



ICUD-SIU International Consultation on Bladder Cancer 2017: management of non-muscle invasive bladder cancer

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Abstract

Purpose To provide a summary of the Third International Consultation on Bladder Cancer recommendations for the management of non-muscle invasive bladder cancer (NMIBC).

Methods A detailed review of the literature was performed focusing on original articles for the management of NMIBC. An international committee assessed and graded the articles based on the Oxford Centre for Evidence-based Medicine system. The entire spectrum of NMIBC was covered such as prognostic factors of recurrence and progression, risk stratification, staging, management of positive urine cytology with negative white light cystoscopy, indications of bladder and prostatic urethral biopsies, management of Ta low grade (LG) and high risk tumors (Ta high grade [HG], T1, carcinoma in situ [CIS]), impact of BCG strain and host on outcomes, management of complications of intravesical therapy, role of alternative therapies, indications for early cystectomy, surveillance strategies, and new treatments. The working group provides several recommendations on the management of NMIBC.

Results Recommendations were summarized with regard to staging; management of primary and recurrent LG Ta and high risk disease, positive urine cytology with negative white light cystoscopy and prostatic urethral involvement; indications for timely cystectomy; and surveillance strategies.

Conclusion NMIBC remains a common and challenging malignancy to manage. Accurate staging, grading, and risk stratification are critical determinants of the management and outcomes of these patients. Current tools for risk stratification are limited but informative, and should be used in clinical practice when determining diagnosis, surveillance, and treatment of NMIBC.

Keywords Bladder cancer · Non-muscle invasive bladder cancer · Transurethral resection of bladder tumor · Staging · Diagnosis · Treatment · Surveillance · Bacillus Calmette–Guerin · Guidelines · ICUD

Introduction

Bladder cancer is the ninth most commonly diagnosed malignancy worldwide [1, 2]. In 2012, there were an estimated 430,000 new cases of bladder cancer globally [3]. Incidence is highest in Europe, followed by the United States, Northern Africa (due to endemic *Schistosomiasis haematobium*) and Western Asia, which has the highest

rates of bladder cancer mortality [3]. Males have a three-fold greater likelihood of developing bladder cancer as compared to females, and the average age of diagnosis is 73 years [2]. At the time of diagnosis, 75% of patients present with non-muscle invasive bladder cancer (NMIBC) [4]. NMIBC is comprised of Ta, T1 or carcinoma in situ (CIS).

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Methods

The Third International Consultation on Urological Diseases (ICUD) working group for the management of NMIBC performed a detailed review of the literature focusing on original high level of evidence in the articles when present. The scientific evidence available was classified when possible using the Oxford method and the summary of the recommendations was graded based on the Oxford Centre for Evidence-based Medicine system [5]. The results of this review provided recommendations on NMIBC. Here, a summary of these recommendations with regard to staging, diagnosis, treatment and surveillance is provided.

Primary assessment of NMIBC

The clinical staging classification of bladder cancer utilizes the 2010 American Joint Committee on Cancer/Union Internationale Contre le Cancer (AJCC/UICC) TNM system 7th edition, which was recently updated in 2017 (8th edition) without changes to the bladder cancer staging classification [6, 7]. The final staging is given by a combination of the three key elements, including: depth of invasion on the transurethral resection of bladder tumor (TURBT) specimen, examination under anesthesia (EUA), and the imaging findings. Risk for disease relapse or progression for patients with NMIBC are based on whether the tumor is primary versus recurrent and based on the tumor(s) stage, grade, number and size. The most widely used risk stratification tools are those put forth by the European Organization for Research and Treatment of Cancer (EORTC) and the Spanish Urological Club for Oncological Treatment (CUETO) [8, 9].

The TURBT is performed after a detailed cystoscopic evaluation and is followed by EUA. These combined procedures serve both diagnostic and therapeutic purposes in the management of bladder cancer. There are two different techniques of bladder tumor resections: staged resection versus en bloc resection. In a staged resection, the tumor is removed gradually, in multiple different pieces, starting on the branched portions of the tumor and proceeding with sequential resections until the base is reached. Then, the base is resected deeply to include muscle to provide adequate staging information [10]. En bloc resection is usually employed for small lesions [11]. Photodynamic diagnosis (PDD) [LE:1a, GR:B] or narrow-band imaging (NBI) [LE:2b, GR:C] may be used for the detection of bladder cancer during cystoscopy and during TURBT. The use of PDD and NBI are covered in detail within another chapter of the ICUD book [12].

