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TOPIC PAPER

Application of new technology in bladder cancer diagnosis and treatment

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Abstract Recent advances in imaging technology may offer the ability to augment bladder cancer diagnosis, staging, and treatment. Fluorescence cystoscopy has been shown in numerous clinical studies to improve the detection of papillary and flat bladder lesions over conventional cystoscopy. Photosensitizing agents like aminolevulinic acid (ALA) and its derivative hexaminolevulinate (HAL) have undergone the most extensive investigation. Prospective clinical trials have demonstrated improved diagnostic ability, enhanced tumor resection, and reduced tumor recurrence. Optical coherence tomography is an emerging technology that shows promise in revealing subsurface information about bladder lesions in real-time, potentially leading to more accurate staging. Narrow-band imaging may augment standard endoscopic tools by providing increased contrast between normal and abnormal tissue. Virtual cystoscopy may allow non-invasive tumor diagnosis, treatment planning, and surveillance. We aim to provide an overview of the strengths and weaknesses of these imaging modalities and examine their potential impact on the diagnosis and management of bladder cancer.

Keywords Bladder cancer · Fluorescence · 5-Aminolevulinic acid · Optical coherence tomography · Narrow-band imaging · Virtual cystoscopy

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Introduction

Bladder cancer is the most expensive of all malignancies treated in the United States (US) from diagnosis to death [1, 2]. Regular endoscopic exams, surgical and medical interventions, and repeated imaging all contribute to a large financial expenditure. With nearly 70,000 new diagnoses of bladder cancer expected in 2008, the fiscal burden of bladder cancer to the patient and healthcare system is expected to continue to rise [3].

Fortunately, the majority of all newly diagnosed bladder cancers are non-muscle invasive urothelial carcinomas confined to the mucosa or lamina propria. Frequently, however, bladder cancer takes a protracted course stemming from its propensity to recur [4]. While the majority of low-grade tumors do not progress, up to 20% of non-muscle invasive lesions can proceed to muscle-invasive or metastatic cancer [5]. Additionally, patients with tumors associated with carcinoma in situ (CIS) have a significantly greater risk of progression.

Although some factors that influence the rate of recurrence, such as tumor size, multifocality, and tumor genetics, are unchangeable, one way to reduce tumor recurrence may be to more completely resect the original lesion(s). What appears to be tumor "recurrence" may actually be residual tumor left behind or lesions missed during diagnostic and therapeutic cystoscopy [6]. The quality of resection can be variable and may account for differences in recurrence rates when bladder tumors of similar characteristics are compared across multiple centers. Improved visualization of bladder lesions may facilitate more complete resection and detection of occult lesions, thereby reducing tumor burden. Moreover, since most bladder lesions are found prior to muscle-invasion and metastasis, early diagnosis, accurate staging, and aggressive intervention offer

the opportunity to intervene prior to progression to a life-threatening disease.

While the goals of diagnosis and treatment of bladder cancer remain focused on reducing the burden of disease and extending life expectancy, in light of ever-rising healthcare costs, judicious application of new diagnostic strategies must be pursued. We review several emerging imaging technologies as well as available evidence for their widespread application that may improve bladder cancer diagnosis, including fluorescence cystoscopy, optical coherence tomography, narrow-band imaging, and virtual cystoscopy.

Current imaging tools

White light cystoscopy (WLC) remains the imaging modality that is the gold standard for primary diagnosis and management of bladder cancer. Traditional imaging techniques, such as ultrasonography, excretory urography, and computed tomography, lack the resolution to detect small papillary and flat lesions. Consequently, direct visual inspection via cystoscopy and histopathologic examination through tumor biopsy continue to be the mainstays of bladder cancer management.

Developments in technology have continued to improve our ability to examine the pathology of the bladder through cystoscopy. Advances in materials and techniques have yielded improved light sources and smaller instruments, enhancing visualization and facilitating intervention. Flexible cystoscopes have evolved from their rigid counterparts, decreasing patient discomfort and increasing accessibility. With the advent of miniaturized microchips and improved sensor technology, digital flexible scopes have been introduced. Charged couple device (CCD) distal chip sensors and complementary metal oxide sensors (CMOS) obviate the need for fragile fiber optics, improving durability while simultaneously providing superior optical resolution [7]. Digital technology has provided high-definition resolution and enhanced images, yielding better optical performance than ever before.

