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Advancements in Bladder Cancer Diagnosis and Staging: From Cytology to Imaging Techniques

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Summary
Bladder cancer ranks as a prevalent malignancy, especially among men, and is a significant cause of morbidity and mortality globally. This review highlights the epidemiology, diagnostic advancements, and current therapeutic approaches for bladder cancer. Bladder cancer commonly presents as either non-muscle-invasive (NMIBC) or muscle-invasive (MIBC), with distinct pathological stages and treatment goals. The primary diagnostic method for bladder cancer remains cystoscopy, though enhanced techniques such as blue light cystoscopy (BLC) and narrow-band imaging (NBI) have improved lesion detection. Diagnostic imaging modalities, including computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET), are critical for staging and assessing metastasis. Additionally, urine cytology and fluorescence in situ hybridization (FISH) provide valuable cytopathological insights, enhancing diagnostic accuracy. Innovative diagnostic approaches, including the Paris System for urinary cytopathology and fluorescence urine cytology, have advanced early detection and staging of bladder cancer. Comprehensive understanding and continuous advancements in these diagnostic and therapeutic modalities are crucial for effective patient management and improved clinical outcomes.

Keywords: Bladder cancer, diagnosis, cytopathology, imaging.

Introduction

Bladder cancer is the sixth most common cancer among men and the seventeenth among women (Bray *et al.,* 2018). Its incidence ranks first among malignant cancers of the urinary system and second only to prostate cancer in Western countries, with an incidence that is three to four times higher in men than in women. (Siegel *et al.*, 2012).

From inner to outer, the urinary bladder comprises four layers: the transitional epithelium, submucosa/lamina propria, muscularis mucosa, and serosa/adventitia. The transitional epithelium or urothelium, is the innermost layer that lines the urinary tract in the renal pelvis, ureters, bladder, and proximal urethra. This is followed by the submucosa/ lamina propria, which contains blood vessels and nerves. The third layer is the muscularis layer, which comprises a network of smooth muscle, also called the detrusor muscle. The outer layer of the superior bladder (bladder dome) is covered by serosa which is part of the visceral peritoneum. The remaining areas without serosa have an outer layer of adventitia that comprises connective tissue. Beyond the outer layer is the perivesicular fat.

The primary lymphatic drainage for bladder cancer includes the internal iliac, external iliac, obturator, and presacral nodes, and secondarily the common iliac, para-aortic, aortocaval, and paracaval nodes. It is rare for bladder cancer to skip primary nodal drainage sites to metastasize to secondary nodes (Bray *et al.,* 2018).

Bladder cancer is classified into non-muscle-invasive bladder cancer (NMIBC) and muscle-invasive bladder cancer (MIBC). The former accounts for 80% of reported cases, and the latter accounts for the remaining 20% (Witjes *et al.*, 2014).

The NMIBC is also known as superficial bladder cancer. Its pathological stages include Ta (papillary), T1 (infiltration lamina propria), and carcinoma in situ. The Ta patients comprise 70% of cases, T1 roughly 20% and carcinoma in situ about 10%. The pathological stages of MIBC include T2, T3 and T4 (Burger *et al.*, 2013). Up to 80% of NMIBC patients relapse within 5 years, 30% of Ta patients progress to MIBC, while those with T1 and carcinoma in situ are more likely to develop MIBC (Knowles *et al.*, 2015). Clinical manifestations at the initial diagnosis include microscopic haematuria, lower urinary tract symptoms and urinary tract infection (Kamat *et al.*, 2014). Transitional cell carcinoma accounts for over 90% of cases and is by far the most common epithelial tumour of the bladder (Kirkali *et al.*, 2015).

In NMIBC, the goal is to prevent progression and limit recurrence (Aldousari *et al.*, 2010), while in MIBC, the goal is deciding on bladder preservation or removal, and whether local bladder therapy alone or systemic therapy is required (Kamat *et al.*, 2016).

Epidemiologic studies show that cigarette smoking is strongly associated with an increased risk of bladder cancer. Moreover, smoking increases the risk of bladder cancer as the second smoking-associated cancer among survivors of kidney, head and neck, and stage I lung cancers (Shiels *et al.*, 2014), a large population-based bladder cancer study revealed that the risk of having bladder cancer was significantly higher (OR=3.08; CI 95%, 1.16-8.22) among female lifelong nonsmokers exposed to tobacco smoke at home during childhood (Jiang *et al.*, 2007)

The goal of any standard diagnostic system should be to define the morphologic criteria for the various categories in urinary tract cytopathology and also to standardize the reporting system to be universally acceptable and globally utilized (Barkan *et al.*, 2016).

Diagnostic Approaches to Bladder Cancer
Cystoscopy

Cystoscopy is a method for the initial evaluation of suspected bladder cancer and is preferentially recommended over invasive testing for the evaluation of asymptomatic microscopic haematuria and thus the identification of bladder cancer or other urological diseases (Flaig *et al.*, 2020).

