Chapter 15

BLADDER CANCER SCREENING BY MAGNETIC RESONANCE IMAGING

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Bladder cancer is the fifth leading cause of cancer-related deaths in the United States. A common test for the cancer is urine dipsticks or standard urinalysis. It is safe, but has a very poor specificity, as low as 70%. The finding is usually at a late stage and not able to provide accurate location and staging of the lesion. As the main method of investigating bladder abnormalities, fiberoptic cystoscopy is more accurate. But it is invasive, time-consuming, expensive, uncomfortable, and has risk of urinary tract infection. Recently, virtual cystoscopy (VC) has been developed as an alternative means for bladder cancer detection and evaluation. In this chapter, we present a novel mixture-based computer-aided detection (CAD) system for VC using multi-spectral ($T_1$- and $T_2$-weighted) magnetic resonance (MR) images, where a better tissue contrast can be achieved as compared to computer tomography (CT) images. As multi-spectral images are spatially registered over three-dimensional space, information extracted from multi-spectral MR images is obviously more valuable than that extracted from each (CT or MR) image individually. In addition, the urine has significantly different $T_1$ and $T_2$ relaxations compared to the bladder wall, the MR-based VC procedure can be completely non-invasive. Because bladder tumors tend to develop gradually and migrate slowly from the mucosa into the bladder wall/muscle, our focus is on the mucosa layer by mixture image segmentation. In order to obtain both geometry and texture information, we scan the bladder at two states of nearly empty and nearly full. Our CAD system utilizes fully the multi-scan and dual-state MR images for tumor detection and evaluation. Experimental results show its feasibility towards screening of bladder tumors and follow-up of recurrences.

*Keywords*: Bladder cancer, virtual cystoscopy, magnetic resonance.
1. INTRODUCTION

Bladder cancer is the fifth leading cause of cancer-related deaths in the United States, primarily in older men, with a 3 : 1 ratio of men to women. In the last decade, the occurrence of bladder malignancies has increased by 36% (Lamm et al., 1996). Over 56,000 cases of developed bladder carcinoma and more than 12,000 deaths were reported in 2002 (Jamal et al., 2002). The lifetime probability of developing the cancer is over 3% and the probability of dying from the cancer is approximately or slightly less than 1% (Cohen et al., 1992; Steiner et al., 1992). Early asymptomatic bladder cancer may be associated with occult bleeding (microscopic hematuria) or the presence of dysplastic cells in the urine.

A common test for bladder cancer is urine dipsticks or standard urinalysis measuring the peroxidase activity of hemoglobin, which is safe and inexpensive and can be performed at home. Its sensitivity can be achieved at 90% whereas the specificity is only approximately at 70% (Shaw et al., 1985). Those findings are usually at the very late stage and unable to provide accurate location and staging information of the tumor.

As most tumors appear as small growths arising from the inner bladder-wall surface in forms of polypoid, sessile, or abnormal plaques, currently available fiberoptic cystoscopy (OC) is the most accurate diagnostic procedure for detecting and evaluating the abnormalities. This method is invasive by inserting an endoscope through the urethra into the bladder. It is also uncomfortable, expensive, lacks an objective scale and has limited field-of-view (FOV). The method also has a risk of 5% to 10% rate of urinary tract infection. Patients are usually reluctant for such examination. Therefore, a minimal or non-invasive, safe, and low-cost method to evaluate the bladder would be preferred by most patients.

Recently, virtual cystoscopy (VC) techniques have been investigated as an alternative means for studying bladder abnormalities. Based on computer tomography (CT) technologies, several spiral CT scanning protocols have tested on patients and clinical VC feasibility studies have been reported (Fenlon et al., 1997; Hussain et al., 1997; Merkle et al., 1998; Vining et al., 1996). Because the earliest stages of bladder lesion development are inside the mucosa with gradual extension into bladder muscle, a desirable “visual gradient” between bladder lumen and wall is required for differentiating the
associated structures (Fielding et al., 2002; Prout et al., 1984). However, CT images cannot provide image contrast difference between the bladder wall and the lumen filled with urine. An invasive procedure is needed to obtain the contrast through bladder insufflation with room air or CO₂ via a Foley catheter. It is still less likely to obtain image contrast inside the wall for differentiation of normal and pathologically altered tissues. Therefore, CT-based VC can only detect the lesions with significantly-developed geometry information.