The premise behind WLC as a diagnostic tool is that it allows detection of lesions that are conspicuous within the visual spectrum. For the majority of bladder lesions, notably papillary tumors, WLC performs quite well. In fact, for lesions that can be "seen", experienced urologists have excellent ability to discriminate benign from malignant lesions. Cina et al. illustrated that practitioners were able to reliably distinguish cancerous from non-cancerous lesions by WLC alone with 100% sensitivity and specificity [8].

However, even under the best optical conditions, WLC has its limitations. While useful in identification of malignancy, visual appearance has been shown to be unreliable in determining tumor grade or level of invasion [8]. Flat lesions, like CIS, can be particularly visually subtle and easily overlooked in up to 50% of lesions [9]. Missing such a lesion could significantly impact a patient's management and outcome [10].

Further limitations in the use of WLC can be seen in endoscopic-guided tumor resection where residual tumor and inadequate staging, especially in high-grade T1 disease, occur. Several studies have investigated performance of a second TUR shortly after initial diagnosis of T1 tumors and demonstrated residual tumor present in 43–62% of cases [11–13]. It has been postulated that the significant recurrence rate of bladder cancer can be attributed in part to non-visualized residual tumor left behind after incomplete resection [6]. Moreover, comparing clinical staging to pathological staging after radical cystectomy, Shariat et al. demonstrated understaging of the primary tumor in 42% of cases, suggesting inadequate tumor sampling as a contributing factor [14]. While WLC remains the current standard of practice in bladder cancer diagnosis and management, better tools for detection, staging, and guidelines for treatment clearly are needed.

Fluorescence cystoscopy

Photodynamic diagnosis (PDD) offers the ability to augment detection of neoplastic tissue through fluorescent enhancement. As applied to urology, this technology may allow identification of urothelial lesions that are not readily visualized with conventional WLC, namely small papillary transitional cell carcinomas and CIS. Early detection and treatment of these lesions may result in decreased rates of recurrence and improved clinical outcomes.

Mechanism of action

Generating fluorescence requires a photosensitive substance, or fluorophore, and appropriate electromagnetic stimulation. A fluorophore is a molecule that efficiently absorbs photons of a particular wavelength and subsequently emits photons of a lower energy and longer wavelength. The specific emission profile of a fluorophore can permit localization and enhancement of particular sites of interest for targeted therapy.

Historical perspective

Multiple fluorophores have been explored in the detection of bladder cancer. Tetracycline was first described as a systemic agent by Whitmore in 1964; however this substance required special ultraviolet equipment for fluorescence and was abandoned in the 1970s [15]. Kelly first

proposed a hematoporphyrin derivative as a potential fluorescent agent in bladder cancer diagnosis in 1975 [16]. However, early work with porphyrin-related substances was limited by side effects of systemic administration and the need for complex detector equipment required because of low-intensity fluorescence. In the 1990s, 5-aminolevulinic acid (5-ALA) was described with the advantages of intravesical application and better fluorescence [17]. More recently, hypericin, a derivative of St. John's wort initially investigated as an anti-viral agent, has shown promise as a photosensitizer and fluorescent marker [18].

Porphyrin-related substances

Of the fluorophores applied in urology, 5-ALA is the most studied and utilized agent. Exogenous ALA induces accumulation of the fluorescent substrate protoporphyrin IX (PpIX) preferentially in neoplastic or rapidly proliferating cells. Exposure to blue light (380–480 nm) under these conditions allows identification of cancerous and pre-cancerous lesions [19]. Hexylester hexaminolevulinate (HAL) is an ester derivative of ALA with increased lipophilicity and better tissue solubility.

