Detection of Bladder Urothelial Carcinoma Using In Vivo Noncontact, Ultraviolet Excited Autofluorescence Measurements Converted into Simple Color Coded Images: A Feasibility Study

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Purpose: A difficulty in nonmuscle invasive bladder cancers is the diagnosis of flat and small lesions during white light cystoscopy. We assessed a prototype that measures ultraviolet laser induced autofluorescence for endoscopic detection of nonmuscle invasive bladder cancer.

Materials and Methods: We compared spectroscopic results with histological findings in 3 groups, including normal urothelium, papillary tumors and flat lesions. The developed method is based on exciting the fluorescence of molecules naturally present in tissue using ultraviolet laser pulses. The diagnostic signal was converted into the intensity ratio of the emitted light at approximately 360 and 450 nm. This ratio depends on the histopathological state of the tissue. The signal was converted into a simple color coded image, in which green indicates normal tissue and red indicates neoplasm.

Results: A total of 14 patients were included in analysis. At 360 and 450 nm excitation wavelengths the overall fluorescence intensity of bladder tumors was clearly decreased compared to that of normal urothelium regardless of tumor stage or grade. At the 308 nm excitation wavelength the shape of the tumor spectra, including carcinoma in situ, was markedly different from that of normal or nonspecific inflammatory mucosa. The correlation between red images and tumor in the specimen was 100%. No absolute intensity determinations were required since a definite diagnosis was established based on the fluorescence intensity ratio at 360 and 450 nm.

Conclusions: This feasibility study confirms the functionality of our clinical prototype for the noncontact imaging detection of nonmuscle invasive bladder cancer via an endoscope using ultraviolet excited autofluorescence measurements.

Key Words: urinary bladder, urothelium, cystoscopy, optical imaging, carcinoma in situ

Abbreviations and Acronyms

AM = autofluorescence measurement
CIS = carcinoma in situ
OCT = optical coherence tomography
PDD = photodynamic diagnosis
TURB = transurethral bladder resection
UV = ultraviolet
WLE = white light endoscopy

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See Editorial on page 000.

FLAT bladder lesions, ie CIS, are often overlooked during routine diagnostic procedures because of their poor visibility under WLE.[1] These lesions are missed or easily confounded with ordinary inflammatory cystitis. To decrease the limitations of the current detection methods new techniques have been developed, such as narrow band imaging, Raman molecular imaging and OCT, which allow better visualization of bladder tumors or more ac-

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curate prediction of histopathological diagnoses in real time.[2–5]

Currently, photodynamic diagnosis using commercially available photosensitizing agents such as hexyl aminolevulinate has been approved to enhance tumor detection.[6–8] Hexaminolevulinate, a porphyrin precursor currently used in blue light endoscopy, is the only approved drug for use in an exogenous PDD system to detect nonmuscle invasive bladder cancer. CIS detection using PDD is much better than detection using simple WLE.[9–11] However, the problem of the cost of blue blight cystoscopy can be an issue that hinders the adoption of this technology.[1,11–13] The diagnostic sensitivity of PDD is up to approximately 96% for CIS diagnosis compared to 73% for WLE.[7] Also, the requirement of a minimal exposure time (urothelium and hexaminolevulinate) of approximately 1 hour before fluorescence cystoscopy is a drawback for the patient.

As an alternative approach to localize invisible neoplasms, endogenous fluorophores in tissue can be used. The spectrum of tissue autofluorescence correlates with the histopathological state due to changes in tissue metabolism or tissue structure.[14] We assessed the ability of an endoscopic clinical prototype based on UV laser induced AM converted into color coded images to detect bladder carcinoma.

MATERIALS AND METHODS

Experimental Setup

There was no commercially available medical catheter with good light transmission from 300 to 600 nm. Therefore, a completely new imaging catheter that could transport the UV induced fluorescence image was conceived in the laboratory and produced in cooperation with 2 industrial partners (Schindler, Freiburg and Thales Optische Systeme, Hessen, Germany). The catheter was divided into the illumination channel, which transports the 308 nm excitation light to illuminate the bladder tissue, and the imaging channel, which acquires the induced fluorescence image to an external spectral separation assembly and the intensified imaging sensor.

The imaging channel of the catheter contains 400 fused silica fibers (FVP050055065, Polymicro Technologies, Phoenix, Arizona), each with a 65 μm outer diameter. The illumination channel is a single 300 μm fiber (FVP300330370, Polymicro Technologies). On the proximal side a special plug-in connector was designed for fast, easy coupling to the 308 nm laser source. Overall catheter length is approximately 2 m. This length enables comfortable manipulation during endoscope insertion. The only semirigid part is the distal 310 mm, which was designed to be introduced into the working channel of a standard rigid cystoscope (fig. 1). The distal part ends in a tiny titanium capsule 3 mm in diameter. This capsule integrates 2 micro-objectives arranged side by side, including one to diffuse the illuminating light and the other to capture the image.

The UV enhanced imaging micro-objective was developed for noncontact tissue measurements at distances from a few mm to several cm. We used biocompatible EPO-TEK® 353ND Epoxy glue to assemble the objectives.

The imaging channel of the catheter was plugged into the external detection system. A fused silica lens condensed the rays into a parallel beam spectrally divided into 2 parts by a dichroic long pass mirror at 420 nm at 45 degrees (420DCLP, Omega Optical, Brattleboro, Vermont) (fig. 2). The 2 resulting spectrally divided images were filtered once more with bandpass filters to enhance spectral accuracy and the signal-to-noise ratio. The greatest numerical distance between the different diagnostic criteria was achieved by choosing a UV bandpass filter centered at 358 nm with a narrow bandwidth of 25 nm (358BP25) for the UV channel and a bandpass filter cen-

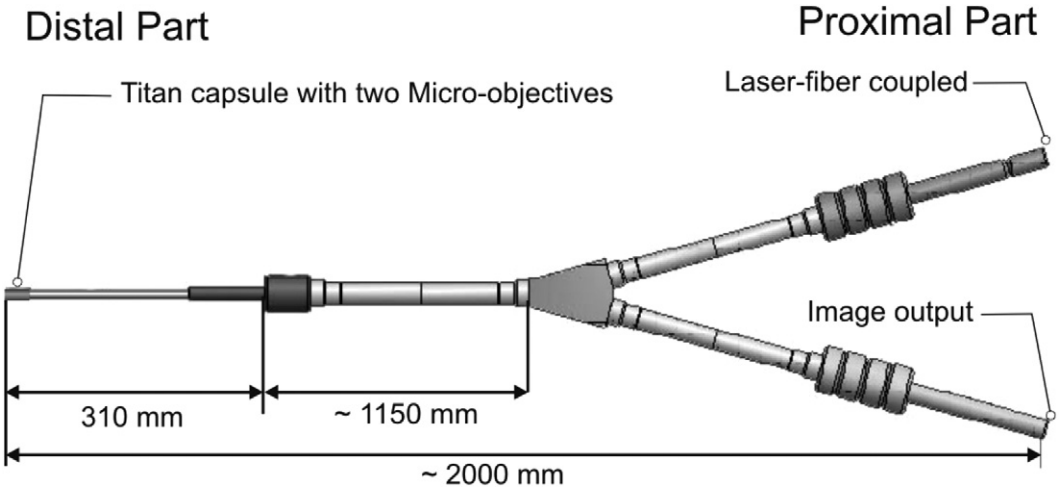

Figure 1. Developed UV imaging catheter. On distal side 2 micro-objectives allow tissue excitation at 308 nm and emitted fluorescence image acquisition. On proximal part imaging channel is separated from excitation arm.