By magnetic resonance (MR) imaging technologies, VC has shown its potential in evaluation of bladder lesions (Chen et al., 2000; Liang et al., 1999; Li et al., 2003a). MR imaging has the potential to differentiate pathologically altered tissues from the normal ones inside the bladder wall. It also provides multi-spectral (T₁- and T₂-weighted) information, as compared to the CT image. Furthermore, the intrinsic T₁ and T₂ contrast of the urine against the bladder wall eliminates completely the invasive air insufflation procedure. MR-based VC shall outperform the CT-based VC in early screening, evaluation of staging and follow up recurrence without the invasive contrasting procedure and the extra radiation to the patients.

2. METHODS

Earliest stages of bladder lesion development are in the mucosa with gradual extension into bladder muscle. Morphological difference and texture variation could appear on the bladder wall when the bladder lumen is at two different states, full of urine or near empty. The dual states provide both geometric and texture information. To suppress motion artifacts, multi-scan of transverse and coronal multi-spectral MR images were acquired at empty and full states, respectively. Our computer aided diagnosis and detection (CAD) system focuses on the mucosa layer of the bladder wall for identifying bladder lesions.

2.1. MR Image Protocols

Multi-spectral MR images were acquired by a Phillips 1.5 T Edge whole-body scanner with the body coil as the transceiver. A spoiled-GRASS sequence was employed to acquire T₁-weighted transverse and coronal
images with parameter of $256 \times 256$ matrix size, 38 cm FOV, 1.5 mm slice thickness, 3 ms $T_E$, 9 ms $T_R$, 30° flip angle, and one-scan average. Correspondingly, an axial FSE (fast spin-echo) sequence was used to collect $T_2$-weighted transverse and coronal images with the same acquisition location and parameters, except for 96 ms $T_E$, 12167 ms $T_R$, 90° flip angle, and two-scan average.

The advantages of MR images are (1) excellent contrast by $T_1$ and $T_2$ relaxations between urine and bladder wall, resulting in a non-invasive approach, (2) good contrast for tissues within the bladder wall, resulting in a possible detection of invasive tumors, and (3) radiation free, resulting in a possible screening modality. In our approach, after the patient voided, patient was asked to drink a cup of water before MR image scan. Images of the nearly empty state of the bladder were acquired first by an acquisition protocol of 15 minutes (including scout and location image acquisition). Waiting another 15 minutes, when the patient feels bladder full, full state MR images were acquired in 15 minutes. An entire procedure takes less than an hour, an average time course of routine MR image study.

In Figure 1, significant image contrasts were observed between urine lumen and bladder wall as well as between bladder wall and other surrounding tissues in the $T_1$-weighted images (Figure 1(a)). It is noted that the bladder wall becomes thicker in the near empty states (Figure 1(b)). On the other hand, $T_2$-weighted images provide reciprocal information with a brighten urine lumen which can be distinguished more easily from other tissues (Figures 1(c) and 1(d)).

![Fig. 1. (a) One slice of a $T_1$-weighted image at the near full state. (b) One slice of a $T_1$-weighted image at the near empty state, where the bladder wall is thicker than that at the near full state. (c) One slice of a $T_2$-weighted image at the near full state, where the urine lumen could be easily distinguished. (d) One slice of a $T_2$-weighted image at the near empty state.](image-url)
Motion artifacts may be observed along the direction of spine in T1-weighted transverse images as the image acquisition time was about two to five minutes. To overcome this artifact, additional coronal images were acquired correspondingly. Our multi-scan MR scheme shall provide more information for reducing motion artifact as well as the false positive (FP) in lesion detection.

2.2. Image Segmentation

We first applied Fourier-domain based interpolation to construct isotropic voxels in the three-dimensional (3D) domain (Li et al., 2003). Following that, a partial volume (PV) image segmentation algorithm was developed to achieve tissue mixture segmentation, and then to extract the bladder wall from the mixture segmentation. The following is a brief description of the image segmentation algorithm.

Let \( Y = \{ y_{il} \}_{i=1}^{L} \) be the intensity vector of \( L \)-channel multi-spectral MR images at location \( i \) over the 3D image array of \( I \) voxels. In our study, we acquired T1 and T2-weighted images, i.e., \( L = 2 \). Assume that the images consist of \( K \) classes (or tissue types) and each class \( k \) is characterized by a Gaussian parameter vector \( \theta_k(\mu_k, \nu_k) \), i.e., the mean and variance. Let \( M \) be a set of vectors \( M = \{ m_1, \ldots, m_2, \ldots, m_f \} \), where the mixture \( m_{ik} \) reflects the fraction of tissue type \( k \) inside voxel \( i \). We utilized the expectation-maximization (EM) algorithm to achieve robust model parameter estimation (Li et al., 2003b; Liang et al., 2003). By the EM strategy, we have