5-ALA and HAL (Hexvix, Photocure, Oslo, Norway) have the most evidence supporting their clinical application. Many retrospective studies and, more recently, prospective multicenter trials have shown fluorescence cystoscopy with 5-ALA or HAL to be superior to WLC in detecting bladder cancer. In the largest series to date using 5-ALA, Hungerhuber et al. examined 875 patients and reported 23.7% of all biopsies found to be malignant were missed by WLC, showing 92% sensitivity for fluorescence cystoscopy over 76% for WLC [20]. Four published prospective multicenter trials involving HAL showed an increase in overall detection rate for papillary lesions ranging from 12 - 23% over WLC [21–24]. In addition to better papillary tumor detection, improved diagnosis of CIS has also been observed. In a pooled analysis of three phase III multicenter trials investigating HAL [22, 24, 25], Liu et al. showed a fluorescence detection rate of CIS of 87% versus 75% for WLC ($P = 0.006$) [26]. With more accurate diagnosis, Jocham and co-workers demonstrated that better post-operative treatment was possible in over 20% of patients with bladder tumors [22]. This finding supports previous studies with 5-ALA, which showed better resection rates of primary tumors [27, 28], and randomized controlled, long-term trials, which have proven lower recurrence rates at up to 8 years of follow-up [29, 30]. Similar results from the largest phase III multicenter trial with 789 patients at centers in North America and Europe examining HAL will soon be published, confirming improved bladder cancer detection and a reduction in tumor recurrence following HAL-guided treatment (Photocure press release, Oslo, Norway, 12 September 2008).

Intravesical preparations of 5-ALA and HAL have eliminated systemic effects and show excellent tolerability. The main side effects reported are local symptoms related mainly to the cystoscopy itself and not the photosensitizing substrate. Clinical trials have shown no significant differences in adverse events between patients undergoing fluorescence cystoscopy and those undergoing WLC [22, 23].

Porphyrin-related fluorescence cystoscopy has some shortcomings. Both ALA and HAL exhibit limited depth of penetration, restricting the evaluation of more invasive lesions. Photobleaching, or loss of fluorescence, is also a factor limiting the amount of time for examination to about 30 min [31]. Finally, false positive rates have been a particular area of concern. Jocham et al. found false detection rates with HAL to be slightly higher than with WLC (37% versus 26%) [22]. Similarly, Grossman and co-workers showed a false positive rate of 39% with HAL compared to 31% with WLC [23]. Inflammation, intravesical therapy, and hyperplasia have been reported sources of false positive fluorescence [32]. Taking these factors into account along with increased operator experience may help to mitigate the intermediate specificity observed. With specificity reported in the range of 43–64%, some studies have shown fluorescence cystoscopy to be no different than WLC [21, 33]. Currently, HAL is the only fluorophore approved in Europe for use in the diagnosis of bladder cancer. It is currently under review for regulatory approval in the US.

Hypericin

In efforts to improve fluorescence cystoscopy, investigators have begun to explore the intravesical use of hypericin. Proposed advantages of this plant derivative are decreased susceptibility to photobleaching, improved specificity, and equipment requirements identical to those for the porphyrin-related substrates. D'Hallewin and colleagues reported 94% sensitivity for hypericin-induced fluorescent detection of CIS and 95% specificity, which was superior to 5-ALA and HAL, in the largest series to date [34]. This study showed excellent tolerability and fluorescence up to 16 h after instillation. Low solubility may represent a challenge in the application of hypericin. Recent studies have investigated the use of solvents, such as polyvinylpyrrolidone and albumin, to improve water solubility [35, 36]. Examination of these new aqueous formulations of hypericin demonstrated overall tumor detection sensitivity and specificity ranging from 82–95% to 53–91%, respectively. The positive characteristics of this fluorophore seem to warrant further investigation.

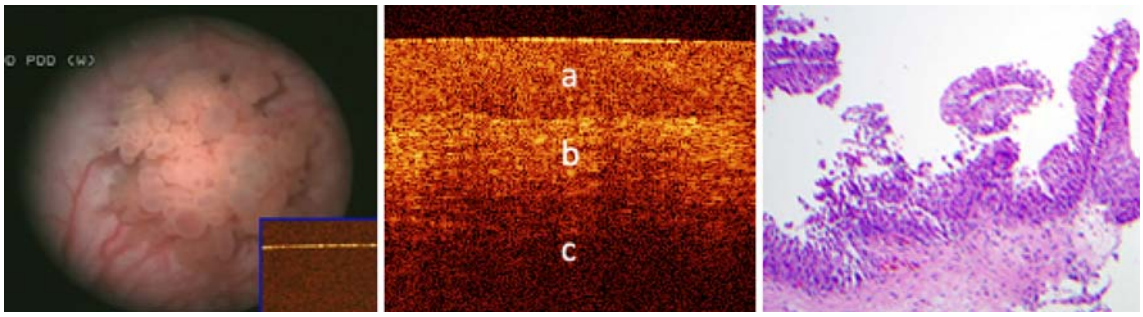

Fig. 1 Endoscopic view of a papillary bladder tumor (*left*). OCT demonstrates the mucosal layer (**a**) is expanded, but intact, without evidence of invasion (*center*). The lamina propria (**b**) is bright and clearly defined, while the muscularis layer (**c**) appears dark below. Histologic analysis shows a TaG1 transitional cell carcinoma (*right*)

