Fluorescence imaging to improve prostate cancer diagnosis

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1. Introduction

The protocol for prostate cancer diagnosis is currently based on PSA determination followed by ultrasound-guided biopsies. These biopsies are normally conducted by covering the prostate volume to increase chances of identifying the tumor. The 12 samples typically taken are particularly difficult for the medical practitioner and painful for patients. In some 30 percent of cases, the biopsies do not reveal any traces of the tumor, resulting in a second or even a third series of sample removals, at several months’ intervals. The number of biopsies cannot be prolonged indefinitely due to the risk relating to their side effects (1). In recent years, the number of biopsies conducted during each series has risen from six (sextant) to 12, according to prostate volume, so as to increase their sensitivity. It is a fact that a certain percentage of false-negative results exist: if a second series of biopsies is conducted, the rate of additional cancers detected is then between 20 and 30 percent. This second series of biopsies often includes a greater number of samples, up to 20. Should this second series of samples prove negative, a third series of biopsies may be carried out.

In such cases, the current trend is to propose an MRI scan, with and without injection of contrast medium, aimed at detecting potential but not specific targets of cancer that will be subjected to an additional series of guided biopsies. The problem of matching localization of the targets detected by MRI and transrectal identification is not easy to solve. Possible solutions are either development of image-fusion techniques based on volume acquisitions obtained with each modality, or injection of contrast media during the scan to re-localize the targets.

Development of a method designed to localize the tumor, or a suspect zone, within the prostatic tissue during the biopsy would have numerous benefits. It would considerably improve detection sensitivity, reduce the number of samples required, avoid the second or third series of biopsies as well as other currently proposed tests that are more costly without proven performance, and, last but not least, avoid recourse to multiple MRI scans and/or complex fusion methods. The possibility of localizing the center(s) of tumor location could have, in the future, an impact on the application strategy of new treatments such as thermotherapy.

As part of an ANR TECSAN project and on the initiative of the Bordeaux University Hospital Center (CHU), a consortium developed a bimodal probe allowing an optical measurement to be added to the traditional ultrasound diagnosis [1].

Combining the two imaging methods should enable the medical practitioner to precisely locate potentially cancerous zones and to produce far more accurately targeted and clearer biopsies (figure 1), thus reducing the number of biopsies required and increasing diagnosis reliability. This type of approach would improve patient management and comfort and consequently lead to a reduction in healthcare expenditure by reducing the number of examinations required.
2. A novel bimodal probe to guide prostate biopsy

This probe was designed to perform two types of optical measurement:

- **Fluorescence measurement**, after injection of a fluorescent tracer specific to tumor cells. This modality ensures localization of these cells with a very high specificity. Its drawback is that it depends on the authorization to market the markers.

- **Light absorption measurement**. The optical probe measures the optical properties of the prostate that tumor presence can cause to vary (detection of hyper-vascularization zones and measurement of the oxygen saturation). Its main drawback is its lack of specificity, as factors other than cancer are able to modify vascularization and oxygen saturation.

The optical module of the probe consists of six excitation fibers and four detection fibers located on the head of an ultrasonic probe. This module collects the diffusion and fluorescence signals and drives them to a fast parallel time-resolved detection system. The fluorescence yield is reconstructed by processing intensity and the mean time of flight of each signal computed from the acquired set of time-resolved signal of source-detector combinations in less than one minute.

The ultrasound imaging transducer is located at the sagittal end of the probe. Both excitation and emission fibers are housed between the plastic shell of the probe and the transducer electronics, as shown on figure 2. The acoustic module is composed of 128 elements and of central frequency 6.7 MHz±10%. Signal was acquired by a standard medical ultrasound system.
3. Photon time of flights measurements to reach millimetric resolution

The second signal is used to establish a mapping of the optical properties of the environment, as well as to provide us with information on the level of the natural fluorescence of the tissues. This natural autofluorescence of tissues may in fact be added to the signal from the fluorescent tracers and thus interfere with localization. An example of these time signals is given in figure 3.

Figure 3: Example of time distributions obtained for each of the 24 source-detection fiber pairs. On the left in green is the excitation and fluorescence light path. The time the photons take to cross the medium directly depends on the distance between the probe and the tumor, thus allowing us to localize the latter. In red is the laser light crossing the tissue without exciting the fluorescence but allowing identification of tissue optical properties.

To evaluate the resolution of the method, measurements and reconstructions were conducted on prostate-mimicking phantoms in which a 45 µL fluorescent inclusion was placed, and translated with a regular step along three axes. The fluorescing inclusion was correctly localized in 100 percent of the studied cases, with a spatial accuracy below 0.15 cm (standard deviation rms) in all directions and reproducibility under 0.1 cm. Localization was possible up to a depth of 2.8 cm. Figure 4 shows an example of combined fluorescence and ultrasound co-localization on a prostate phantom.
4. Conclusion

A novel device for time-resolved fluorescence imaging of the prostate was presented. The millimetric resolution of the reconstructed fluorescence map obtained on the prostate-mimicking phantom is compatible with the size of early stage tumors. The limited depth of investigation was measured at 2.8 cm, which statistically corresponds to the most frequent location of prostatic tumors. However, several solutions are explored to push further the depth of investigation.

The bimodal probe will be tested on a set of volunteers without fluorescent marker injection during 2012, followed by clinical trials of the fluorescent markers.

References