\[
\mu_{kl}^{(n+1)} = \frac{\sum_{i} x_{i(k)}^{(n)}}{\sum_{i} m_{ik}} \tag{1}
\]

\[
(\sigma_{kl}^{2})^{(n+1)} = \frac{1}{I} \sum_{i} \frac{(x_{i(k)}^{2})^{(n)} - 2m_{ik}\mu_{kl}^{(n+1)}x_{i(k)}^{(n)} + (m_{ik}\mu_{kl}^{(n+1)})^{2}}{m_{ik}} \tag{2}
\]

where \( \sigma_{kl}^{2} \) is the variance of tissue type \( k \) in image \( l \) and \( x_{ik} \) is the contribution of tissue type \( k \) to the observation \( y_{il} \) and

\[
x_{i(k)}^{(n)} = m_{ik}\mu_{kl}^{(n)} + \frac{m_{ik}\sigma_{kl}^{(n)}}{\sum_{j=1}^{K} m_{ij}\sigma_{jl}^{(n)}} \left( y_{il} - \sum_{j=1}^{K} m_{ij}\mu_{jl}^{(n)} \right) \tag{3}
\]
Fig. 2. (a)–(b): A slice of T₁- and T₂-weighted images in the transverse scan. (c) The extracted mucosa layer indicating the space between the bladder wall and the lumen.

\[
(x_{ik}^{(n)})^2 = (x_{ik}^{(n)})^2 + (m_{ik} \sigma_{ik}^2)^{(n)} \cdot \frac{\sum_{j \neq k}^K (m_{ij} \sigma_{ij}^2)^{(n)}}{\sum_{j=1}^K (m_{ij} \sigma_{ij}^2)^{(n)}}.
\]  

In order to perform the PV segmentation for \{m_{ik}\}, we employed the maximum a posterior (MAP) framework, in which a Markov random field (MRF) model-based prior was applied to integrate neighborhood information (Held et al., 1997; Leahy et al., 1991; Liang et al., 1992, 1994). The developed framework iteratively estimates the model parameters through the EM algorithm and segments the voxels by MAP in an interleaved manner. Each voxel is then labeled as a mixture voxel (mixel) with different tissue percentages inside.

Based on the PV image segmentation, a mixture (mucosa) layer indicating the space between the bladder wall and lumen was extracted (Figure 2). The extracted mixture layer provides us both geometric and texture information, which can be further used for lesion detection. By choosing a seed point from the lumen, the bladder lumen could be extracted by means of region growing algorithm.

2.3. Interactive Visualization System

A real-time interactive visualization system was developed for facilitating physicians to diagnose 3D MR images. The system is composed of a display of the original dataset and segmentation results, fully interactive control on bladder skeleton for viewing the dual states of bladder at any angle and direction, and cut view of the bladder for inner surface inspection. At each state, we reconstructed both the inner and outer bladder wall from the mixture-based segmentation (Wang et al., 2002). Registration is needed for
simultaneously displaying the dual-state scans of the bladder. In this study, we calculated the central mass of the bladder and chose the central mass as a reference for the purpose of flexible registration (Chen et al., 2000). When the physician rotates the bladder in one window, the system will calculate the relative parameter, and rotate the bladder at the other three windows to display the same section of the bladder.

2.4. Detection of Bladder Lesions

From the mixture segmentation, we extracted the bladder mucosa layer, which provides us the geometric features of tissues around bladder wall. Our approach minimized the PV effects on the tissue boundaries and provided tissue growth tendency in addition to the anatomical structure of the tissues. In order to detect bladder lesions, we developed a CAD system to utilize the mixels for analyzing the features and tendency of mucosa layer for abnormalities (Wang et al., 2003). A 3D geometrical feature extraction algorithm was applied to extract the principal curvature, shape index, and curvedness of each mixel. The extracted geometry information is utilized to distinguish bladder lesions from the normal bladder wall.

For describing the local shape of the surface across through bladder 3D volume, principal direction and curvature are two important geometrical attributes of the 3D surface (Dorai et al., 1997). For a given point \( p \), we employed two quantitative measurements: the shape index \( SI \) and the curvedness \( R \). They are defined as:

\[
SI(p) = \frac{1}{2} \left[ k_1(p) + k_2(p) \right] - \arctan \left( \frac{k_1(p) + k_2(p)}{k_1(p) - k_2(p)} \right)
\]  

\[
R(p) = \sqrt{\frac{k_1(p)^2 + k_2(p)^2}{2}}
\]

where \( k_1(p) \) and \( k_2(p) \) are the principal curvatures, and \( k_1(p) \geq k_2(p) \). \( SI \) represents what kind of type the surface is, while the \( R \) represents what "curve" the surface is.

