Emerging optical techniques in advanced cystoscopy for bladder cancer diagnosis: A review of the current literature

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ABSTRACT

Background and objective: The current standard for the diagnosis and followup of bladder cancer remains white light cystoscopy, despite its well-known limitations. The aim of this paper is to review the current literature on three optical diagnostics that have been developed to improve the performance of white light cystoscopy: photodynamic diagnosis, narrow-band imaging and optical coherence tomography.

Materials and Methods: A PubMed search was performed for all articles on bladder cancer and photodynamic diagnosis, narrow-band imaging, and optical coherence tomography. Relevant papers on the working mechanism or clinical performance of the techniques were selected.

Results: Photodynamic diagnosis and narrow-band imaging both aim to improve the visualization of bladder cancer. Both techniques have demonstrated an improved detection rate of bladder cancer. For photodynamic diagnosis, decreased residual tumor rates and increased recurrence free survival after photodynamic diagnosis-assisted transurethral resection have been shown. Both techniques have a relatively high false positive rate. Optical coherence tomography is a technique aiming at real-time noninvasive pathological diagnosis. Studies have shown that optical coherence tomography can accurately discriminate bladder cancer from normal bladder mucosa, and even suggest that a reliable estimation of the stage of a bladder tumor can be made.

Conclusions: Photodynamic diagnosis is the technique with most evidence of clinical effectiveness to date, but low specificity is limiting a widespread use. For the novelties, narrow-band imaging, and optical coherence tomography, more evidence is needed before these techniques can be implemented in daily urological practice.

Key words: Diagnosis, fluorescence cystoscopy, imaging, narrow-band imaging, nonmuscle invasive bladder cancer, optical coherence tomography, photodynamic diagnosis, urothelial carcinoma

INTRODUCTION

Worldwide, about 357,000 of new bladder cancer cases are being diagnosed each year, which makes bladder cancer the 7th most common cancer in males and the 17th most common cancer in females.[1] Approximately 75% of patients present with non-muscle invasive disease and, therefore, have a relatively good prognosis

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in terms of cancer-specific survival. However, in up to 75% of these patients the cancer will recur despite transurethral resection (TUR) and adjuvant intravesical instillations with either chemotherapy or immunotherapy.[2] Because of this high recurrence rate, lifelong follow-up with cystoscopy and cytology and often repeated treatments are required, which make bladder cancer one of the most expensive cancers of today's medical practice.[3]

In several fields efforts have been made to improve the management of these patients.

First, the role of bladder cancer screening has been studied extensively. The goal of screening, which is mainly based on hematuria detection by dipstick tests, is to identify the disease in an earlier stage in order to improve the chance of favorable outcome. However, to date there is no evidence that screening does achieve this goal, nor in which population the screening should take place and with what test.[3] In addition, many studies have been conducted on

urinary markers, which are based on detection of antigens, changes in cellular morphology or molecular genetic alterations in urine samples. These markers have been developed to potentially serve as a noninvasive test to replace cystoscopy during followup or as a prognosticator at initial diagnosis. To date, no marker or combination of markers can outperform cystoscopy nor serve as a reliable prognostic tool.[4,5] Attempts have also been made to replace cystoscopy with novel imaging modalities, such as virtual cystoscopy. This technique is based on 3D digital reconstruction of CT or MR images of the contrast or air-filled bladder and could possibly serve as a noninvasive technique to evaluate the bladder mucosa. Studies have shown that it is feasible to perform a virtual cystoscopy, but at present the sensitivity is not sufficient yet to replace cystoscopy.[6,7] Because of the lack of possible therapeutic intervention and the inability to detect flat lesions or changes in color of the mucosa, it can be questioned whether this technique will ever replace cystoscopy.

Despite the introduction of these new modalities, the current standard for initial diagnosis as well as followup remains the direct visualization of the bladder mucosa by cystoscopy.

