

MRI-HISTOLOGY REGISTRATION IN PROSTATE CANCER

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INTRODUCTION

Prostate cancer (PC) is the first cancer in terms of incidence and the second leading cause of death from cancer among men in France: 40309 new cases in 2000 and 10004 deaths this same year. The mean detection age is 74 years but cases have been reported for younger men (in the fifth decade).

PC detection requires a digital rectal exam and a Prostatic Specific Antigen screening. The diagnosis is confirmed by pathological analysis of systematic needle core biopsy. Transrectal ultrasound (TRUS) is currently used to guide this prostate sampling. In the 12-pattern protocol, twelve different transrectal ultrasound-guided biopsies are routinely performed: 6 biopsies in each side of the prostate, which are paired in the apex, the mid and base regions of the prostate. The positive detection rate for the first biopsy series is about 20-30% [8].

For optimal therapy, the precise localization and staging of PC is critical; indeed it allows the urologist to adjust his treatment in order to either cure the patient or extend his life span while limiting therapeutic adverse events. An early diagnosis of localized PC will result in a surgical procedure (radical prostatectomy) or radiotherapy. Moreover, with the emergence of disease-targeted therapy such as interstitial brachytherapy, intensity-modulated radiotherapy, and high intensity focused ultrasound, the assessment of PC localization and extent has become an important consideration in treatment selection and planning.

Once the diagnosis is confirmed by pathological analysis of the biopsies, patients undergo a magnetic resonance imaging (MRI) examination obtained by using endorectal coil. Radiologists look for a low-intensity intraglandular area on T2-weighted images, which is suggestive of a cancer area. Unfortunately, this signal of low intensity is not specific of PC.

Moreover, it has proven difficult for radiologists to detect an extra-capsular extension which would imply a different therapeutic procedure. In literature, the sensitivity of extracapsular extension detection has been reported [1,3] between 22 and 91% and its specificity between 49 and 100%. New MRI developments (higher strength fields, new endorectal coils, new image acquisition sequences, analytical image correction, etc.) try to differentiate pathological processes in the prostate. New technologies such as magnetic resonance spectroscopic imaging (MRSI) yield better results in cancer detection with a sensibility of 95% and a specificity of 91% [7]. Combined anatomical and metabolic imaging (3D MRI/MRSI) can provide accurate localization of PC.

However, since those new techniques are only emerging and because histological data are the gold standard, correlating them with pre-therapeutic anatomical MRI images may bring very interesting pieces of information. This is one purpose of the work described in this paper.

In order to prepare this work, a feasibility study has been conducted with cadaver prostates. The study is now conducted with radical prostatectomies (prostate removed for cancer). The correlation of those resected prostates examined both through anatomopathology and MRI may improve further image understanding and staging issues.

In this paper, the MRI and the histology protocols are described; some results

obtained for prostate specimens are presented and discussed.

METHODS

In the context of this study, data come from patients for which a prostatectomy has been planned. Before resection, a MRI examination is performed. After resection, the prostate is prepared for a specific anatomo-pathology protocol. Based on those information (MRI volume and histological slices with cancer localization), data registration is performed thanks to a specific software named Procur. This allows to superimposing and comparing those two types of data.

1. *MRI protocol*

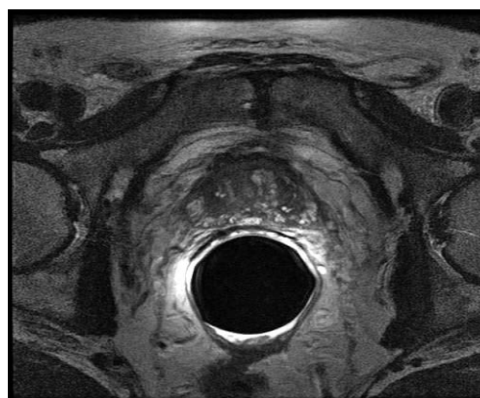


Fig. 1
FSE T2-weighted axial MRI image of the prostate (with endorectal coil)

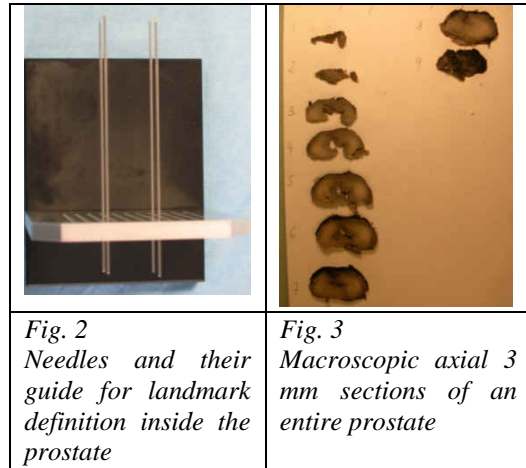
Patients undergo a MRI examination with an endorectal coil (Philips Medical System, 1.5T, fast spin echo, T2-weighted images). Axial (0.39 x 0.39 x 3.2 millimetres), coronal and sagittal slices are acquired (voxel size: 0.486 mm³).

