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Advancements in optical techniques and imaging in the diagnosis and management of bladder cancer

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Abstract

Accurate detection and staging is critical to the appropriate management of urothelial cancer (UC). The use of advanced optical techniques during cystoscopy is becoming more widespread to prevent recurrent nonmuscle invasive bladder cancer. Standard of care for muscle-invasive UC includes the use of computed tomography and/or magnetic resonance imaging, but staging accuracy of these tests remains imperfect. Novel imaging modalities are being developed to improve current test performance. Positron emission tomography/computed tomography has a role in the initial evaluation of select patients with muscle-invasive bladder cancer and in disease recurrence in some cases. Several novel immuno-positron emission tomography tracers are currently in development to address the inadequacy of current imaging modalities for monitoring of tumor response to newer immune-based treatments. This review summaries the current standards and recent advances in optical techniques and imaging modalities in localized and metastatic UC.

Keywords: Oncologic imaging; Bladder cancer; Staging; Urothelial tumors

Introduction

Accurate detection and staging is critical to the appropriate management of urothelial cancer (UC), the fourth most common cancer in men and sixth most common cancer overall in the United States [1]. Due to the location of UC predominantly within the bladder, unique challenges for imaging studies exist. Optimal detection, staging, and surveillance of UC requires a combination of direct visualization during cystoscopy, noninvasive cross-sectional imaging, and pathologic review. The use of advanced optical techniques during cystoscopy is becoming more widespread to prevent recurrent nonmuscle invasive bladder cancer (NMIBC). Standard of care for muscle-invasive UC still includes the use of computed tomography (CT) and/or magnetic resonance imaging (MRI), but staging accuracy of these tests remains imperfect. Novel imaging modalities are being developed to improve current test performance. Positron emission tomography (PET)/CT has a role in the initial evaluation of select patients with muscle-invasive bladder cancer (MIBC) and in disease recurrence in some cases. Several novel immuno-PET tracers are currently in development to address the inadequacy of current imaging modalities for monitoring of tumor response to newer immune-based treatments. Providers must be aware of the strengths and limitations of available imaging options for use in patients with urothelial cancer.

Optical techniques during cystoscopy

Cystoscopy is the preferred method for evaluation of a bladder tumor. White light cystoscopy is the most widely used visualization technique during cystoscopy (Fig. 1A) but can miss small or flat lesions, including carcinomas in situ (Cis). Recurrences of UC are common after transurethral resection of the bladder (TURB) using white light [2]. Improved imaging techniques have therefore been developed to improve sensitivity of diagnosis of small lesions and prevent recurrences.

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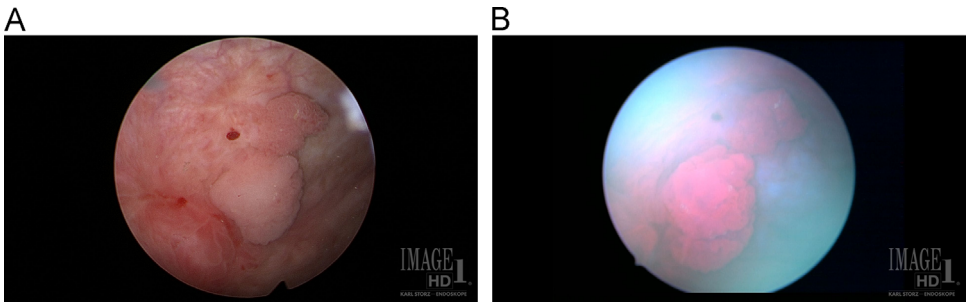

Fig. 1. (A) Image of a bladder tumor using white light cystoscopy. (B) Image of a bladder tumor using photodynamic diagnosis or blue light cystoscopy.

Photodynamic diagnosis

In photodynamic diagnosis (PDD), also known as fluorescence cystoscopy or blue light cystoscopy, an optical imaging agent (mainly hexaminolevulinate, trade names Cysview/Hexvix) is instilled intravesically. Bladder cancer cells selectively take up the imaging agent and appear pink when visualized under blue light (Fig. 1B). There have been extensive studies demonstrating that PDD improves detection of bladder cancers, including Cis, and reduces recurrences in patients with known or suspected NMIBC [3]. Decreasing recurrence rates can abrogate the need for repeat TURB, bacillus Calmette-Guerin treatment, or cystectomy in some patients. Current guidelines from the European Association of Urology and American Urological Association (AUA) recommend the use of PDD if possible in all patients with a new diagnosis of NMIBC undergoing initial TURB [4]. In addition, use of PDD in initial TURB may be cost-effective given the lowered risk of tumor recurrence with its use [5].

A role for PDD is also emerging in the surveillance setting and is recommended for use in patients with NMIBC with high-risk features (high-grade disease, Cis, and multifocal tumors) [4]. A recently presented phase III trial compared PDD with white light cystoscopy using flexible cystoscopes in the surveillance setting and showed blue light cystoscopy detected bladder cancer recurrence in 21.5% of patients that otherwise would have been missed with white light alone [6].

Narrow band imaging

Similar to PDD, narrow band imaging (NBI) is designed to improve detection of cancer compared to white light but instead of enhancing tumors directly, it aims to improve visualization of blood vessels. NBI uses an optical enhancement technology to narrow the bandwidth of light output to 415 and 540 nm, which is strongly absorbed by hemoglobin and only penetrates the surface of tissue, enhancing detection of vessels. In contrast to PDD, this technique does not require instillation of an intravesical imaging agent. As most tumors are vascular, this helps with detection of bladder cancer. A recently published Dutch study evaluated the use of NBI in 955 patients undergoing cystoscopy and found a small but significant improvement in sensitivity of NBI to detect NMIBC compared to white light alone (sensitivity 100% vs. 83%, respectively, $P < 0.05$), although specificity was somewhat lower than that of white light (87% vs. 92%, $P < 0.05$) [7]. A meta-analysis including 6 trials with 1,084 patients found that NBI-TURB was associated with improvement in the recurrence risk at 3 months, 1 year, and 2 years compared with white light-TURB. The AUA guidelines for NMIBC, therefore, state that a clinician may consider use of NBI to increase detection and decrease recurrence [8].

Newer imaging methods

Microscopic imaging methods such as optical coherence tomography and confocal laser endomicroscopy (CLE) are used to provide real-time cross-sectional views of the bladder. Optical coherence tomography can aid in determining the extent of tumor infiltration (stage) and CLE produces images resembling histopathological slides to estimate tumor grade. These methods can be combined with other methods such as PDD, although they are limited by a small field of view. Therefore, microscopic methods can be time intensive and result in a high number of false-positive lesions [9,10]. Other new methods attempt to use individual 2D images from cystoscopy to reconstruct 3D models of the bladder to visualize the shape and surface appearance of the entire bladder organ [11]. Although initial studies are provocative, all these techniques have not been adopted for widespread use given cost and convenience issues, and lack of translation to documented clinical benefit.

Use of CT in staging of urothelial cancer

Abdominal and pelvic CT is used as standard staging for muscle-invasive UC to evaluate the extent of the primary tumor, the upper urinary tracts, and the presence of metastatic disease. Unfortunately, CT imaging is notoriously insensitive for diagnosing tumors within the bladder and radiographic features of the bladder can be influenced by recent tumor resection, cystoscopy, chemotherapy, or other treatments [12]. Although CT can be useful for