Eight representative shapes and their corresponding shape index values are provided in Figure 3. Normal bladder wall usually has regular shapes that are described as "elliptic curvature." That is, the shape description of the inner bladder wall should be "spherical cup" or "trough." This shape
Fig. 3. Eight representative shapes on the shape index scale. Top (from left to right): spherical cap (1.0), dome (0.875), ridge (0.75), and saddle ridge (0.625). Bottom (from left to right): spherical cup (0.0), trough (0.125), rut (0.25), and saddle rut (0.375).

description can be applied to distinguish the bladder lesion from the normal bladder wall. Since this shape information only reflects a relative relation between this mixel and its neighborhood in a local region, we call it as “local” geometrical shape information. Besides the local shape information, we also integrated the corresponding “global” shape information into our CAD scheme to reduce false positive (FP) detection rate. The “global” shape index and curvedness are derived from a convolution operation on the “local” shape index and curvedness (Wang et al., 2004). We evaluated the corresponding “global” shape index and found its variance remains smooth for most of the irregular bladder wall section. Therefore, all mixels whose “global” shape description is different from that of the normal bladder wall were extracted first. Based on the connectivity in the 3D space, all selected mixels were clustered into several groups, which are called as initial bladder lesion candidates.

The initial bladder lesion candidates can be further divided into three groups: real bladder lesions, noise candidates, and mimic candidates. Noise candidates are usually generated due to MR imaging scan, patient movement, or image segmentation error, which induce several little protuberance regions on the bladder wall. According to our observation, they are usually very small with a tiny spherical top section. On the other hand, the mimic candidates are generated due to normal tissue shape variations on the
bladder wall. Both noise and mimic candidates are called FP candidates. In order to eliminate FP candidates, we utilized the following filtering steps in our CAD method.

Step 1. If the total voxel number of the candidate is small, this candidate will be classified as a FP candidate. Similarly, if the size of the continuous spherical top in either local or global geometrical measures is small, this candidate will be classified as a FP candidate.

Step 2. If the position of the initial lesion candidate whose “local” and “global” general shapes does not lie in the spherical shape domain, this candidate is a FP candidate.

3. RESULTS

Two patients and four healthy male volunteers were recruited in this study. Figure 4 shows the outer view of a transverse and coronal scans of bladder at

Fig. 4. The outer view of a transverse (left) and coronal (right) scans of a bladder at the two states of full (top) and near empty (bottom).
two states of full and near empty. Figure 5 shows a cut view of the bladder. The presented multi-scan virtual cystoscopy system provides physicians for texture analysis and visualization of bladder structure. Physicians can easily locate those locations where abnormal (morphological and pathological) tissues were observed from inner or outer view of bladder wall. Lesion detection by our CAD scheme were also performed for both healthy volunteers and patients. In the patient study as shown in Figure 6, one lesion with a size of 25–30 mm was detected at both states. A small one with 8–10 mm size was detected in the full state while missed in the near empty state. When the presented CAD scheme further examined the texture information at the corresponding location in the near empty state, this small one was detected as a candidate. The CAD results were further examined and verified by physicians using our interactive visualization system.

4. DISCUSSION AND CONCLUSIONS

The proposed MR image-based virtual cystoscopy is a non-invasive, safe, and patient-comfortable procedure. We have developed a MR image acquisition protocol to acquire multi-scans on two states of the bladder for mitigating motion artifacts and obtaining both geometric and texture information. We further developed a PV segmentation scheme to extract the bladder wall mucosa layer from the multi-spectral MR images. A flexible registration was explored to integrate the information from the multi-scans of the dual states. A display system was developed to visualize the integrated information. A CAD scheme, which combines both “local” and “global”
Fig. 6. One lesion with size of 25–30 mm was detected at both the near empty state (top) and full state (bottom left). A small one with size of 8–10 mm was detected in the full state (bottom right) and missed in the near empty state when only geometrical information is used. By the use of the texture information, the small tumor was detected in both states.

shape index and curvedness, was also developed to identify candidates quickly and then present them to the physician for final assessment. From the presented pilot patient study, we conclude that information extracted from multi-spectral MR images contains more valuable information than that from each image individually. The dual states of the bladder provide dynamic (both geometric and texture) information. The multi-scan (transverse and coronal) images mitigate the breathing motion artifacts. The developed CAD system with flexible registration and inner and outer wall visualization shows the feasibility towards non-invasive mass screening of bladder tumor and evaluation of following recurrence.

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References