A computerized tomography (CT) scan of the abdomen and pelvis is recommended in all cases where there is cystoscopic identification of a solid lesion, appearing to be high grade, or suggesting invasion [LE:4]. Ideally, CT should be performed before or at least 7 days after the TURBT to avoid false-positive results due to postoperative inflammation, perivesical swelling, or fluid infiltration [LE:3] [13]. Magnetic resonance imaging (MRI) has reported a bladder tumor detection rate of 98% utilizing diffusion-weighted sequences [14]. Staging sensitivity and specificity rates are similar to CT [15]. Lymph node metastases are detected by CT with a sensitivity and specificity of ≤ 50 and 100%, respectively [LE:3] [16]. Although MRI has better overall detection rates of lymph nodes than CT, particularly nodes smaller than 5 mm, its ability to identify malignant disease within normal or slightly enlarged lymph nodes is limited [17]. Positron emission tomography (PET), especially when combined with CT, has applications in more advanced disease and identification of recurrent nodal or distant organ and bone metastatic sites.

The American Urological Association (AUA) in conjunction with the Society of Urologic Oncology (SUO), as well as the European Association of Urology have created risk stratification groups based on the literature of known risk factors (Table 1).

Identification and management of modifiable risk factors for patients with NMIBC

Patients should undergo detailed history and physical examination, including inquiry into working/living conditions to identify potentially modifiable risk factors for bladder cancer. Ecological, cohort, and case-control studies have established an association between tobacco smoking and bladder cancer incidence. Even for patients diagnosed with bladder cancer, smoking cessation can significantly decrease the risk for disease relapse over time. Diet has not been clearly shown to influence bladder cancer risk. Exposure to *Schistosoma haematobium* is via exposure to snails along rivers of Northern Africa and contributes to significant burden of squamous cell bladder cancer. Prevention in these populations is aimed at eliminating the parasite and treating affected patients. All medications should be checked and patients taking pioglitazone (Actos) may consider discontinuing its use due to the association of this drug with bladder cancer.

Table 1 AUA/SUO (A) and EAU (B) risk stratification for NMIBC

Low risk	Intermediate risk	High risk	Highest risk
A. Low grade solitary Ta \leq 3 cm	Low grade Ta recurrence within 1 year Low grade solitary Ta > 3 cm Low grade, multifocal Ta High grade Ta \leq 3 cm Low grade T1	High grade T1 Recurrent Ta high grade High grade Ta > 3 cm or multifocal Any CIS Any BCG failure in high grade disease Any variant histology Any lymphovascular invasion (LVI) Any high grade prostatic urethral involvement	
B. Low grade, primary, solitary Ta < 3 cm without CIS	All tumors not otherwise defined as low or high risk	T1 tumor High grade tumor Any CIS Multiple, recurrent, and low grade Ta > 3 cm	T1G3 associated with concurrent bladder CIS, multiple and/or large T1G3 and/or recurrent T1G3, T1G3 with CIS in prostatic urethra, unusual histology of urothelial carcinoma, LVI BCG failures

Management of primary and recurrent low grade Ta (LGTa) bladder cancer

The gold standard initial treatment of LGTa bladder cancer (and the means to the initial diagnosis) is with a TURBT [18, 19]. As the incidence of upper tract urothelial carcinoma is small, the value of routine imaging of the upper tracts at the time of diagnosis of bladder cancer remains controversial [20]. Whilst the incidence of synchronous and metachronous upper tract tumors is somewhat higher in patients with bladder cancers affecting the trigone, the incidence of this occurring in LGTa cancers is small [21]. Across all tumor categories, the risk of synchronous upper tract urothelial carcinoma appears to be higher in multifocal bladder cancers [22]. Whilst recurrent bladder cancers should be, in principle, managed no differently than the primary lesion, i.e., TURBT; the surgical rigor of carrying out a formal TURBT can be avoided in many recurrent LGTa consequent to the recurrent lesions being small and non-invasive in most instances, and the risk of progression to a higher grade or stage being infrequent to rare [8, 23]. Therefore, in selected patients with LGTa recurrences, taking into account the urine cytology, cystoscopy appearance, and pathological evaluation of the recurrent tumor grade and stage, a more conservative approach could be adopted, such as office fulguration with diathermy, laser, chemo-resection, and expectant management. Regarding intravesical treatment in LGTa bladder cancer, there are two approaches traditionally used

