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Review of current optical diagnostic techniques for non-muscle-invasive bladder cancer

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Introduction Urinary bladder urothelial cell carcinoma is one of the most commonly diagnosed cancers in Europe. After prostate, lung and colon cancers, bladder cancer rates as the fourth most common cancer in men in the world.
Urinary bladder cancer detection, treatment, and staging have traditionally been based on an endoscopic examination – cystoscopy.
Material and methods A Medline, and Web of Science database search was performed on September 2015 without setting time limits, using the terms 'bladder cancer' in conjunction with 'cystoscopy', 'diagnosis', 'detection', 'fluorescence', 'blue-light', 'PDD', 'narrow band imaging', 'molecular imaging', 'optical coherence tomography' or 'confocal laser endomicroscopy'.
Results The new imaging techniques can be classified according to their scope as macroscopic, microscopic, and molecular. Macroscopic techniques, such as narrow band imaging, are similar to white light cystoscopy; however, they help visualize even very minute lesions in the bladder mucosa by means of contrast enhancement.
Microscopic imaging techniques, such as optical coherence tomography and confocal laser endomicroscopy, provide high-resolution cross-sectional views of vesicular tissues, which resemble images obtained by histopathological examination. Therefore, these are referred as 'optical biopsy'. Molecular imaging methods offer highly specific real-time visualization of cancer cells and their differentiation from healthy tissue, by combining optical imaging with fluorescent labeling of elements such as antibodies.
Conclusions In this article we present a review of studies and literature concerning modern optical diagnostic techniques for non-muscle-invasive bladder cancer. We present available technology with its advantages and disadvantages, and studies regarding its effectiveness.

Key Words: bladder cancer ‹› cystoscopy ‹› diagnosis

INTRODUCTION

Urinary bladder urothelial cell carcinoma (BC) is one of the most commonly diagnosed cancers. After prostate, lung and colon cancers, BC rates as the fourth most common cancer in men in the world [1]. Approximately 75% of over 330 000 diagnosed BC cases in males in 2015 can be at the non-invasive stage (i.e. without infiltration of the muscularis mucosae: stages Ta, T1, Tis), and could thus be successfully treated endoscopically [2, 3].

Due to the combined effect of intensive routine follow-up, and multiple therapeutic procedures, the treatment costs of non-muscle-invasive BC are very high. Therefore, BC is a considerable burden for both patient and national health funds [4]. Owing to high overall BC one-year and five-year recurrence rates (61% and 78%, respectively), the frequent need for repeated TURB procedures and life-long endoscopic follow-up has elevated the cost of BC treatment to one of the highest of all cancer treatments [5, 6].

The natural course of urothelial BC may vary, ranging from low-grade tumors, which recur after transurethral resection of bladder (TURB) in one-third of cases, to high-grade tumors, which tend to have high recurrence rates and often progress to incurable metastatic disease. However, progression rates depend on a variety of factors. According to EAU Guidelines, in order to predict short- and long-term recurrence and progression risks, the European Organization for Research and Treatment of Cancer (EORTC) has developed a scoring system. The system is based on the six most significant clinical and pathological factors characterizing BC [3]. A corresponding scoring model for BCG-treated patients has been published by the Club Urológico Español de Tratamiento Oncológico (CUETO) [7].

Subtle urothelial changes or small structural bladder pathologies cannot be detected by ultrasound or other imaging techniques including computed tomography [CT] or magnetic resonance imaging [MRI]. Therefore, BC detection and staging is based on an endoscopic examination, namely white light cystoscopy (WLC), aided by secondary procedures [8].

MATERIAL AND METHODS

A Medline and Web of Science database search was performed in September 2015, without setting time limits, using the terms 'bladder cancer' in conjunction with 'cystoscopy', 'diagnosis', 'detection', 'fluorescence', 'blue-light', 'PDD', 'narrow band imaging', 'molecular imaging', 'optical coherence tomography' or 'confocal laser endomicroscopy'. Boolean operators (NOT, AND, OR) were also used in succession to narrow and broaden the search. Autoalerts in Medline were also run, and reference lists of original articles, review articles, and book chapters were searched for further eligible articles. The search was limited to English, Polish, German and Spanish literature. Articles that did not address the topics were excluded, and the full text of the remaining articles was subsequently reviewed.