2. *Anatomo-pathology protocol*

The prostate specimens are sent to the Pathology Department where they are processed using a protocol similar to the one described by Egevad et al [2]. The major difficulty is to be able to reconstruct a 3D model from the histological elements. Indeed, the specimen is step-sectioned every 3 millimetres and each macroscopic section is cut in 4 parts in order to be glass-mounted. One important stage consists in adding landmarks making possible assembling histological data (in a single slice and among different slices).

The protocol follows:

- ✓ The prostate weight and volume are measured.
- ✓ Parallel needles (1 mm diameter) are inserted from the apex through the base of the prostate in order to provide the landmarks mentioned above (cf. figure 2) for histology model reconstruction.
- ✓ The prostate is fixed free-floating so as to preserve its shape. Its volume after fixation is measured.
- ✓ The needles are removed. The specimen is then step-sectioned with a meat cutter, every 3 millimetres perpendicular to the rectal surface (see figure 3). The slices are numbered from the apex to the base and photographed. As mentioned, each macroscopic section is cut in 4 parts.
- ✓ After hand-embedding, 5 microns tissue sections are cut from each cassette, and stained with Haematoxylin (H) and Eosin (E) for histological evaluation.



- ✓ The slices are reconstructed. Each microscopic slice is analyzed by a pathologist who defines the contours of relevant structures such as the capsule, the urethra, the peripheral zone and the tumour. An optical microscope is used (x4) to be able to localize the tumour.

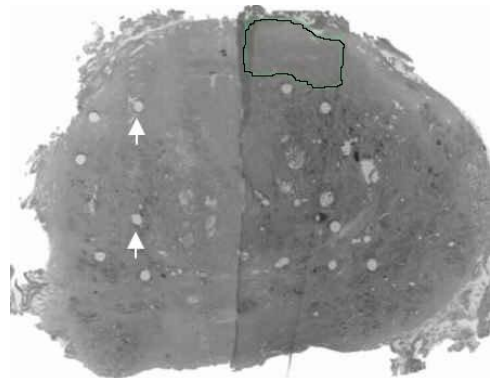


Fig 4.
Slice reconstruction. The arrows point on landmarks. The cancer region has been outlined by the pathologist.

- ✓ Then, the marked H and E glass-mounted sections are scanned and

data are introduced into the Procur software.

3. Data registration

Procur was originally developed in order to match pre-operative MRI with-operative TRUS prostate images for prostate brachytherapy [5]. It has been slightly modified to enable MRI/histology data fusion.

Before registration, a first stage consists in segmenting the two data sets with manual tools. This results in two clouds of 3D points. One represents the prostate surface (the capsule) in the MRI coordinate system. The second one represents this same surface in the histology coordinate system. In this second reference systems are defined the urethra, the peripheral zone and the tumour (see figure 5). Procur computes the transformation that optimally superimposes the histology and MRI prostate capsule.

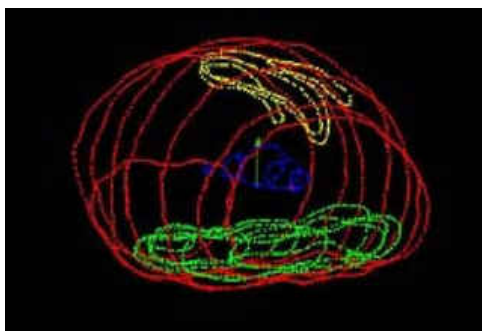


Fig. 5
Histological model including prostate capsule, urethra, peripheral zone and tumour.

The algorithm minimizes the distance between the 3D point clouds using Levenberg-Marquardt optimization (see

[6] for more details). Elastic or rigid registration can be used.

After registration a composite image can be constructed: for each histology slice, the corresponding pixels are located in the MRI volume using the computed optimal transformation. This composite image combines histological and MRI data in a four quadrant interface that the urologist can manipulate (see figure 6).

RESULTS

In a first stage, we have tested this approach with 4 cadaver prostate specimens. The registration accuracy determined on composite images was visually estimated to about 2 to 3mm (see figure 6).

