, which is often induced by variable probe pressure during the procedure [17]. The algorithm is activated by the user whenever a mismatch between the ultrasound and the MRI is apparent.

Registration between MRI and real-time ultrasound is achieved by combining the registrations between 3D-US and real-time ultrasound, and between MRI and 3D-US.

\[ T_{MRI\rightarrow rtUS} = T_{3D\text{-US}\rightarrow rtUS} \cdot T_{MRI\rightarrow 3D\text{-US}} \]

Where \( rtUS \) refers to real-time ultrasound, \( T_{MRI\rightarrow rtUS} \) is the initial manual registration between the reconstructed 3D-US and MRI, and \( T_{3D\text{-US}\rightarrow rtUS} \) is the registration between reconstructed 3D-US and real-time ultrasound images. In the absence of prostate motion, that transformation is determined by the tracking system and the ultrasound probe calibration, i.e.

\[ T_{3D\text{-US}\rightarrow rtUS} = T_{Localizer\rightarrow rtUS} \cdot T_{3D\text{-US}\rightarrow Localizer} \]

Where \( T_{Localizer\rightarrow rtUS} \) is provided by the probe calibration, and \( T_{3D\text{-US}\rightarrow Localizer} \) is computed during 3D-US reconstruction. The reconstructed 3D-US is in a fixed position relative to the localizer, and can thus be used as a reference for motion compensation.

If the prostate moves after acquisition of the 3D-US, the registration between 3D-US and real-time ultrasound becomes invalid, and an image-based registration algorithm is used to recover it.

The registration algorithm uses the original \( T_{3D\text{-US}\rightarrow rtUS} \) as a starting point for optimization, assuming that the prostate typically does not move far from its original position. The image registration algorithm is based on minimizing the sum-of-squared differences (SSD) between the current ultrasound image and the reconstructed 3D-US. The SSD is an attractive similarity measure for online registration because the mathematical formulation of the SSD allows the objective function to be efficiently optimized using standard optimization approaches, such as the Gauss-Newton algorithm.

Since the spatial tracking of the probe assigns a physical location in space to each image pixel, the 2D image is actually a single slice 3D image, allowing 3D/3D registration to be conducted. However, the registration of a single image slice is very sensitive to noise. There are many local minima along the off-plane direction, decreasing the algorithm’s efficacy for clinical use. Therefore, a number of 2D images are registered simultaneously, including images with the largest translational and rotational distance within the recent history of images. Unavoidable motion with the hand-held probe guarantees that some prostate tissue in the off-plane direction is covered; the registration can therefore be categorized as 2.5D to 3D registration. The registration algorithm uses rigid transformations with six degrees of freedom.

**Phantom studies**
Phantom studies were conducted to validate the accuracy of motion compensation. The prostate phantom was kept in a fixed position relative to the electromagnetic tracking system. The prostate inside the phantom, immersed in a tissue-mimicking gel matrix, was assumed to be stationary. A 2D ultrasound sweep over the prostate was acquired and the 3D-US was reconstructed. For 20 different ultrasound sweeps, an artificial rotational and translational misregistration of 5 - 15 mm was created between the real-time ultrasound and the reconstructed 3D ultrasound. The misregistration was uniformly distributed in 3D space, and was quantified by calculating the mean distance between corresponding voxels in the real-time 2D ultrasound and the corresponding 3D-US MPR. The artificially misregistered real-time ultrasound was used as the starting point for the 2.5D to 3D registration.

**Clinical studies**
Clinical studies were conducted at the NIH Clinical Center under a research protocol approved by the institutional investigational review board. The nature of the procedure was explained to the patients and written informed consent was obtained.
Interventional biopsy and seed placement procedures with fused ultrasound/MR imaging were carried out in 32 patients following the workflow described above.

