Prostate Cancer: Computer Aided-Diagnosis on Multiparametric MRI

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ABSTRACT

Prostate cancer (PCa) is one of the most common cancers in men, being also the second most deadly cancer after lung cancer. There is increasing interest in active surveillance and minimally invasive focal therapies in PCa to avoid morbidities associated with whole gland therapy. Tumor volume represents an essential prognostic factor of PCa and the definition of index lesion volume is critical for appropriate decision making, especially for image guide focal treatment or in case of active surveillance. Multi-parametric Magnetic Resonance Imaging (mp-MRI) is the modality of choice for the detection and the localization of PCa foci. However, little has been published on mp-MRI accuracy in determining PCa volume, especially at 3T. There is insufficient evidence and no consensus to determine which of the methods for measuring volume is optimal.

The objective of this study concerns the elaboration of an algorithm for automatic interpretation of mp-MRI. We determine the accuracy of the proposed method by comparing the prostate tumor volume issued from the automated volumetric mp-MRI measurements of the tumoral region, with manual and semi-automated volumetric measurements done by and respectively with radiologists. Information issued from whole mount histopathology is used to validate the whole approach.

1. INTRODUCTION

The prostate is a gland of the male genital tract at the genitourinary intersection, located in the pelvic cavity, below the bladder. A normal prostate has a chestnut shape and can be differentiated in three distinct zones; Central zone: area surrounding the ejaculatory channels comprises 25% of the glandular tissue. This region is mainly subject to inflammatory processes. However, only 5% of the cancers come from this region; Transition zone: representing about 5% of the tissue glandular tissue, up to the age of 40 years. 20% of prostate cancers are generally originating from this area. Peripheral zone: about 75% of cancers come from this area.\textsuperscript{*}. Taking the representative example of the United States, Prostate cancer (PCa), prostate cancer (PCa) is the most common cancer in men, after skin cancer. It is also the second leading cause of death from cancer in men (after lung cancer).\textsuperscript{†}. Today it affects nearly 61% of men after 50 years. Approximately 180 890 new cases have been detected in 2016, and 26 120 deaths have been recorded.\textsuperscript{‡}. There is increasing interest in active surveillance and minimally invasive focal therapies in PCa - especially in image guided ablation - to avoid well-known morbidities associated with whole gland therapy. Tumor volume represents an essential prognostic factor of PCa\textsuperscript{1} and the definition of index lesion volume is critical for appropriate decision making, especially for image guide focal treatment\textsuperscript{2} or in case of active surveillance.\textsuperscript{3} Multi-parametric Magnetic Resonance Imaging (mp-MRI) is the modality of choice for detection and localization of PCa foci\textsuperscript{4,5}. However, little has been published on mp-MRI accuracy in determining PCa volume, especially at 3T. There is insufficient evidence and no consensus to determine which of the methods for measuring volume is optimal.

\textsuperscript{*}Canadian Cancer Society: \url{http://www.cancer.ca/en/cancer-information/cancer-type/prostate/prostate-cancer/the-prostate/?region=on}.
\textsuperscript{†}National Institute of Health - National Cancer Institute: \url{https://www.cancer.gov/types/prostate}.
The objective of this study concerns the elaboration of an algorithm for automatic interpretation of mp-MRI. The purpose of this algorithm is to support radiologists with an effective detection and a refined segmentation of the prostatic tumor volume. We determine the accuracy of the proposed method by comparing the prostate tumor volume issued from automated volumetric mp-MRI measurements of the PCa tumoral region with semi-automated and manual volumetric measurements done by experienced radiologists. Information issued from the whole mount histopathology is used for final validation.

2. PROTOCOL AND DATABASE

Our study mainly focused on moderate risk tumors (Gleason 6/7) in order to monitor its evolution. These cancers, not very aggressive, do not necessarily need treatment right away, but imperatively need to be regularly checked, in order to determine their growth. We aim at increasing the detection accuracy, in order to improve the precision, the number and the relevance of the biopsies, in order to reduce patients risk and to considerably upgrade the quality of care.

Our mp-MRI database, consolidates three MRI sequences: T2, diffusion MRI and contrast MRI. The designed algorithm needs to be able to assist radiologists in the detection of PCa, by defining its aggressiveness. Indeed, this aspect - still little developed in literature, allows a longitudinal monitoring of prostate tumors evolution. The aim of the study is to extract, from different MRI sequences, the volume of the tumor, as well as to determine its aggressiveness.

The pipeline of our method follows the following main steps: First, we apply a quantitative analysis using the segmentation of the tumor zone and prostate with a combination of region growing segmentation and superpixel method. Secondly, the qualitative analysis is used to define the tumor aggressiveness. Finally, we create the interface in order to capture and capitalize radiologist relevance feedback and test its usability. The interface is now in test at the partner hospital.

