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Invited Review

What is new in non-muscle-invasive bladder cancer in 2016?

Kasa invaze olmayan mesane kanserinde 2016 yılındaki yenilikler neler?

Ashish M. Kamat[1], Murat Bağcıoğlu[2], Emre Huri[3]

ABSTRACT

Approximately 75% of bladder cancers are non-muscle-invasive bladder cancer (NMIBC), and 50% of NMIBC patients who are treated with transurethral resection (TUR) have a recurrence of the disease and 5–25% of these patients progressed to muscle-invasive disease after repeated recurrences. NMIBC patients receive various treatments aimed at reducing disease recurrence and progression. Although the recurrence rate of disease remains above target, thus increasing treatment cost, the true rate of recurrence after the primary surgery is controversial. Recurrences can be categorized as either true recurrence due to aggressive tumor biology and implantation of floating cancer cells or false recurrence such as small, flat, or carcinoma in situ lesions overlooked in the primary procedure. Here we discuss new diagnostic methods and treatment options to improve outcomes and reduce recurrence rates in NMIBC.

Keywords: Bladder cancer; diagnostic assessment; intravesical chemotherapy; intravesical immunotherapy; predictive markers.

ÖZ

Mesane tümörlerinin yaklaşık %75'i kasa invaze olmayan mesane kanseridir (KİOMK). Transüretral rezeksiyon (TUR) ile tedavi edilen KİOMK olan hastaların %50'sinde nüks gözlenirken, %5-25'inde ise hastalık tekrarlayan nükslerin sonunda progresyon göstererek kasa invaziv hale gelir. KİOMK olan hastalarda nüks ve progresyonu azaltmak amacıyla çeşitli tedavi protokolleri uygulanmaktadır. Hastalığın nüks oranı hedeflenen değerin üstündedir ve bu da tedavi masraflarının artmasına neden olmaktadır. İlk TUR sonrası gerçek nüks oranları tartışmalı bir konudur. Nüksler, agresif tümor biyolojisi ve kanser hücrelerinin implantasyonuna bağlı olan gerçek nüksler ile ilk prosedürde gözden kaçan flat, küçük ya da karsinoma in situ lezyonları nedeniyle olan yalancı nüks olmak üzere sınıflandırılmaktadır. Bu çalışmada, KİOMK sonuçlarının iyileşmesi ve nüks oranlarının azaltılması amacıyla tanı yöntemleri ve tedavi alternatiflerindeki yenilikler tartışılmıştır.

Anahtar kelimeler: Mesane kanseri; teşhis yöntemleri; intravezikal kemoterapi; intravezikal immünoterapi; tümör belirteçleri.

[1]Department of Urology, The University of Texas, MD Anderson Cancer Center, Texas, USA

[2]Department of Urology, Kafkas University School of Medicine, Kars, Turkey

[3]Department of Urology, Hacettepe University School of Medicine, Ankara, Turkey

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Correspondence: Ashish M. Kamat
E-mail: akamat@mdanderson.org

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Introduction

Bladder cancer is the fourth most common cancer in men, and the eleventh most common cancer in woman, with approximately 400,000 new patients diagnosed annually worldwide.[1,2] Approximately 75% of bladder cancers are non-muscle-invasive bladder cancer (NMIBC), and the remaining are either muscle-invasive or metastatic disease. Half of NMIBC patients who are treated with transurethral resection (TUR) have a recurrence of the disease and 5-25% of these patients progressed to muscle-invasive disease after repeated recurrences.[3]

Following primary resection, NMIBC patients receive various treatments aimed at reducing disease recurrence and progression. Although the recurrence rate of disease remains above target, thus increasing treatment cost, the true rate of recurrence after the primary surgery is controversial; recurrences can be categorized as either true recurrence due to aggressive tumor biology and implantation of floating cancer cells or false recurrence such as small, flat, or carcinoma *in situ* (CIS) lesions overlooked in the primary procedure.[4] Here we discuss new diagnostic methods and treatment options to improve outcomes and reduce recurrence rates in NMIBC.

Diagnostic Assessment of NMIBC

Small solid or flat lesions (e.g., CIS) are generally not detected by ultrasound, computed

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tomograph (CT) or magnetic resonance imaging (MRI). Therefore, white light assisted cystoscopic (WLC) examination is used for the diagnosis of NMIBC. However, the detection rate for WLC can be limited (as low as 60% based on experience of urologist) and WLC is not suitable for the detection of small, and satellite tumors, or surgical margins.[5,6] In fact, residual tumors can be detected 4-6 weeks after the primary procedure in 40-70% of repeat-TUR.[7,8] Two novel techniques, blue light cystoscopy (BLC, also known as photodynamic diagnosis) and narrow band imaging (NBI), have been developed to address the limitations of WLC.