Blue light cystoscopy (BLC) and narrow-band imaging (NBI) are newer enhanced cystoscopy techniques which improve lesion detection compared to conventional white-light cystoscopy (WLC). The BLC is a photodynamic diagnostic technique that utilizes hexaminolevulinate (HAL) or 5-aminolevulinic acid (5-ALA) which are induced into the bladder and taken up by urinary epithelial cells. These form photoactive intermediate porphyrins which accumulate in neoplastic cells and fluoresce after excitation, appearing as bright pink or red colour (Kamat *et al.*, 2016)

Even though cystoscopy is the most common procedure in daily urology practice, it is invasive and is associated with pain and discomfort. Conscious patients are directly exposed to various stimuli during cystoscopy, which increases anxiety. The pain and anxiety associated with cystoscopy can activate the sympathetic nervous system resulting in various physiological responses, such as elevated blood sugar level, increased cardiac output, elevated blood pressure and peripheral vascular contraction (Schlereth *et al.,* 2008). A variety of medical interventions, such as intra-urethral injection of lidocaine lubricant and flexible cystoscopy have been used to alleviate pain and anxiety during the procedure. Flexible cystoscopy is generally less painful than rigid cystoscopy. However, it is expensive, visualizes a smaller area, requires more skill from urologists, and is therefore not favoured (Gratzke *et al.,* 2015).

Despite the use of these medical interventions, patients undergoing cystoscopy still complain of post-procedural pain and anxiety (Biardeau *et al* 2017). Generally, acute pain causes anxiety, which increases the fear of pain, sleep disturbances (Chouchou *et al.,* 2014), depression (Glowacki 2015), and interferes with concentration and cognition (Glowacki 2015).

However, music and/or video therapy are effective non-pharmacological interventions that lower pain and anxiety in patients during

cystoscopy (Gezginci *et al.,* 2018). Handholding during the procedure has also been shown to reduce patients' anxiety, pain, and dissatisfaction (Kwon *et al.,* 2018).

Radiologic examination.

As with all cancers, imaging plays a significant role in the management of patients with bladder cancer, including the locoregional staging and evaluation for distant metastatic disease, which cannot be assessed at the time of cystoscopy and biopsy/resection (Galgano *et al.,* 2020). Computed tomography (CT) is the most commonly utilized imaging modality and demonstrates excellent performance for the evaluation of nodal and distant visceral metastatic disease. Magnetic resonance imaging (MRI) has been evaluated for locoregional staging, including the evaluation of muscularis propria invasion. Positron emission tomography (PET) with fluorodeoxyglucose (FDG) is valuable in the whole-body staging and restaging of many cancers, and its use in cases of suspected metastatic BC or follow-up staging in cases undergoing treatment for metastatic BC is common (Zheng *et al.,* 2017).

Computed Tomography.

Computed tomography (CT), specifically CT urography (CTU), is the most commonly used imaging method worldwide to diagnose and stage urothelial malignancies, for the localization, locoregional staging, and detection of distant metastases. The most common presenting symptom is gross haematuria, which is typically followed by direct visual examination via cystoscopic evaluation and imaging using a CTU as the first-line modality for gross haematuria (Wolfman *et al.,* 2020).

There are two typical approaches to how a CTU is performed. The first approach is with a "split-bolus" two-phase exam with a non-contrast phase and a single urothelial and excretory phase exam by administering a partial bolus, waiting until excretion, and then administering the remainder to better enhance the renal/urothelial parenchyma. The second is a three-phase exam consisting of non-contrast, urothelial, and delayed excretory imaging. While the "split-bolus" does save patient radiation exposure, however, it comes at the potential cost of masking small lesions compared with a dedicated urothelial phase alone. A CTU of up to 87% sensitivity and 99% specificity may miss very small or flat lesions that are more easily detected by cystoscopy (Helenius *et al.,* 2015).

The limitations of CTU in the diagnosis of bladder cancer include false-positive and false-negative results when compared with cystoscopy (Trinh *et al.,* 2018). False-positive results arise from interpretation errors, most commonly due to benign prostatic hypertrophy mimicking a bladder lesion, followed by bladder trabeculation, intravascular blood clots and post-treatment changes. False-negative results primarily arise from flat urothelial lesions or image artefacts and inadequate bladder lumen filling during the excretory phase of the CTU imaging study.

Ultrasound

Ultrasound is a commonly utilized imaging modality that is widely available and low-cost in relation to advanced imaging modalities such as MRI and PET/CT. Frequently, ultrasound may be the initial examination performed in patients with haematuria, as it is recommended as the initial diagnostic evaluation for microscopic haematuria by the American College of Radiology (ACR) (Wolfman *et al.,* 2020).

However, a known limitation of ultrasound is its inability to provide comprehensive abdominopelvic staging in the setting of malignancy, and its use is likely limited to the screening of the urinary bladder and/or its possible use in local staging.

Magnetic Resonance Imaging

MRI is currently the superior imaging modality for soft-tissue resolution, which allows for more accurate locoregional bladder cancer staging than CT (Verma *et al.,* 2012). However, the use of MRI may be limited in some patients due to potential safety concerns with implanted metallic devices or foreign bodies. Thus, it is important to identify any potential safety hazards before performing an MRI for bladder cancer staging (Tekes *et al.,* 2005).