Optical coherence tomography

Optical coherence tomography (OCT) is a novel technology that provides real-time, high-resolution, cross-sectional imaging of biological tissue. Utilizing near-infrared light and the unique backscattering pattern of specific tissue characteristics, it permits detection of microarchitectural features to a resolution of 10–20 μm in a fashion similar to B-mode ultrasound [37]. Compared to high frequency ultrasound, OCT is able to distinguish structures up to 10–25 times smaller [38]. OCT has been utilized for imaging of retinal tumors, gastrointestinal pathology, cervical dysplasia, and cutaneous disorders. The feasibility of in vivo detection of human bladder pathology by OCT was demonstrated by Zagaynova and colleagues [39]. Current endoscopic implementations of this technology allow real-time examination and simple integration with standard cystoscopic instruments.

As an adjunct to visual inspection, OCT can provide unique information about underlying tissue microstructure to a depth of 1–2 mm that may augment diagnosis and improve staging of bladder tumors. OCT is able to resolve layers of the bladder and distinguish benign from malignant characteristics (Fig. 1) Studies have demonstrated the efficacy of OCT as a diagnostic tool for bladder cancer. Manyak et al. [40] reported 100% sensitivity and 89% specificity for classifying lesions as benign or malignant in 24 patients. In a series of 32 patients, Goh et al. [41] showed 100% sensitivity, 90% specificity, and 100% negative predictive value for detection of muscle-invasion. This study suggested that disruptions of the bladder wall from erosion, scarring, or granuloma could result in false positive results. Contemporaneous examination with OCT may help to increase the yield of biopsy and tumor resection by minimizing unnecessary removal of normal tissue. Integration of fluorescence guidance with OCT may provide more efficient examination and improve the diagnostic characteristics of both imaging modalities [42]. The utility of OCT in the diagnosis of CIS and its role in bladder cancer management has yet to be elucidated in large controlled studies. A multicenter trial in the US is currently in progress with the primary aim to assess the accuracy and positive predictive value of OCT for determining tumor stage correlated by histopathology.

Narrow-band imaging

Narrow-band imaging (NBI) cystoscopy attempts to improve the contrast between abnormal lesions and normal bladder by restricting the optical spectrum used for examination. This narrowed bandwidth is accomplished by filters which permit transmission of light at wavelengths of 415 nm and 540 nm [43]. Hemoglobin preferentially absorbs these wavelengths and thus increases the visibility of capillaries and submucosal blood vessels. NBI has been shown to be useful in identification of metaplastic and precancerous lesions in the stomach and esophagus as well as increasing detection of malignant tumors during colonoscopy [44, 45].

Since urothelial carcinomas tend to be hypervascular, NBI endoscopy may provide enhancement of visually subtle lesions, improving detection of otherwise missed lesions. In contrast to WLC, abnormalities with increased angiogenesis assume a bluish tint and appear darker than the surrounding mucosa (Fig. 2) Two published series have investigated the application of NBI as a diagnostic tool in bladder cancer. Bryan and colleagues showed in a preliminary study of 27 patients that NBI increased bladder tumor detection over WLC [46]. In the largest published series ($n = 427$), Herr et al. [47] demonstrated NBI to be superior to WLC for detecting recurrent tumors (100% vs. 87% sensitivity, $P = 0.05$) and more importantly for identification of CIS (100% versus 83% sensitivity, $P = 0.01$). This study showed no statistically significant difference in false detection rates and specificities between NBI and WLC. An advantage of this technique is that no additional photosensitizing staining is needed; however a specialized filtering