STILL THE DIAGNOSTIC STANDARD: WHITE LIGHT CYSTOSCOPY

Cystoscopy is an ancient technique that was first attempted in 1806 by Philipp Bozzini.[8] His "Lichtleiter" was composed of aluminum tubes with several angled mirrors to project the internal image to the human eye and a single candle to serve as a light source.[8] Since this first prototype, many advancements have been made, among which are the development of resectoscopes, video cameras, charge-coupled devices (CCDs), and flexible scopes.[9]

Although operator-dependent, the sensitivity and specificity of white light cystoscopy range from 62-84% and 43-98%, respectively.[10] Especially the detection of small papillary bladder tumors and satellite lesions as well as carcinoma *in situ* (CIS) is known to be suboptimal with white light cystoscopy.[10] This is expressed in the high early recurrence rate after TUR,[11] because "what the eyes cannot see, the hands cannot resect." In order to decrease the number of tumors that are overlooked or not completely resected during TUR, it is important to improve the endoscopic visualization of bladder tumors.

Once a tumor has been detected by white light cystoscopy, it can be difficult to accurately predict the stage or grade based on its visual appearance.[12] Nevertheless, many urologists nowadays will opt for surveillance once a small papillary tumor recurs in a patient with a history of low grade, nonmuscle invasive bladder cancer (NMIBC).[13] In order to increase the safety of this strategy (i.e., not to defer active

treatment of high grade or invasive lesions), it is desirable to have some kind of real-time pathological information during cystoscopy. The same goes for laser fulguration of bladder tumors, where no pathological confirmation is available due to lack of tissue specimen. In addition, real-time pathological information is desired to discriminate between inflammatory lesions due to previous instillation therapy and CIS, which both can present as red lesions.

While white light cystoscopy remains the current standard for diagnosis and followup, further improvements of the technique are clearly needed. The aim of the following review is to provide a timely overview of three relatively new optical techniques that have been introduced to advance endoscopy either by improving visualization of bladder tumors or by providing real-time pathological information.

MATERIALS AND METHODS

A literature search by PubMed was performed to retrieve all published articles on photodynamic diagnosis, narrow-band imaging, and optical coherence tomography as a diagnostic tool for bladder cancer. We used the search terms "bladder cancer" and "optical coherence tomography" or "photodynamic diagnosis" or "fluorescence cystoscopy" or "narrow-band imaging." Papers written in English and concerning clinical evidence of the technique or explanation of working mechanism were selected. Reference lists of retrieved papers were scrutinized for additional relevant articles. Throughout the paper, the strength of the evidence on which the statements in the review are based is expressed in a narrative fashion.

EMERGING TECHNIQUES IN ADVANCED CYSTOSCOPY

Photodynamic diagnosis
Photodynamic diagnosis or fluorescence cystoscopy aims to improve the visualization of bladder cancer based on cystoscopic detection of fluorescent signals from neoplastic tissue. This fluorescence is accomplished by the intravesical administration of photosensitizing agents (5-aminolevulenic acid (5-ALA) or its derivative hexaminolevulinate (HAL)) which cause selective accumulation of photoactive porphyrins in rapidly proliferating cells (e.g., tumor cells). The solution containing the photosensitizing agents is instilled in the bladder via a transurethral catheter prior to surgery. The timing of instillation depends on the type of agent used: approximately 1 hour before surgery for HAL versus approximately 2-3 hours for 5-ALA. By illuminating the mucosa with blue-violet light, the neoplastic cells appear red or pink against a blue background [Figure 1].[10]