In this article we present a review of literature concerning modern optical diagnostic techniques for non-muscle-invasive bladder cancer. We present currently available technology with its advantages and disadvantages, and studies regarding its effectiveness.

DISCUSSION

WLC was first introduced in the mid 1800s. Despite constantly emerging innovations, WLC has its significant limitations. Firstly, WLC does not allow for cancer grading or determination of infiltration status. Secondly, while sufficient in identifying papillary lesions of over 0.5 cm in diameter, WLC can sometimes be inadequate in identifying small or flat solid tumors, including carcinomas in situ (Cis), whose detection rates in WLC do not exceed 58–68% [9, 10]. The high risk of Cis oversight may lead to incorrect, conservative treatment rather than a radical approach; this may ultimately lead to progression of BC into incurable metastatic disease.

Finally, the use of WLC does not allow for thorough examination of surgical margins and the detection of small or satellite tumors, contributing to 40–70% rates of residual tumors found in the revision TURB performed 4–6 weeks after primary procedure [11, 12]. On the other hand, the high rate of incomplete resection may also be a result of technical difficulty and lack of training in TURB. Passing a straight instrument into an oval structure poses a challenge in removing some tumors because of their location and the desire to avoid bladder perforation.

Limitations of WLC have led to the emergence of new optical imaging techniques, which optimize BC detection and resection. Some of them, such as fluorescence cystoscopy (FC), also known as photodynamic diagnosis (PDD), have already become well-established diagnostic methods, while others are still undergoing clinical trials [13].

The new imaging techniques can be classified according to their scope as macroscopic, microscopic and molecular.

Macroscopic techniques, such as PDD and narrow band imaging (NBI), are similar to WLC; however, they help to visualize even very small lesions in the bladder mucosa by the addition of contrast enhancement.

Microscopic imaging techniques, such as optical coherence tomography (OCT) and confocal laser endomicroscopy (CLE), provide high-resolution cross-sectional views of vesicular tissues. These views resemble images obtained by histopathological examination. Therefore, microscopic imaging techniques are referred as 'optical biopsy'.

By combining optical imaging with fluorescent labelling of elements such as antibodies, molecular imaging methods offer highly specific real-time visualization of cancer cells and their differentiation from healthy tissue.

Fluorescence cystoscopy

FC or PDD, also known as blue-light cystoscopy (BLC), offers fluorescent images of the inner bladder walls. Prior to cystoscopy, a photosensitizing agent is administered intravesically. All urothelial cells absorb this agent; however, it is excessively

accumulated by cancer cells. Following exposure to blue light (wave lengths of 380–480 nm), cancer cells emit a characteristic red fluorescence, which is easily discernible against the blue background of healthy urothelium. In the human body, endogenous 5-ALA is the first component in the heme biosynthesis pathway and does not fluoresce itself [14]. Administration of exogenous 5-ALA overwhelms the metabolic capacity of the physiological pathways, resulting in accumulation of protoporphyrin IX – a fluorescent precursor of the heme molecule. Protoporphyrin IX is mainly accumulated in cancer cells, as cancer cells express lower levels of the ferrochelatase, the enzyme, which inserts iron into protoporphyrin IX to form the heme molecule. Subsequently, protoporphyrin accumulation can be detected through exposure to blue light. BC detection using PDD, with 5-aminolevulinic acid (5-ALA) as a photosensitizer, is a well-known method and has been reported in a number of publications since the early 1990s.