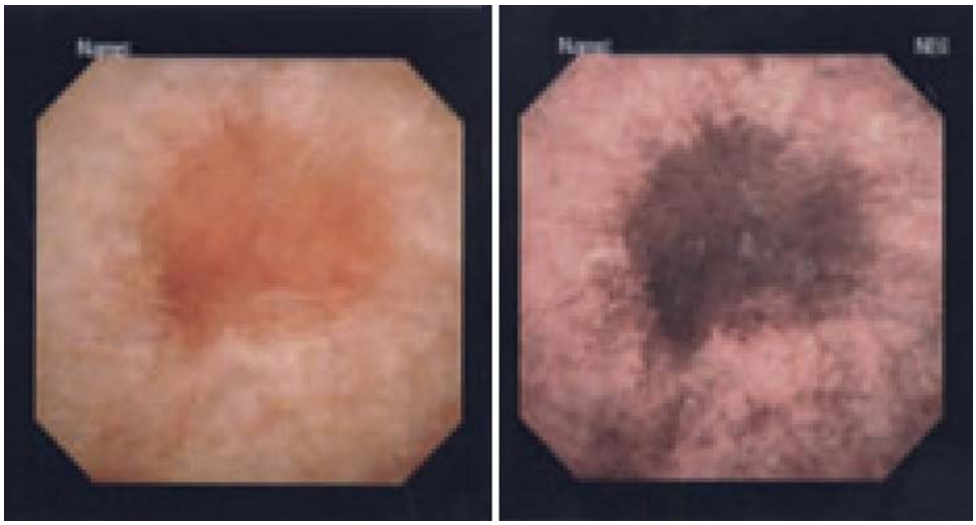

Fig. 2 WLC shows an area of CIS (*left*). NBI enhancement reveals a larger peripheral area of CIS involvement (*right*). (Wiley 2008)

system is required. As hypervascularity is a non-specific finding, further controlled multicenter studies are needed to confirm the strength of NBI in diagnosing precancerous and malignant bladder lesions.

Virtual cystoscopy

With the goal of examining bladder pathology less invasively, virtual cystoscopy (VC) utilizes three-dimensional (3D) model reconstruction of cross-sectional imaging data. Magnetic resonance imaging and ultrasound have been explored, but application of computed tomographic (CT) scans has been most widely investigated. While early studies of VC showed poor sensitivity for small bladder tumors, technical improvements in helical CT, contrast agents, and post-acquisition image processing have fueled interest in this area [48]. Current techniques employ 1–3 mm slices and 3D perspective volume-rendering algorithms to generate a virtual endoscopic view of the bladder. Yazhan et al. [49] examined 39 patients with VC using WLC as the gold standard and reported a sensitivity of 96% for polypoid tumors and 89% for sessile lesions with a mean lesion size of 1.9 cm. Their use of 3 mm slices limited their ability to detect lesions under 5 mm. Using air contrast and a 16-multidetector CT, Tsampoulas and co-workers evaluated 50 patients with VC compared to WLC and showed a sensitivity of 90% (18 of 20) for bladder lesions less than 5 mm [50]. This study confirmed previous findings by Kim et al. [51] showing a sensitivity of 88% for lesions of similar size.

While recent advances in multidetector image acquisition and multiplanar reconstruction have improved the detection ability of VC, a few drawbacks remain. Flat lesions without bladder wall thickening, especially CIS, cannot be identified, representing a persistent challenge. Abnormalities detected using this modality are strictly morphologic and give little discriminatory information regarding malignancy. With regard to invasiveness, air contrast studies which seem to provide improved visualization require insertion of a catheter, while IV contrast studies do not [52]. Additionally, VC by definition does not allow simultaneous intervention, such as biopsy or resection, which can be performed during standard cystoscopy. Finally, radiation exposure is a concern, but low tube current protocols may reduce this exposure [53]. VC also may be integrated into planned routine cross-sectional imaging studies, limiting additional exposure. As resolution and computational processing improve, the potential for application of VC in bladder cancer diagnosis, staging, and surveillance appears promising.

Conclusion

Bladder cancer remains a significant physical, psychological, and financial burden to the patient and society, where the need for innovation persists. Technological advances have the potential of improving detection and treatment. Controlled studies have proven fluorescence cystoscopy can enhance the diagnosis of bladder lesions, guide the adequacy of resection, and reduce tumor recurrence. Further investigation is required to confirm the utility of OCT, NBI, and VC and to define their specific role in bladder cancer management. Future applications will require evidence-based integration of these imaging tools in a complementary fashion to provide maximal clinical benefit.

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