in case of additional intravesical therapy: an immediate single dose intravesical instillation (SI) of chemotherapy agents following TURBT or adjuvant regimens using full courses of chemo- or immunotherapy agents, with or without maintenance. When referring to LGTa disease, the rationale of any adjuvant intervention will be the reduction of disease recurrence, since the risk of progression is negligible. The EAU NMIBC guidelines panel recommends a single, immediate, postoperative instillation of chemotherapy, with a level of evidence 1a and a grade of recommendation A [18]. The AUA recommends the use of immediate instillation in LGTa disease [19]. With respect to multiple adjuvant instillations of chemotherapy, there is still no consensus regarding the optimal schedule and duration of treatment. A short intensive schedule of instillations within the first 3–4 months after a SI may be as effective as longer term treatment schedules [24]. Considering the higher toxicity demonstrated by BCG, BCG is not recommended in low risk disease. However, in patients with intermediate risk disease and those patients in whom previous intravesical chemotherapy has failed, BCG may represent a therapeutic alternative and its use may be considered. While the management of low risk (SI alone) and high risk (BCG plus maintenance) appear clear, the best treatment option for intermediate risk (IR) patients remains undefined. Risk stratified approach, for IR (multiple or recurrent low grade Ta tumors), takes into account four key factors: tumor size, tumor multiplicity, timing and frequency of recurrences and previous treatment. Patients

with none of these factors are at low risk of disease recurrence and progression and, therefore, can be treated similar to low risk patients. Patients with 1–2 factors are classified as “low–intermediate”. IR patients with ≥ 3 factors are at the higher risk of recurrence and progression and, therefore, are classified as “high–intermediate”. Indeed, some patients from the IR cohort, the “low–intermediate” patients, will be better treated with intravesical chemotherapy instillations and maintenance. On the contrary, patients with a more aggressive profile, the “high–intermediate” cohort, will be better managed with BCG and maintenance for 1 year [25]. The summary of recommendations discussed in this section is listed in the Table 2.

Management of primary and recurrent high risk disease (HG Ta, T1, CIS)

Among patients with non-muscle invasive bladder cancer (NMIBC), 20–40% will present with tumors that have a high risk of recurrence and progression [8]. While there is some variability in the definition of high risk NMIBC, patients with histologic high grade disease have the highest risk of recurrence and progression and are considered high risk by all professional guidelines [18, 19]. A thorough and complete TURBT is the first step in the management of all patients with a bladder tumor and is critical for disease risk stratification, staging, and treatment response. The goal of a TURBT is to completely resect all tumors if bladder preservation is planned. Grossly incomplete resections have been reported to be as high as 70% [26]. Patients who have detrusor sampled are more likely to be staged accurately, and will have fewer

intravesical recurrences and improved survival [27]. At repeat TURBT rate from 17 to 37%, patients with Ta or T1 disease will have residual disease, most often at the site of the initial resection. Patients with clinical T1 disease have a risk of understaging upwards of 30–50%, particularly if no muscle is obtained in the specimen [28]. Several studies have examined the effectiveness of intravesical chemotherapy before inducing BCG. None of them were associated with improved recurrence rates. Due to the risk of toxicity and uncertain benefit [29], if a patient is likely to require induction of BCG then a single dose of chemotherapy should not be given. BCG has proven to be the most effective intravesical agent for treatment of high risk NMIBC. Meta-analyses of these randomized trials demonstrate that compared with observation, adjuvant intravesical BCG is associated with a 44–65% decreased risk of intravesical recurrence. In addition, adjuvant intravesical BCG is associated with a 60% decreased risk of progression compared to observation [30]. Patients with high risk NMIBC who respond to induction of BCG should be offered 3 years of full-dose maintenance BCG in accordance with the SWOG schedule [31]. Dose reduction for induction therapy has been considered as a means of reducing toxicity and improving compliance without compromising effectiveness. When maintenance therapy is given, intravesical BCG is associated with a 20–30% lower recurrence risk compared with chemotherapy. Without maintenance, BCG may have a similar or higher risk of recurrence compared to chemotherapy, specifically MMC. Based on trial data from the Club Urologico Espanol de Tratamiento Oncologico (CUETO) group, 1/3 dose BCG has been shown to have similar effectiveness to full-dose BCG and with fewer side effects [32]. Smoking is an independent risk factor for recurrence and progression in