A number of clinical studies have demonstrated the efficacy of PDD with 5-ALA as a diagnostic technique that increases detection rates of BC, including residual tumors and Cis. In contrast to WLC, it also improves recurrence-free survival [15]. Unfortunately, the disadvantages associated with 5-ALA, such as its hydrophilicity at physiological pH and low solubility in fats leading to poor bioavailability, result in a non-uniform distribution of protoporphyrin IX across tissues. The need for long-lasting bladder 5-ALA instillations before cystoscopy, together with the rapid disappearance of tissue fluorescence (photobleaching) during cystoscopy, considerably limit the use of 5-ALA in everyday practice. These limitations have been overcome with the introduction of the hexyl ester derivative of ALA (hexyl aminolevulinic acid, HAL, Hexvix®). Hexvix is characterized by better physicochemical properties, including higher fat solubility. Following its relatively rapid and uniform absorption by urothelial cells, HAL is transformed into 5-ALA by an esterase, allowing PDD to be performed.

Over the last two decades, more than 200 studies on FC have been published. There have been six meta-analyses on PDD with either HAL or 5-ALA based on over 80 randomized, prospective and retrospective cohort clinical trials [16]. In 2013 two new meta-analyses and one systematic review summarizing studies of the use of HAL-BLC [4, 17, 18] have been published. All these analyses demonstrated PDD to be significantly more effective than WLC in terms of BC detection and recurrence reduction. Despite the fact that PDD does not differentiate between high-grade and low-grade tumors, a number of studies showed this technique to have a significantly higher rate of Cis detection than conventional cystoscopy [10, 18]. The meta-analysis by Burger et al. showed that 22.6% patients had tumors that had been previously undetected by WLC. Moreover, 25.4% of Cis lesions were detected only by PDD [18]. The same meta-analysis found that patients at low risk of recurrence also benefit from HAL-PDD. The use of this technique prevents recurrence in one in six low risk patients over a period of 12 months. Therefore, establishing the final diagnosis during the first TURB procedure with PDD may affect further treatment, including the need for BCG immunotherapy or cystectomy. Furthermore, higher rates of tumor detection may reduce the number of patients requiring another TURB procedure and the need for histopathological evaluations.

On the basis of these findings, HAL-PDD is currently recommended by the European Association of Urology (EAU) and International Consultation on Urological Diseases (ICUD) experts, as well as the individual national associations of Germany, Scandinavia, and the UK [10, 18–23]. Accordingly, HAL-PDD should be used in every patient with primary non-muscle-invasive BC (NMIBC) undergoing first-time TURB. The purpose of BLC is to improve the quality of TURB procedures and to reduce the risk of recurrence, thus decreasing rates of repeated TURB and re-hospitalization.

All guidelines emphasize the role of PDD in follow-up of high-risk patients; those with high-grade BC, Cis, and multifocal tumors. A further benefit can be achieved in all patients presenting with positive urine cytology and negative WLC. In these patients, HAL-PDD, instead of the usually fruitless 'blind' random biopsy, allows for detection of invisible Cis. Current literature shows, that the use of PDD with the first TURB is cost-effective. It is possible, that its use with subsequent TURB procedures would also be recognized as advantageous, but as of now, there has not been available data to support this hypothesis.

If no lesion has been found during PDD cystoscopy, the upper urinary tract or the prostate urethra may need to be examined for urothelial cancer. It should be mentioned, that almost half of late recurrences of BC after failed BCG therapy are not located in the bladder, but rather in the upper urinary tract or urethra [24].

HAL-PDD is practically free from side effects; however, the rate of false-positive diagnoses reaches 10–12% and may have lower specificity than WLC [18]. This phenomenon is caused by both autofluorescence by endogenous tissue fluorophores and the high capability of immune cells to accumulate the photosensitizing agent. Due to photosensitizer accumulation,

tissues with inflammatory and postinflammatory lesions may yield false results following intravesical treatment. Hence, the use of PDD shortly after (6–12 weeks) intravesical chemotherapy or immunotherapy is not recommended [19, 20]. Results can be also misrepresented in case of bleeding during the procedure or when evaluating tangential sections. Nonetheless, it is believed that the rate of misdiagnoses, including those following intravesical therapy, depends on the examiner's experience and decreases rapidly as the learning curve rises [16].