Multiple studies have demonstrated that photodynamic diagnosis, in addition to white light cystoscopy, improves the detection of bladder cancer, for both papillary lesions

and CIS.[14-18] A recent meta-analysis, which comprised 12 prospective trials, revealed that the overall additional detection rate of photodynamic diagnosis was 20% (range 5-49%). If specified for CIS only (seven trials), this was 39% (range 17-78%).[19] However, the false-positive detection rate of photodynamic diagnosis was also higher if compared to white light cystoscopy (8.8-62.5% vs. 7.1-47%, respectively).[19] False-positive fluorescence can be induced by inflammation, recent TUR, or tangential illumination of the bladder mucosa.[14-18] False-positives will also occur more frequently in patients who recently have had intravesical therapy, especially bacillus Calmette-Guérin.[20,21] Whether the improved detection also results in more complete resection can be examined by assessing the residual tumor rate at second resection up to 6 weeks after the initial photodynamic diagnosis-assisted TUR. In the meta-analysis, the average residual tumor rate for white light-TUR and photodynamic diagnosis-assisted TUR was 35% and 15%, respectively (OR 0.28).[19] The positive effect of photodynamic diagnosis on therapeutic outcome was also demonstrated in a recent randomized, multicenter phase 3 study: the recurrence rate at 9 months was statistically significantly reduced with 10% for HAL-assisted TUR.[22] These results were confirmed by a longer recurrence-free survival if compared to white light TUR: 15.8-27% higher at 12 months and 12-15% higher at 24 months.[19] This difference seems to extend on the longer term (over 5 years).[23,24] Photodynamic diagnosis has a good safety profile: only mild to moderate adverse events may occur after instillation.[14-18] Based on the decreased recurrence rate of photodynamic diagnosis-assisted TUR and consequently decreased need for re-TUR, one can hypothesize that this technique will have a positive effect on health care costs. Only few model-based analyses have investigated the cost-effectiveness of photodynamic diagnosis assisted TUR to date.[24-26] Two studies suggest that the technique indeed reduces the overall expenses, when taking into account the acquisition and usage costs of the photodynamic diagnosis system.[24,25] However, these studies are derived from 5-ALA data only and based on German health economics, which may hamper extrapolation of the outcome.[27] In a very recent extensive systematic review from the United Kingdom, the cost-effectiveness of photodynamic diagnosis was only borderline.[26]

In summary, photodynamic diagnosis improves detection of NMIBC and photodynamic diagnosis-assisted TUR decreases residual tumor rate and seems to increase recurrence-free survival. The relatively high false-positive rate is the major limitation to date. More multi-institutional studies are needed to confirm the additive value of photodynamic diagnosis on the long-term and to further evaluate its cost-effectiveness.

Narrow-band imaging

Narrow-band imaging is a straightforward optical technique designed for endoscopy to enhance the visualization of (sub) mucosal vessels. The working mechanism is based on the filtering of white light into two narrow bandwidths of light that are centered around 415 nm (blue light) and 540 nm (green light), which penetrate tissue only superficially and are specifically absorbed by hemoglobin.[28,29] Because bladder tumors tend to be well vascularised, narrow-band imaging will increase the contrast between these lesions and normal bladder mucosa [Figure 2].

In 2007, Bryan *et al.* were the first to describe the additive value of narrow-band imaging in flexible cystoscopy performed on 29 patients in followup for NMIBC. In 12 (41%) patients, 15 additional lesions were detected by narrow-band imaging only.[30] Although these lesions appeared to be malignant, histopathological confirmation was not available. Since this preliminary report, four studies have been published on the value of narrow-band imaging cystoscopy for the detection of NMIBC.[31-34] Although the studies had a different set-up (flexible vs. rigid cystoscopy, etc.) and different patient population (outpatient followup vs. scheduled for TUR, etc.), all showed improved bladder cancer detection for narrow-band imaging over white light cystoscopy. Based on the data provided in the manuscripts, we calculated the additional detection rate of narrow-band imaging (over white light cystoscopy) to range from 17% to 31%.[30-32] Overall, in 22–56% of NMIBC patients narrow-band imaging detected additional tumors.[30-32,34] It has to be noted that in the studies of Herr *et al.*[32,33] and Naselli *et al.*[34] white light cystoscopy and subsequent narrow-band imaging cystoscopy were performed by the same urologist, which may introduce some observational bias, as is acknowledged by the authors. However, the improved detection rate of
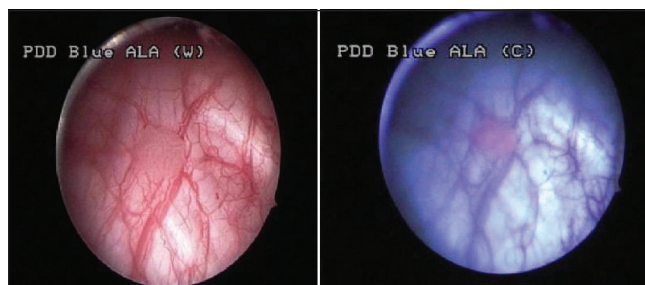