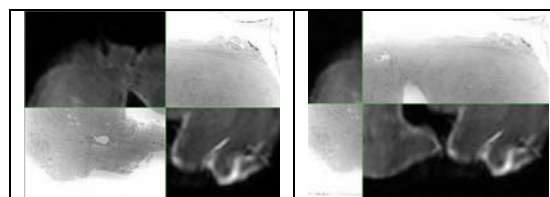


Fig. 6
Composite image combining MRI data (top-left and bottom-right quadrants) to histological data (top-right and bottom-left quadrants).

In a second stage, 3 prostates resected from patients were processed. Procur allows computing the remaining distance after registrations between the histological and MRI capsule. In the example shown in figure 7, the mean, maximal distances and standard deviation are respectively 1.32mm, 4.25mm and 0.64mm. The rather poor visual result is discussed in the following section.

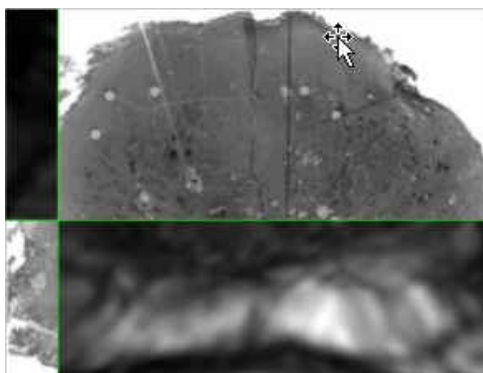


Fig. 7
Composite image for patient data.

DISCUSSION

The first bricks of histology/MRI data fusion for PC have been defined, implemented and tested. Figure 7 shows that the process is not yet perfect and different problems must be solved. Inaccuracy results from several elements of the protocol.

One of them is prostate deformation and shrinkage occurring during fixation. Moreover, there can be a tissue loss in the microscopic cutting. We assume that the shrinking prostate is isotropic. A mean correction factor of 1.22 is usually used. It was determined by [2] from 28 prostate specimens. Elastic registration can take account of this deformation and shrinkage but a pre-processing based on the 1.22 factor could make the registration algorithm more robust. Based on our further experiments this factor will be confirmed or refined.

The major drawback of the histology protocol is that the integrity of the axial section is lost; each slice is cut because a complete prostate slice is larger than standard microscope cover-glasses. We tested with pathologists the processing of entire slices but as no automation could be used, the manual process was far too tedious to be envisioned for a large scale study. Thus, the landmark approach was proposed. However, it turned out that the needles are too flexible and get deformed whilst introduced in the gland. This results in inaccuracies in slice and 3D reconstruction of histological data. Larger needles (2 or 3 mm) will be used for further patients.

As regards MRI, the 3D prostate segmentation based on coronal, sagittal and axial slices is not very easy. Some tools are currently developed to facilitate this stage and produce more precise MRI models.

Concerning registration, it is only based on the prostate capsule. Outlining the other structures (urethra, peripheral zone) in the MRI data and using them for a more precise registration could make the overall process more accurate. The relative position of data before registration (named initial attitude) is a very important element of registration accuracy and robustness. In Procur, the setting of the initial attitude is based on the brachytherapy case where both modalities are acquired in very similar conditions (patient position, endorectal sensors, axial slices). This has to be modified for histology/MRI fusion in order to improve robustness of this stage.

Finally, as can be seen on figure 7, the composite image quality may be rather limited for MRI retrospective analysis. This is due to the fact that the image scales are very different in the two modalities: in the MRI, the field of view is 16 cm whilst microscopic images correspond to the prostate (about 6 cm) being zoomed four times. Different strategies can be developed; firstly, smaller MRI volumes with thinner slices will be acquired. Multi-resolution visualization can also make image interpretation easier.

CONCLUSION

We are investigating MRI-histology fusion in PC in order to improve the cancer detection. In spite of the underlined limitations, MRI-histological fusion is still a very promising and novel technology which development may be followed up. In the clinical side, the future prospects are numerous.

- Firstly, the aim of this work is to compare retrospectively pre-operative MRI images with histological data in order to improve

the pre-therapeutic disease staging. More data are necessary to draw conclusions on this objective.

- A statistical atlas of PC could also be created using a radical prostatectomy database. A computer-aided application could use this reference to optimize biopsy strategy and decrease the diagnosis morbidity [6,8].
- Finally other applications exist such as improving the positive repeat biopsy rate in men with persistently elevated PSA after initial negative biopsy or improving cancer localization in minimally invasive therapy for increased control and reduced morbidity.

ACKNOWLEDGEMENTS

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