Blue light cystoscopy allows fluorescent imaging of inner bladder walls. Hexaminolevulinate (HAL) hydrochloride is administered intravesically 1-3 hrs before the endoscopic procedure. By this approach, under blue light (380-480 nm), cancer cells appear fluorescent red and normal uroepithelium as blue. A meta-analysis of data from 1,345 patients found that BLC detected significantly more Ta tumors (14.7%; p<0.001; odds ratio [OR], 4.90; 95% CI, 1.94-12.39) and CIS lesions (40.8%; p<0.001; OR, 12.372; 95% CI, 6.34-24.13) than WLC, and was associated with lower recurrence rates for up to 12 months in patients with T1 or CIS lesions.[9]

The effect of BLC on the progression of NMIBC was reported in a controlled Phase III study with a median 4.5 year follow-up.[10] The new International Bladder Cancer Group definition of progression(an increase in T stage from Ta to CIS or T1, CIS to T, indicating invasion of lamina propria, development of T2 or greater, lymph node disease [N+], distant metastasis [M1] or an increase in grade from low to high) was applied and 4 (1.6%) patients from the BLC group and 11 (4.2%) from the WLC group progressed from Ta to CIS. We found that there was a trend towards a lower rate of progression with BLC. Time to progression was also significantly longer in the BLC group (p<0.05).[10,11]

Narrow band imaging also provides better visibility of blood vessels without the need for intravesical contrast administration. Enhanced contrast between the mucosa and blood vessels is achieved and, with the use of special filters, well vasculated pathological lesions are more visible than normal uroepithelium. A network meta-analysis found a lower recurrence rate in patients undergoing NBI than patients undergoing WLC (OR, 0.48; 95Cl, 0.26-0.95) but no significant difference in the recurrence rates of BLC and NBI treated patients.[12] Another study found that NBI can provide higher diagnostic precision of NMIBC than WLC.[13]

Improved detection with either HAL or NBI has been shown to lead to a lower rate of recurrence and a longer recurrence free interval than with WLC. Additional imaging techniques in the early stages of experimental research include optical coherence tomography, computer tomography virtual cystoscopy, confocal laser endomicroscopy, Raman spectroscopy, multiphoton microscopy, scanning fiber endoscopy, ultraviolet auto fluorescence, and molecular imaging, which might eventually be added to the diagnostic assessment for NMIBC.

Predictive Markers of NMIBC

Cystoscopy and voided urine cytology remain the standard for NMIBC diagnosis.Urine cytology has a high sensitivity for the detection of high grade tumors but its sensitivity decreases (ranging from 4-31%) for low grade tumors.[14] Real world data suggest however that the sensitivity of cytology is decreasing across the spectrum, even for high grade disease and it suffers from intra-observer variation. Although several urine-based tumor markers have been investigated and developed (e.g., NMP22, BTA test, Immunocyt, microsatellite analysis, CYFRA21-1, FISH,and Lewis-X), their low sensitivity and low specificity have prevented their application to NMIBC diagnosis and prognosis.[15,16] The pooled sensitivity of most molecular markers ranges from 50-80%, which is higher than for urine cytology. The specificity of most molecular markers ranges from 70-90%, lower than for urine cytology.[14,17,18]

The measurement of urine methylation level has been proposed for the early diagnosis of NMIBC.[19-21] It seems that new studies on RNA and methylation techniques could improve on present technology, but future studies using large cohorts are required before these can become standard methods of NMBIC diagnosis. As yet, there are no recommended non-invasive biomarkers for the diagnosis and monitoring of NMIBC and several guidelines (eg AUA, EAU) recommend against their routine use.[17]

Transurethral Resection Technique and Tools of NMIBC

Transurethral resection of the bladder tumor (TUR-BT) remains the gold standard for the management of NMIBC. In the initial TUR-BT all visible tumors should be removed. In addition, the histological type and grade of the tumor, as well as the presence, depth, and type of the tumor invasion should be determined. TUR-BT quality affects the diagnosis, treatment and even prognosis of NMIBC.[22] A repeat TUR-BT is recommended within 4-6 weeks of the primary procedure.[23-25] Repeat TUR-BT results in upstaging and a change of management in 24-49% of patients with high grade T1 tumors.[8]

Adjuvant Intravesical Chemotherapy of NMIBC

The necessity of adjuvant therapy in NMIBC patients comes from the high variability in the 3-month recurrence rate that indicates the incomplete TURB or recurrences in a high percentage of patients.[26] Immediate or post-operative intravesical instillation of chemotherapy that should be administered within 24 hours, is a first choice adjuvan therapy to decrease recur-