Nowadays, numerous high-quality studies supporting the positive effects of HAL-PDD on patients' quality of life and treatment cost reduction are available. These reports evaluate not only the one-time intravesical fluorophore administration, but also the cost of PDD equipment [6, 25–28]. Based on the data obtained from insurance providers, public health care facilities, and specially developed calculation models, it has been demonstrated, that the use of HAL-PDD with the TURB procedure provides cost reduction and a rise in quality-adjusted life years (QALY). Although PDD implementation does not bring savings immediately, it helps to reduce the number of procedures and hospitalizations in the long follow-up [16].

Narrow band imaging (NBI)

NBI is a relatively new macroscopic technique of endoscopic imaging that improves tumor detection without the need for intravesical contrast administration. By using special filters, the light spectrum is reduced to its blue (415 nm) and green (540 nm) components, which are well absorbed by haemoglobin. As a result, enhanced contrast between the mucosa and blood vessels is achieved and pathologicaly well-vasculated lesions are clearly visible. Like WLC and PDD, NBI does not allow for tumor grade differentiation and determination of infiltration status, yet, it improves detection of non-invasive BC [29]. NBI technology (Olympus Corp. Tokyo) is available both in the form of integrated videocystoscope and as a camera that can be attached to a regular cystoscope. Operating this equipment is very simple: during the examination, the urologist can switch repeatedly between NBI and white light.

NBI has been approved for clinical use both in the EU and the US. However, there have only been a few studies published examining its effectiveness. In 2007, Bryan et al. were the first to publish NBI cystoscopy findings in 29 patients with recurrent bladder tumors [30]. The authors found 15 additional tumors in 12 patients, in comparison to those detected with WLC. A prospective randomized single-centre study of 220 cases demonstrated better non-invasive carcinoma detection rates than those achieved with WLC (95% *vs.* 68%, respectively) [31]. The effect of NBI on therapeutic outcomes has not yet been confirmed; however, it seems obvious that better visualization would offer better local control, and fewer recurrences. Additionally, the use of new technologies forces the urologist to perform better and more careful cystoscopies with higher detection rates of tumors even with WLC. An ongoing large prospective international study of the Clinical Research Office of the Endourological Society (CROES) aims to evaluate the effectiveness of NBI [32]. Preliminary findings are to be published soon.

Based on similar technology, Storz has recently introduced the Storz Professional Image Enhancement System (SPIES). The addition of different colours (e.g. orange or violet) to the image obtained by reflected blue- and green-spectrum light offers three different viewing options depending on needs in various clinical situations. SPIES is currently at the early clinical study stage of investigation.

Microscopic imaging

Microscopic imaging techniques, including OCT and CLE, are currently in the early stages of experimental research. Both of these techniques reveal the histopathologic structure of the tumor during cystoscopy.

The OCT technique provides real-time high-quality cross-sectional images of superficial tissues. Similarly to ultrasonography, this technique utilizes the signal created by waves reflected from various tissue surfaces. In contrast, however, it uses the waves of the near-infrared light spectrum (890–1,300 nm). This allows for tissue imaging at 10–20 mm resolution and up to 2 mm in depth, which is sufficient to identify most urothelial tumors. OCT differentiates between abnormal and healthy urothelium, and although it does not differentiate tumor grades, it allows for assessment of tissue infiltration status. Thanks to the probe, compatible with the cystoscopy equipment, tumor stage assessment can be conducted during cystoscopy and TURB procedures. Several available studies estimated the sensitivity of the technique at 90-100% and specificity at 65-89% [33, 34]. Despite the initially promising findings, OCT is difficult to use in its present form in everyday practice. Scanning the entire bladder to search for neoplastic lesions is a laborious task. Schmidbauer et al. reported a significant improvement in both sensitivity and specificity of the examination with the use of OCT combined with PDD [35].