All studied patients have all mildly aggressive cancers (Gleason score 6/7), but require active surveillance. According to the routine protocol, a T2 MRI of the prostate corresponds to approximately 70 slices and a DWI to 20 slices.

2.1 Tumor volume estimation

The proposed algorithm will be applied to each 2D slice, in order to extend it through marching cubes algorithm, being so able to detect the tumor zones on full 3D sequence. After studying and testing different segmentation techniques, in order to stimulate the interaction with the radiologist, as to insure a proper traceability for the radiologist to double checked when needed, we apply 2D seed region growing segmentation. This technique consists in gradually magnifying a region around a starting pixel. Indeed, it is possible to perceive the diffusion sequence images with a high diffusion gradient factor (b), two distinct homogeneous regions are detected, corresponding to the tumor and non-tumor regions.

The method involves two steps: the selection of a seed pixel of the region to be segmented and the aggregation of the pixels according to a double criterion: the homogeneity of the intensity and the spatial adjacency of the pixels. This approach examines neighboring pixels and determines whether it should be added to the region according to the fixed threshold.

2.1.1 Selection of a germ pixel.

The seed pixel is a pixel of coordinates (x, y) in a 2D image. This pixel must be a part of the region to be segmented. In our case, the seed pixel is determined by the higher value of the pixel intensity, in a delimited zone. This zone has been defined statistically with the mean values of the main axes of 20 prostates.

2.1.2 Aggregation of pixels.

The iterative process of region growth adds the pixels to the initial region following a double criterion of homogeneity intensity and spatial connectivity. The simplest criterion is to aggregate the pixel if its intensity and the mean intensity of the pixels of the growing
region are sufficiently close.
If the intensity of the candidate pixel is close to the average of the intensities of the growing region, the pixel is merged with the segmented region. The criterion of similarity is defined by the following relation:

\[ R(s) = X \cup R(n + 1) \iff I_x - IR(n + 1) < \delta \]  

then:
R (s): segmented region
X: candidate pixel
R (n + 1): growing region
Ix: mean intensity of the candidate pixel
IR (n + 1): mean intensity of the pixels of the growing region after the nth iteration.

Once the germ pixel is found, a study is carried out in order to find the optimal similarity threshold. In order to choose the optimum threshold allowing having the entire zone of interest without incorporating the other regions, the ROC curve has been produced.
20 threshold values were tested on each slice. After searching for fractions of true positive and false positive, the threshold value applied is 0.5. Nevertheless, in the interface, the user has the possibility to change this value, to have a more precise segmentation.
One of the constraints of segmentation of diffusion sequences is the low precision of the contours. The tumor appears as hypo signal on the T2 IRM.
Therefore, T2 slices segmentation is recommended. The result of this segmentation is then combined with the segmented image of the diffusion MRI.

Figure 1. Prostate cancer on T2 weighed MRI.

Superpixel\(^7\) has been applied with success in MRI segmentation. This method makes is very compliant with complex internal structures, corresponding to groups of relatively homogeneous pixels.
According to different characteristics of the segmentation, the desired result corresponds to grouping the pixels belonging to the tumor zone under one and the same superpixel. The algorithm is initialized with Simple Linear Iterative Clustering (SLIC).\(^8\)

2.1.3 T2 segmentation.
The method begins with a phase where the centers of superpixels are initialized on a regular grid, spaced pixels

\[ S := S\sqrt{NK} \]  

With N, the total number of pixels in the image and K, the desired number of superpixels. The centers can be moved to prevent them from being on an outline of the image. This iterative method includes two steps:

1. Assigning pixels to a center CK according to a membership criterion
2. Updating the centers
The membership criterion of step 1 corresponds to a distance between CK and the pixel p. The goal is to minimize this distance defined by the formula:

\[ DSLIC^2(CK, p) = dcolo^2(CK, p) + dxy^2(CK, p)S^2c^2 \]  \hspace{1cm} (3)

when : c: pixel compactness dcolo: color distance (between pixels) dxy: difference between the positions in the current image such as:

\[(pj - xi)^2 + (yj - bi)^2 + (yibxi)^2 + dcolo^2 \]  \hspace{1cm} (4)

When c is close to zero, the superpixels are flexible and adhere to the contours of the image. When c is important, the superpixels take a more geometric form.

Figure 2. Superpixel method on T2 weighed MRI , a) with value c important, b) with a weak c.

2.1.4 Registration .

The aim of the two previous segmentations (superpixel on T2 MRI, and seed region growing on diffusion MRI), is to improve the segmentation of the tumor zone. Starting from the fact that the SLIC groups the pixels of the same intensity under the same contour, and knowing that the tumor zone is in hypo signal on the image, according to the criteria of the SLIC segmentation, the entire area of the Tumor should be grouped under the same contour (superpixel).