Figure 1: Small pTaG2 bladder tumor, increased visibility with photodynamic diagnosis (right) versus white light cystoscopy (left).

Figure 2: Field of pTaG2 bladder tumor, increased visibility with narrow-band imaging (right) versus white light cystoscopy (left).
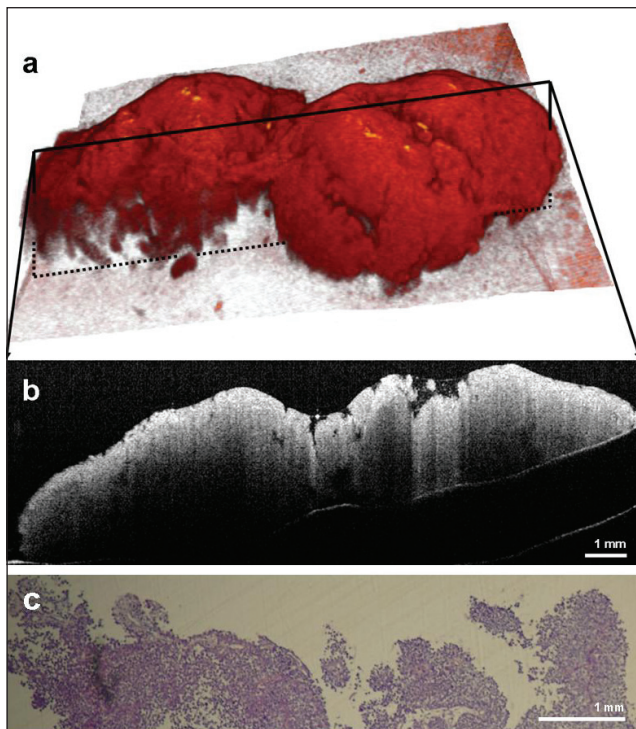
Figure 3: Bladder tissue specimen of papillary pTaG2 tumor. (a) 3D optical coherence tomography image (*ex vivo* biopsy measurements with 1310 nm optical coherence tomography system, Innervision, Santec Corporation). (b) 2D optical coherence tomography image of the same biopsy (*ex vivo* biopsy measurements with 1310 nm optical coherence tomography system, Innervision, Santec Corporation). (c) Corresponding hematoxylin and eosin-stained histology.

narrow-band imaging was also demonstrated in the study conducted by the authors of this review where white light cystoscopy and narrow-band imaging cystoscopy were performed independently by various urologists.[31] The reported false-positive rates ranged from 32% to 36%.[32-34] Besides this relatively high false-positive rate, another limitation of this technique was noted by two groups: in case of severe hematuria, visualization is suboptimal because of the absorption of the narrow-band imaging light by circulating erythrocytes.[31,32] Herr *et al.* also performed a study on the interobserver variability of narrow-band imaging cystoscopy. Captured images of narrow-band imaging cystoscopy performed on 50 patients on followup for NMIBC were independently reviewed by four urologists. All observers performed equally, suggesting that there is no learning curve for narrow-band imaging.[35]

In summary, to date only a few studies with relatively small patient numbers have been conducted on the value of narrow-band imaging for the detection of bladder cancer. Nevertheless, the results of these series are very promising and collectively indicate improved detection of NMIBC, though with relatively high number of false-positives. The major advantage of narrow-band imaging is the fact that no intravesical agent is needed before application. Further prospective, preferably randomized, comparative studies need to be conducted to prove these initial results.