Laboratory Diagnosis.

Urine cytology.

More than five decades ago, Dr. George Papanicolaou hypothesized that urinary tract malignancies can be detected by the evaluation of exfoliated cells in urine (Barkan *et al.*, 2016). This procedure involves the microscopic screening of urine from a subject suspected of bladder cancer.

Urine cytology is the mainstay in the diagnosis of bladder cancer due to its high specificity for high grade urothelial carcinoma though it is limited by its low sensitivity. A systematic review of urinary markers in 2005 found that cytology had a median sensitivity and specificity of 35% and 94%, respectively, however in grade 1 tumours the sensitivity was only 17% compared with 58% in grade 3 tumours (van Rhijn *et al.,* 2005).

Other urinary tests are currently available that have improved sensitivity include the NMP22, bladder tumor antigen (BTA), stat/BTA TRAK, ImmunoCyt, and UroVysion fluorescence in situ hybridization (FISH). These tests often sacrifice specificity for the increase in sensitivity but have some unique characteristics which can make them useful to the practicing urologist.

Spontaneously voided urine is the most common sample sent for cytopathological examination. Apart from that, bladder wash samples, catheterized urine samples or urine obtained by retrograde catheterization of the ureters or renal pelvis are occasionally sent for the cytopathological examination. The most ideal sample which contains a sufficient number of preserved cells is the second morning voided urine sample. The first morning or overnight urine contains more cells but shows different degrees of degeneration as they are exposed to the acid milieu of urine throughout the night and are less suitable for cytological evaluation. As the urothelial cells exfoliate intermittently, it would be right to examine three urine samples from three consecutive days to ensure that diagnostic cells are adequately sampled (Flezar *et al.,* 2010)

Reporting systems for urine cytology went through a series of modifications in accordance with the changes in the histopathological classification of urothelial neoplasms. The lack of a uniform reporting system caused significant inter-observer variability and created a great deal of confusion.

The earliest system was proposed by Papanicolaou way back in 1947 which included classes 1-5, Absence of abnormal or atypical cells, Atypical cells present but without abnormal features, cells with abnormal features but not sufficiently pathognomonic, Fair number of pathognomonic cells and cell clusters, and Large number of conclusive cells and cell clusters, respectively

The Paris System (TPS) for Reporting Urinary Cytopathology was later conceived in May 2013 during the 2013 International Congress of Cytology in Paris and published in 2015 (Barkan *et al.,* 2016). This system outlined 6 stages of grading, non-diagnostic or unsatisfactory, negative for high grade urothelial carcinoma, atypical urothelial cells, suspicious for high grade urothelial carcinoma, low grade urothelial carcinoma, and high-grade urothelial carcinoma

Fluorescence in situ hybridization

Fluorescence in situ hybridization (FISH) technology is a molecular cytogenetics technology that originated in the late 1960s. This technique detects chromosomal or genetic abnormalities in cell and tissue samples by detecting fluorescence signals hybridized between the probe and the DNA in the sample through the complementarity of DNA base pairs, with the characteristics of rapid detection, good repeatability and accurate spatial positioning. The technique can

Urine Fluorescence in situ hybridization (U-FISH) is more sensitive for the detection of malignant cells in urine or bladder washes and is not affected by haematuria, urinary tract infection or BCG-induced inflammatory response. Despite its sensitivity, FISH has a limitation of low sensitivity to detect low-grade tumours due to their diploid or nearly diploid chromosomes similar to normal cells.

5-Aminolevulinic Acid-Induced Fluorescence Urine Cytology.

This method involves the detection of 5-

aminolevulinic acid (5-ALA), a precursor in heme biosynthesis, and protoporphyrin IX, a metabolic product of 5-ALA, which accumulates more in tumour cells than in healthy cells. Protoporphyrin IX emits red fluorescence when excited with a blue light at a wavelength of 405 nm and produces a peak at a wavelength of 635 nm that is used to visualize cancer cells. The sensitivity of urine cytology using 5- ALA has improved to 82% (Yoder *et al.,* 2007).

Conclusion

The advancements in bladder cancer diagnostic and staging methods have significantly improved the accuracy and early detection of this prevalent malignancy. Enhanced cystoscopy techniques, such as blue light cystoscopy and narrow-band imaging, along with advanced imaging modalities like CT, MRI, and PET have optimized the diagnostic process, allowing for a more accurate assessment of tumour stage and progression. Urinary cytopathology, particularly with the advent of the Paris System and fluorescence in situ hybridization, has provided a more sensitive and specific approach to cytological evaluation. Despite these advances, further studies are needed to refine these methods, particularly for low-grade tumours, to mitigate recurrence and improve survival outcomes in bladder cancer patients. Embracing these evolving diagnostic techniques will lead to better-informed clinical decisions and improved patient outcomes in bladder cancer management.

Conflict of interest: The authors declare that they have no competing interests.

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