Finally, we superpose the contour of the grown region, on the SLIC image. In order to avoid incorporating healthy tissues into the tumor zone, we increase the number of superpixels and reduce the weight compactness of the pixels (c). Thus, each superpixel traversed by the contour will be included in the tumor zone. An image registration is applied by using the next geometric transformation: \( \min f(I_1, t(I_2)) \) when :

I1 and I2 images to be recalculated
t: transformation
f: similarity / dissimilarity criterion

In our case, only a rigid transformation is used. Indeed, a translation is performed, according to the criteria of similarity. The registration will be carried out between the sequences T2 and the scattering sequences with a low b (diffusion gradient) in order to have a maximum of homologous attributes. During the registration process, no rotation was applied.

Figure 3. Registration of DWI MRI and T2 weighed MRI.
The left-hand figure represents the superposition of the SLIC segmentation with the growth region segmentation. The white zone of FIG. is, the zone considered as a tumor. When this process is applied to each cut, it is possible to reconstruct the 3D volume from the masks found.

Figure 4. Mask of the tumoral found after combining superpixel and region growing segmentation.

2.1.5 3D representation and volume calculation.

Once all the slices are segmented, in order to have a more complete view, we perform a 3D reconstruction. This reconstruction is performed by the cubing marching algorithm \(^\S\). allowing creating a polygonal object from a scalar field in three dimensions (voxel).

In order to represent a volume, the space is divided into elementary cubes. Then, we set a density threshold and we will go through the cubic space per cube. For each cube, the number of vertices above the threshold is counted. These vertices will determine associated triangles. Depending on the number of vertices, a table is used to list all the possible topologies of triangles displayed inside the cube. Each configuration corresponds to a set of facets traced inside the volume. These triangles represent the surface of the volume to be determined. The volume element is a cube, so we have 8 vertices, 12 edges and each vertex can take 2 states. There are \(2^8 = 256\) possible configurations.

Using the symmetries of rotation and inversion of the internal / external points, one can reduce that number to 15 basic configurations.

We have therefore identified the tumor zones on the different MRI sequences. We group the slices and apply the cube marching algorithm.\(^9\)

Following the cube marching algorithm, we obtain the following 3D representations:

Figure 5. 3D representation of the tumoral volume.

The images in which we are working on are with DICOM extension. It makes it possible to standardize access to the results. These images have the advantage of containing all the desired information. Thanks to a simple "dicominfo" it is possible to retrieve a structure containing the name of the patient, the date of the examination, the size of the file, the name of the machine,... We have thus calculated the volume of the tumor; this result will be used in the interface developed to monitor the evolution of the cancer over time.

2.2 Definition of the aggressiveness

Once the tumor zones are identified, it becomes possible to calculate the aggressiveness of the tumors with the characteristics of MRI-DWI. Indeed, the apparent diffusion coefficient (ADC), can be calculated from the

\(^{9}\)Polytech Unice: \url{http://users.polytech.unice.fr/~lingrand/MarchingCubes/algo.html}.\
intensities. Indeed, aggressive cancers have less diffusion, and then appear white on the DWI. The ADC is defined by the following formula:

\[ S_1 = S_0 e^{-b\text{ADC}} \]  

where:

- \( S_1 \) is the DWI signal intensity with the highest value of \( b \)
- \( S_0 \) is the DWI signal intensity with the lowest value of \( b \)
- \( b \): is the diffusion gradient
- \( \text{ADC} \): represents the apparent diffusion coefficient

An ADC value is therefore obtained for each pixel of the ROI and then compared to the associated Gleason score.

3. RESULTS

Exact volumes of tumors, extracted from surgical specimens by an anatomopathologist, were provided to validate the accuracy of our algorithm. The algorithm was applied on 30 patients, already diagnosed with prostate cancer. The area under the curve (AUC) was used as metrics. The proposed system achieved an AUC of 0.7507. PROSTATEx challenge 2017 was conducted on quantitative image analysis methods for the diagnostic classification of clinically significant prostate lesions. From the 32 participants with 71 methods, submitted, the AUC = 0.87 +/-0.027 represents the best score. In the MICCAI 2012 challenge, The Imorphics and ScrAuto-Prostate teams achieved the highest overall scores of 0.8572 and 0.8429, respectively among the 11 teams from academic research groups and industry. ScrAutoProstate’s algorithm is a region-specific segmentation method using discriminative learning; Imorphics’ algorithm is based on the active appearance model.

In our case, the weak AUC value is due to an over-estimation of the tumoral volume. Indeed, it is possible for the user to double-check the segmentation on the interface, and to change the threshold value of the region growing segmentation, if necessary. Under the guidance of our radiologist, in order to diminish the risk of false negative (cancer tissues being judged as healthy), we intentionally overestimated the tumoral volume for each patient. The system will be implemented in the hospital partner for a routine relevance feedback.

REFERENCES