Table 1. Reccomendations for intravesical BCG

RCTs and practice pattern research demonstrate that BCG immunotherapy in NMIBC reduces recurrences and progression, and affects mortality
3-week BCG maintenance is confirmed to reduce recurrence rates compared with induction alone, as well as metastasis and mortality compared with
BCG maintenance schedules other than the 3 week schedule show no significant benefit in RCTs
After the second BCG failure, or if the disease is BCG-refractory, radical cystectomy should be considered with alternatives considered a matter of investigation by clinical trials
In the period of around 1.5–2 years after the identification of high-grade NMIBC, nonradical alternative treatments for patients experiencing BCG-failure can be explored
Patients with BCG-refractory disease who are not candidates for cystectomy can be considered for chemoradiation
After the first BCG failure, patients (who have not progressed) have several treatment options, including repeated BCG (or continued maintenance), BCG plus interferon, single-agent intravesical chemotherapy (for example, mitomycin, gemcitabine, or valrubicin), sequential chemotherapy (for example, gemcitabine–docetaxel) or device-assisted chemotherapy

NMIBC: non-muscle-invasive bladder cancer; RCTs: randomized controlled trials; BCG: Bacillus Calmette Guerin

Table 2. The definitions of the terms BCG relapse, BCG-refractory and BCG-intolerant

BCG Relapse	- A recurrence of tumour after a period of disease-free status. - The time point for evaluation should be at 3 months for papillary tumours and 6 months for CIS (except when disease progression was observed at 3 months) - Relapse can be further stratified as early (<1 year after treatment), intermediate (1-2 years) or late (>2 years), as the disease-free interval is a prognostic variable; early-relapsing patients are more likely to progress and late-relapsing patients can possibly derive some benefit from reinduction with BCG.
BCG-refractory	- BCG-refractory is the persistence of disease after adequate induction and one maintenance course of BCG. - This category includes any progression in stage or grade by 3 months if patients received induction BCG only
BCG-intolerant	- BCG-intolerant is defined as the inability to tolerate at least one full induction course of BCG. - The tumour recurs largely because of inadequate therapy, which does not have the same negative prognostic implications as a true BCG failure.

BCG: Bacillus Calmette Guerin; CIS: carcinoma in situ

rence of NMIBC during the follow-up. Single instillation (SI) reduced the 5-year recurrence rate by 14%, in the most recent systematic review and individual patient data meta-analysis of 2,278 eligible patients.[27] SI was not effective as a single adjuvant treatment in these two subgroups of patients; EORTC recurrence score >5 and/or patients with a prior recurrence rate of >1 recurrence per year. In EAU Guidelines, it was reported that Mitomycin C (MMC), epirubicin, and pirarubicin have all shown a beneficial effect.[27] No randomized comparisons of individual drugs have been conducted [EAU Guidelines] (LE: 1a). In practical manner, the drugs should be advised to be prepared before the surgery to catch up the time for instillation. However, traumatic surgery, bladder perforation risk and hematuria after the surgery are the situations that should be avoided to do intravesical SI. Intermediate Risk (IR)-NMIBC has a critical threshold when urologists choose intravesical chemotherapy protocol, either SI or maintanance therapy. Lammers et al.[28] reported a risk tablefor IR-NMIBC patients treated with intravesical chemotherapy including five relevant predictors of reccurence-free survival: history of recurrences, history of intravesical treatment, grade 2, multiple tumors and adjuvant treatment with epirubicin. These individual predictors were used to subdivide IR patients into three risk groups, which is related to recurrence outcome. The urologist together with the patient can choose for an individualized treatment approach.[28] However, further chemotherapy instillations after SI improved recurrence-free survival in intermediate-risk patients.[29] The available evidence does not support treatment longer than one year of intravesical chemotherapy (LE: 3). However, we still do not have optimal maintanence protocol for intravesical adjuvan chemothrapy. The data reported that maintenance therapy with BCG appears to be significantly better in preventing recurrences than chemotherapy (LE: 1a) although BCG causes significantly more side effects than does chemotherapy (LE: 1a).[30]

Advances in Intravesical Immunotherapy (BCG).

Bacillus Calmette Guérin (BCG) is stil the most effective intravesical treatment which decreases both progression and recurrence, that was proven by high quality meta-analyses, and randomized controlled trials.[30,31] This beneficial effect was seen in both papillary and CIS lesions. The protocol of induction BCG should be consist of six weekly intravesical instillations, followed by maintenance consisting of three weekly treatments at three month, and six month, for a total of 36 months, as de-

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scribed in SWOG trial.[32] BCG is indicated not only in high-risk disease, also in intermediate -risk disease. The benefit of BCG on recurrence and progression is greatest in those with both intermediate and high-risk disease.[30] In these patients, aggressive, and appropriate adjuvant intravesical treatment with BCG should be provide to improve disease specific survival.[31] BCG there is, once again, the potential for a global shortage with regards to this crucial, lifesaving therapy for bladder cancer.[33] Kamat et al.[34] reported the "Expert Consensus Document" that provides a comprehensive review of immunomodulatory therapy with BCG, recommends best practice guidelines to improve overall use and patient outcomes (Table 1). However, the definitions of the terms BCG relapse, BCG-refractory and BCG-intolerant were described in Table 2.[34]

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