In-vivo bladder tumor stratification using Confocal Laser Endomicroscopy

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Abstract

Confocal laser endomicroscopy (CLE) is a novel optical technique to obtain in-vivo microscopic imaging of tissue. In urology, this technique can potentially be used for real-time bladder cancer diagnosis and grading of bladder tumors. However, the assessment of the CLE images is quite elaborative with six CLE features to evaluate, and a varying interobserver agreement. Therefore, there is a need for a reproducible and reliable interpretation of CLE images. To this end, a unique dataset of in-vivo bladder tumors imaged with CLE was obtained. These 66 suspicious lesions, comprised with 50 normal urothelium, from 53 patients will be analysed using a recurrent convolutional neural network.

1 Introduction

Bladder cancer is the most common malignancy of the urinary tract for both men and women. White-light cystoscopy (WLC) is used for the visualisation of the urothelium, and is therefore of major importance for diagnosis and treatment management of bladder tumor patients. Nonetheless, WLC does not provide essential information on the grading of the tumor and is therefore inconclusive on patients diagnosis and prognosis [1]. Therefore, lesions as detected by WLC will be endoscopically resected for histopathological examination as well as treatment of the patient. This histopathological examination is needed to assess the grade and stage of the tumor. A schematic representation of the various grades in the bladder can be seen in Figure 1. Confocal laser endomicroscopy (CLE) has the potential to provide this histopathological grading information. CLE is a high-resolution optical imaging technique in which a fluorescent dye is excited by a low-power laser. By administrating a non-specific fluorescent dye into the bladder, the extracellular matrix of the bladder mucosa can be visualised.

Figure 1: The tumor grades as can be present in the bladder, in which urothelial dysplasia and reactive atypia are defined as benign lesions. Figure adapted from hexvix.com.
The high recurrence rate combined with a low mortality rate of bladder cancer requires long and intensive follow-up of patients. This follow-up comprises the examination of the bladder mucosa with WLC. When combined with real-time histopathologic information, WLC could result in better treatment decision making. In the future, this could decrease the costs associated with treatment and follow-up of bladder cancer patients. However, the current six criteria for histopathologic decision making based on the CLE movies are available but embedded in clinical practice [2]. This can be attributed to the novelty of the technique, the elaborate scoring method with variable interobserver agreement and the relatively low concordance rate with the histopathologic examination. Therefore, there is a need for a reproducible and reliable interpretation of CLE images.

2 Materials & Methods

2.1 Patient selection

Patients with a suspected primary or recurrent bladder tumor, that were scheduled for endoscopic resection of the tumor, were recruited in the Academic Medical Center (AMC, Amsterdam). All patients signed a written informed consent before they were included in the study. A total of 73 patients was included in the study. After applying the inclusion criteria of this study, 53 patients with 66 tumors were eligible for this study. The patient selection is illustrated by the flowchart in Figure 2. In total, 23 patients were diagnosed with high-grade (HG) cancer, comprising a total of 27 HG lesions and one benign lesion. A total of 19 patients were diagnosed with low-grade (LG) cancer, with 26 LG lesions and one benign lesion. Eleven patients, with 13 benign lesions, were not diagnosed with cancer. Finally, a region of healthy urothelium, if present, is examined with both histology and CLE for every patient [3].

2.2 Data acquisition

The CLE movies were acquired using the Cellvizio 100 series (Mauna Kea Technologies, Paris, France), in combination with the Cystoflex UHD-R probe (Mauna Kea Technologies, Paris, France). This probe has a 2.6 mm outer diameter, and can be introduced through the working channel of a rigid cystoscope. The images that were obtained by the probe had a field of view of 240 µm, with a 1 µm lateral resolution and image depth ranging between 50 µm and 65 µm. The framerate of the video was between 8 and 12 frames per second. The probe is loosely positioned on the tissue, and the papillary character of many bladder tumors results in a field of view that might only be partially filled with tissue.

2.3 Image pre-processing

After exporting the movies from the Cellvizio system, the contrast of the individual frames was automatically optimized using the Cellvizio Viewer1. Every image was automatically sorted on data

1Available via www.maunakeatech.com, free of charge.

Figure 2: Flow chart of the included patients.
content of the images, e.g. the number of edges in the image and the variation in grey value throughout the image, to exclude non-informative images. Subsequently, this selection was confirmed by two expert observers (M.L. and E.I.M.L.L.). Examples of included and excluded frames can be seen in Figure 3.

2.4 Classification

All lesions are classified using a recurrent convolutional neural network, and results are expected to be available in July. A total of 107,000 frames is selected from 116 different regions (including normal urothelium) derived from 53 patients.

3 Discussion

A unique dataset of in-vivo bladder tumors imaged with CLE was obtained. CLE has the potential to be of major importance in the management of bladder cancer. To exploit its assets, good concordance with the histopathologic examination is required. The suggested pre-processing of the image frames only excludes frames without any functional information. More extensive pre-processing is likely to improve results. Future implementations of this method are aimed at the real-time grading of the tumor. Therefore, labour intensive and subjective pre-processing should be avoided.

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References