CLE uses a fiber optic probe bundle inserted into the lumen of an operating cystoscope and a fluorescent

agent administered intravesically to obtain real-time microscopic images of the examined tissue. CLE has already been successfully used in the diagnostic endoscopy of gastrointestinal tumors. With the reduced calibre of the probe, the technique can be used in endourology. Because of its high resolution (2–5 μm) and depth of imaging penetration (240 μm), CLE helps to achieve detailed images of tissue structure and evaluate the appearance of individual cells. This technology makes it possible to obtain data on tissue differentiation status and thus distinguish high-grade and low-grade urothelial carcinomas, as well as identify non-invasive carcinomas during cystoscopic examination. However, it does not improve tumor visualization of occult lesions. In upper tract tumors CLE may be complementary to a bad quality biopsy, yet, in BC, suspected areas must be resected by TURB to make an accurate diagnosis. The first atlas created to determine diagnostic and tumor grading criteria, based on CLE images from 66 patients with bladder tumors, is already available [36]. As in the case of OCT, a limitation of this technique is the fact that it offers a very small field of view with limited tissue penetration. There are ongoing studies on computerized fusion of images from multiple fields of view.

New imaging techniques

Raman spectroscopy

Raman spectroscopy (RS) relies on the inelastic scattering of photons following interaction with intramolecular bonds. RS uses infrared light (785–845 nm) to excite intrinsic chemical bonds in order to create optical contrast. In *ex vivo* studies, RS was able to differentiate the normal bladder wall and low-/high-grade BC, and determine BC invasiveness [37]. Those findings were confirmed in *in vivo* human studies [38]. Limitations include time shift (1–5 seconds), weak signals and a narrow view area. Recently, surface-enhanced Raman scattering (SERS) nanoparticles have been shown to enhance the signals from CARS [39].

Multiphoton microscopy

Autofluorescence of cells and extracellular matrix components in multiphoton microscopy (MPM) is obtained after the simultaneous absorption of two or more photons of lesser energy. MPM makes use of intrinsic tissue fluorophores such as NADH, FAD or collagen. In a recent study, *ex vivo* tissue MPM analysis allowed differentiation of normal urothelium from malignant structures [40]. Limitations of MPM include lack of visualization of nuclear morphology and shallow penetration, thus not allowing formal cancer staging.

Scanning Fiber Endoscopy

Scanning Fiber Endoscopy (SFE) employs a 1.2 mm wide angle, colour, high-resolution flexible endoscope. The image is generated by red, green and blue laser scanning of tissues and analysis of backscattered light. SFE can be used in automatic devices to create a panoramic view of the mucosa [41].

Ultraviolet autofluorescence

Ultraviolet autofluorescence is designed to distinguish normal, inflammatory and cancerous urothelium by discriminating variances in their molecular contents. After exposure to UV laser radiation, endogenous fluorophores (e.g. NAD and tryptophan) emit autofluorescence diagnostic signals that are converted into an intensity ratio between different wavelengths. A recent *in vivo* pilot study demonstrated the feasibility of this method in differentiating BC from normal mucosa. However, further studies are needed to establish this method's role in BC detection [42].

Molecular imaging

Molecular imaging is achieved by combining optical (macroscopic and microscopic) imaging and intravesical administration of fluorescent-labeled elements, such as antibodies, peptides, and other molecules, which selectively bind to cancer cells. A recently published study demonstrated the use of the fluorescent-labeled antibody CD47 to detect bladder cancer by combined CLE and PDD techniques [43]. Given that the monoclonal antibody CD47 is currently being evaluated for its possible use in targeted therapy against urothelial carcinoma, this may be an attractive prospect of combining targeted therapy and targeted molecular imaging.

CONCLUSIONS

Current advances in endoscopy and endoscopic urogenital surgery are the result of two centuries worth of ingenuity and the perseverance of countless researchers and innovators. These new technologies introduced the concept of minimally invasive surgery and revolutionized treatment not only in BC, but in all urologic neoplasms.

The most recent advances in optic imaging of the urinary bladder offer a unique opportunity to improve

bladder cancer detection and assessment that can allow for the use of specially-tailored therapies. Additionally, a combination of macroscopic and microscopic techniques may improve diagnostic accuracy.

HAL-PDD is currently the only imaging diagnostic technique for bladder cancer approved in both the EU and US, and recommended by most international urological associations for routine diagnosis and treatment of urothelial carcinoma. The emerging new techniques of microscopic and macroscopic imaging, often combined with PDD, may dramatically alter the current management of bladder cancer. Urologists and oncologists should be aware of these emerging prospects.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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