Three studies were conducted:

In 10 patients, the accuracy of manual 3D-US to MRI registration was evaluated retrospectively. In 10 patients, the accuracy of manual 3D-US to MRI registration was evaluated retrospectively. In a further 12 patients, the motion compensation was evaluated. In these patients, the reconstructed ultrasound was segmented by one radiologist, in addition to the segmentation in the MRI. The manual registration between the 3D-US and the MRI obtained during the fusion imaging procedure was applied retrospectively to the 3D-US segmentation in order to align it with the MRI segmentation. The Hausdorff, mean, and root mean square (RMS) distances measured between the MRI segmentation and the registered 3D-US segmentation were computed [15]. In addition, the volumetric overlap between the MR-based segmentation and 3D-US-based segmentation was analyzed.

Furthermore, in 15 patients, targeted biopsies using the US/MR fusion system were obtained in addition to conventional 12-core sextant biopsies. All biopsies were performed with intravenous sedation for patient comfort. The patient population included men with elevated PSA and/or abnormal digital rectal examination, men with a history of elevated PSA but multiple negative TRUS-guided biopsies, and men with known prostate cancer who were not candidates for therapy and were therefore on “watchful waiting”. In addition to T2w MRI, DCE, DWI, and MR spectroscopy images were obtained in each patient.

The images were reviewed by two radiologists, and 1 - 4 suspicious targets per patient were identified. The identified targets were loaded into the fusion workstation and selected sequentially.

Patients were positioned in left decubitus orientation, and a digital rectal exam was performed, followed by ultrasonic examination of the prostate. Subsequently, the 2D ultrasound sweep of the prostate was performed in coordination with the operator of the fusion workstation.
The sweep was reconstructed into a 3D-US volume, and a manual 3D-US to MRI registration was carried out (Figure 3). At the same time, conventional sextant biopsies were obtained. The system was then switched to live fusion mode in which the current real-time ultrasound image is displayed jointly with the corresponding MRI MPR. In addition, the projected biopsy needle path and MR-based segmentation were visualized, and the MR-selected target was highlighted in both the MR MPRs and ultrasound images. The projected needle path was aligned with the selected target, and 1 - 4 biopsies per target were obtained.

Results

The distance measures between the manually registered prostate segmentations obtained in 3D-US and in MRI are summarized in Table 1. Also summarized are the prostate volumes and the volumetric overlap computed from the same segmentations.

In the phantom study, 20 measurements of 2.5D to 3D registration accuracy were obtained. The registration error of each voxel was defined as the distance from the recovered position to its original position before introduction of the artificial misregistration. As an example shown in Figure 4, the registration starting point (Figure 4c) was significantly different from the real-time image (Figure 4a). Since the prostate was stationary, a correct registration should recover the known initial position. Figure 4b shows the corresponding image of (a) in the ultrasound volume after the registration. The mean registration error obtained in the study was 2.3 ±1.0 mm.

The efficacy of the motion compensation was quantified by measuring the overlap of the ultrasound and MRI-based segmentations in 12 patients. The normalized overlap increased from 77 ±17% before motion compensation to 93 ±5% after motion compensation. The difference was statistically significant based on the student t-test at p = 0.01. Figure 5 shows an example of ultrasound and MRI fusion before and after motion compensation.

Prostate cancer was found in seven patients (47%) using sextant biopsy, and in six patients (40%) using targeted biopsy. In two patients, one of the sextant biopsy cores showed cancer, while none of the targeted cores showed cancer. In one patient, one of the targeted biopsy cores showed cancer while none of the sextant cores showed cancer. Prostate tissue abnormalities other than cancer were found in seven patients

![Figure 5. Example of a motion compensation result in a patient study. The upper row shows real-time ultrasound images, the lower row shows corresponding MPRs of the T2w MRI. Also superimposed is the corresponding cross-section of the MRI-based prostate segmentation. The columns from left to right show the US/MR registration. Left: before prostate motion. Center: after prostate motion but before motion compensation. Right: after motion compensation. Note that the registration error in the center image is compensated in the right-hand image.]
pre-MRI transrectal ultrasound guided biopsy.