Importantly, future research should also focus on the effect of narrow-band imaging on residual tumor rate and recurrence-free survival as well as cost-effectiveness of the technique.

Optical coherence tomography

Optical coherence tomography is a noninvasive optical technique that can provide cross-sectional images containing subsurface tissue information. It is the optical equivalent of B-mode ultrasound imaging, except that it is based on depth-resolved detection of backscattered light instead of reflected sound waves. This results in images with a high resolution of up to 2 μm (approaching the resolution of microscopy) and a maximum imaging depth of 2–3 mm.[36] Because optical coherence, tomography does not require a medium or direct contact with the tissue under investigation; it is well suitable for endoscopic applications (by inserting a (flexible) optical coherence tomography probe through the working channel of a cystoscope) [Figure 3].[37]

Over the last decade, several studies have been conducted on the ability of optical coherence tomography to detect bladder cancer, both *ex vivo*[38-40] and *in vivo* (e.g., endoscopically).[41-45] These studies have shown that it is feasible to distinguish the different bladder wall layers including lamina propria and muscularis propria with optical coherence tomography.[38,40,46] Furthermore, optical coherence tomography can differentiate urothelial carcinoma (UC) from normal bladder mucosa with a sensitivity and specificity ranging from 84% to 100% and from 78% to 90%, respectively.[40,41,44,45] The discrimination of normal urothelium versus UC is based on qualitative analysis of the optical coherence tomography images: in normal tissue, the urothelium is uniform and the bladder wall layers are clearly delineated based on their different backscattering capacities, whereas UC shows increased backscattering, heterogeneity, and broadened urothelium in case of papillary tumors.[38,40,43,47] Two groups demonstrated that optical coherence tomography also has the power to determine the stage of a detected UC. Lerner *et al.* demonstrated that optical coherence tomography could discriminate Ta, T1, and T2 tumors with a sensitivity of 90%, 75%, and 100%, respectively and a specificity of 89%, 97%, and 90%, respectively. The group of Zagaynova *et al.* evaluated 28 cases with optical coherence tomography during TUR and discrimination between muscle-invasive and nonmuscle-invasive tumors could be done with a sensitivity of 100% and specificity of 77%.[48] Although the studies on optical coherence tomography as a bladder cancer diagnostic appear very promising, the technique does have some limitations that need to be addressed. False-positives may be induced by scarring[45] or inflammation of the mucosa.[44] In general, for large tumors with extensive broadened urothelium imaging depth will be impaired, thus compromising the staging ability of optical coherence tomography.[45] However, Zagaynova *et al.* have shown that this problem may be overcome by applying optical

coherence tomography to the tumor base.[48] In addition, the technique is not very suitable for bladder mapping because of its limited field of view.

In summary, optical coherence tomography is a noninvasive optical technique that can provide in-depth tissue information. Although the first studies indicate the capability of optical coherence tomography to discriminate UC from normal mucosa and even to give some stage information, more clinical series are needed to confirm these promising results. Special attention should be given to the potential of optical coherence tomography to diagnose CIS, since this highly aggressive disease is difficult to detect with white light cystoscopy. In addition, the effect of prior intravesical therapy on the specificity of optical coherence tomography should be examined.