Figure 6. MRI in a 62-year-old Caucasian male showing a suspicious lesion (arrows).
Figure 6a. Axial T2w MRI.
Figure 6b. Coronal T2w MRI.
Figure 6c. ADC map based on DWI.
Figure 6d. DCE image at the same slice location.

Figure 7. Screenshot of the fusion workstation showing corresponding real-time ultrasound (left) and T2w MRI MPR (right) at the time of biopsy needle deployment in the MR-identified target (red) shown in Figure 6. Also visualized are the MR-based prostate segmentation (green), the projected biopsy needle path (white), and additional MR-identified suspicious lesions (blue).

Figure 8. MRI in a 73-year-old Asian male showing a suspicious lesion (arrows).
Figure 8a. Axial T2w MRI.
Figure 8b. Coronal T2w MRI.
Figure 8c. ADC map based on DWI.
Figure 8d. DCE image at the same slice location.

Figure 9. Screenshot of the fusion workstation showing the identified target in the same patient as depicted in Figure 8 in T2w MRI fused with 3D reconstructed ultrasound (top row), as well as real-time ultrasound at the time of biopsy needle deployment without (lower left) and with (lower right) superimposition of the MRI-based segmentation and target information.

(47%) using sextant biopsy, and in nine patients (60%) using targeted biopsy. Cancer was found in 21 (23%) of the 90 sextant biopsy regions; 43 (48%) of the regions showed benign prostate tissue only, and 26 (29%) showed abnormalities other than cancer. Cancer was found in 12 (30%) of 40 targeted biopsy regions; 10 (25%) showed benign prostate tissue only, and 18 (45%) showed abnormalities other than cancer.

Figure 6 shows an example of a suspicious lesion identified on T2w MRI, DWI and DCE-MRI in a 62-year-old Caucasian male with a PSA value of 11 ng/mL and negative pre-MRI transrectal ultrasound guided biopsy. The lesion was selected as a target in the fusion workstation, and the urologist obtained a biopsy from the target location based on the real-time fusion feedback (Figure 7). This screenshot from the fusion workstations shows corresponding real-time ultrasound (top) and MRI MPR views (bottom) at the time of needle deployment.

Figure 8 shows a lesion identified on T2w MRI, DWI and DCE-MRI in a 73-year-old Asian male with a PSA value of 45 ng/mL and negative pre-MRI transrectal ultrasound guided biopsy.
The screenshot in Figure 9 shows the same T2w MRI, here registered and fused with the 3D reconstructed ultrasound (color map), as well as the real-time ultrasound and target information.

Discussion

A system fusing pre-acquired MRI with real-time ultrasound for prostate biopsy and therapy guidance has been developed and is being evaluated at the NIH Clinical Center. Phantom studies and retrospective quantitative assessment of 3D registration accuracy and motion compensation errors suggest that clinically useful system accuracy can be achieved.

The system accuracy is determined by the accuracy of electromagnetic tracking, ultrasound probe calibration, MRI to 3D-US registration – which in itself depends on the relative deformation of the prostate between MR and ultrasound scans – and real-time ultrasound to 3D-US motion correction. In addition, targeting accuracy depends on the operator’s ability to use the fusion display for precise deployment of the needle in the target location, which may be affected by needle tip visualization, needle bending, and prostate motion and deformation during needle deployment.

Currently, the system is being optimized to account for motion during the examination and to improve the registration between the pre-acquired MRI and the real-time ultrasound. Initial study results indicate the ability to target an MR lesion within 0.5 cm. This opens the possibility of providing more precise diagnoses of areas that are suspicious on MR images. This device may prove most useful in the short term in patients with rising PSA values, but negative systematic biopsies. If the MRI demonstrates an abnormality, it would be highly desirable to biopsy that area directly using this system. This may lead to earlier diagnosis when the prostate cancer is still curable. In the long term this system may be useful in guiding local therapies into the prostate cancer itself, thus sparing the remaining gland unnecessary treatment and thereby reducing side effects typically associated with whole-gland therapies (e.g. erectile dysfunction and incontinence).

References