DISCUSSION

The three optical techniques discussed above all have their strengths and weaknesses. However, they also have different goals: whereas photodynamic diagnosis and narrow-band imaging both focus on improvement of the visualization of bladder tumors, optical coherence tomography focuses on real-time pathological diagnosis. Narrow-band imaging and photodynamic diagnosis both can aid in reducing the high rate of early recurrences, because more radical resection can be performed due to better visualization of UC. In addition, in case of positive cytology and negative white light cystoscopy, photodynamic diagnosis (and perhaps also narrow-band imaging) can improve detection of CIS. Optical coherence tomography may possibly assist in differentiation between inflammation and CIS, which both can present as red lesions. It may also aid in accomplishing a more complete resection, by measuring the resection margins with optical coherence tomography and extending resection if vital tumor is still present. In addition, optical coherence tomography may provide pathological diagnosis for the patients with recurrent tumors under followup or before laser treatment.

As mentioned above, all three techniques discussed in this review may aid in accomplishing a more complete resection of bladder cancer. In theory, this consequently will result in lower residual tumor rates and also in longer recurrence-free survival, as already has been proven for photodynamic diagnosis. One can hypothesize that the effect of these techniques may render adjuvant intravesical instillations that aim at reducing recurrences redundant. This is now being evaluated in an international prospective trial randomizing patients to white light-TUR with adjuvant intravesical therapy or photodynamic diagnosis assisted TUR without adjuvant intravesical therapy (HELENA protocol, personal communications, 26-04-2010, Th.M. de Reijke).

When comparing the two visualization techniques, detection rates and false-positive rates seem to be comparable, but photodynamic diagnosis is more established with stronger supporting evidence so far. Photodynamic diagnosis has been recommended in the European guidelines for the detection of CIS.[49] In addition, the contrast provided with this technique seems more apparent than with narrow-band imaging. However, given the practical disadvantages of photodynamic diagnosis (need for intravesical instillation of fluorescent agent and high costs), narrow-band imaging may be a valid alternative for the detection of NMIBC. Because narrow-band imaging does not rely on intravesical instillation of fluorescent agents, the technique is also well suitable for use in the outpatient clinic.

In future, one may consider combining some of these optical techniques so that the strengths of one technique can be used to overcome the limitations of the other. For example, the combination of photodynamic diagnosis and optical coherence tomography in an animal study led to increased specificity of diagnosing UC in rat bladders.[50] These results were also shown in human studies that combined photodynamic diagnosis with optical coherence tomography: in one study on 26 patients with suspicion of UC, the false-positive rate of photodynamic diagnosis only (84%) could be decreased (78.7%) by adding optical coherence tomography. In other words, the 16% positive predictive value of photodynamic diagnosis increased to 43% if combined with optical coherence tomography.[48] Recently, Schmidbauer *et al.* showed that adding optical coherence tomography to photodynamic diagnosis increased the overall diagnostic accuracy: sensitivity and specificity were respectively 69.3% and 83.7% for white light cystoscopy, 97.5% and 78.6% for photodynamic diagnosis, and 97.5% and 97.9% for photodynamic diagnosis combined with optical coherence tomography.[51] These results suggest that combining optical coherence tomography with photodynamic diagnosis can reduce the number of unnecessary false-positive biopsies. To our knowledge, no studies on the combination of narrow-band imaging and optical coherence tomography have been published yet.

Optical coherence tomography and narrow-band imaging may also be applied as diagnostics in the upper tract in future. For photodynamic diagnosis, it seems that this is not feasible due to problems with instillation of the fluorescent agent and inevitable tangential illumination in the ureter causing false-positivity. Narrow-band imaging is not hampered by tangential light beams nor requires fluorescent agents and, therefore, may improve the detection of CIS or small papillary lesions, which can be easily missed by conventional imaging studies of the upper tract (retrograde studies, IVP or CT). Optical coherence tomography may overcome the limitations encountered in upper tract biopsies, which tend to have a high rate of nondiagnostics due to insufficient or low-quality specimen. By applying optical

coherence tomography measurements of an upper tract lesion before taking a biopsy (or even replacing biopsy), the diagnostic accuracy may be increased. These days, a correct pretreatment stage and grade is becoming quite essential because more and more upper tract tumors are being treated endoscopically and organ-sparing.

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