Table 2 Summary of evidence and recommendation for LGTa

Recommendation	LE	GR
Routine imaging of the upper tracts is not recommended in patients with LGTa bladder cancer	3	B
Upper tract imaging could be carried out in patients with multifocal tumors and those with tumors centred in the trigone	3	B
Routine imaging of the upper tracts is not recommended for surveillance in patients with LGTa bladder cancer	3	B
Office fulguration or cysto-diathermy can be carried out in patients with small (< 10 mm) recurrent LGTa with no previous history of high grade cancer or cis	2	B
Holmium: YAG laser could be used to fulgurate recurrent LGTa bladder cancers	2	B
Chemo-resection is not recommended for routine use in recurrent LGTa bladder cancers outside the setting of a clinical trial	3	B
Expectant management or active surveillance can be adopted in patients with established recurrent LGTa bladder cancers	3	B
The ideal tumour(s) for expectant management or active surveillance are those that are small (5 mm or less), papillary in appearance and three or less in number	3	B
If a strategy of expectant management/active surveillance is adopted, a clear protocol (with criteria for intervention) must be followed	3	B
Examination of urine cytology must be a part of the expectant management or active surveillance protocol	3	B
For low risk disease, a single dose instillation post-TURB (SI) is sufficient and no further adjuvant treatment is needed	1a	A
For low–intermediate, a single dose instillation post-TURB (SI) followed by induction chemotherapy followed by maintenance (6–12 months)	2a	B
For high–intermediate, a single dose instillation post-TURB (SI) followed by induction with full-dose BCG instillations and maintenance for 1 year	1a	A

NMIBC [33]. Compared to current smokers, patients who quit smoking 10 years prior to TURBT had a lower risk of disease recurrence and lower risk of disease progression [34]. Definitions of BCG failure include BCG refractory, BCG relapsing, BCG unresponsive, and BCG intolerant. BCG refractory: patients with NMIBC who have progressive disease after a single induction cycle (at 3 months) or persistent high-grade or progressive disease after two induction cycles or an induction cycle and a 3 week maintenance dose (at 6 months) [35]. BCG relapsing: patients with NMIBC who have a complete response to BCG by 6 months, and then recur following a disease-free period. BCG unresponsive: it includes both very early relapses within 6–9 months of BCG exposure and BCG refractory patients. BCG intolerant: patients who are unable to complete induction therapy due to severe symptoms. Patients with BCG refractory high risk NMIBC are at significant risk of progression and metastasis, and should be offered a radical cystectomy [36]. Patients with BCG refractory high risk NMIBC who are unfit for or unwilling to have cystectomy should be referred to centers with clinical trials in this space. There are multiple ongoing clinical trials evaluating novel treatments, including systemic immunotherapies with or without intravesical agents, for BCG unresponsive NMIBC [37]. If a clinical trial is not available, there are a variety of intravesical chemotherapies that have been tested as salvage agents with modest results such as valrubicin, gemcitabine, and docetaxel [38, 39]. Patients who relapse over 12 months from their last BCG treatment may be offered additional BCG [40]. Conversely, patients with an early relapse should be managed more aggressively [41]. Regarding alternative therapies, intravesical radiofrequency-induced chemohyperthermia (RF-induced CHT) is an effective and promising treatment option in BCG unresponsive and highly recurrent intermediate and high risk NMIBC patients [42]. BCG strains and host variations, such as age, genetics and smoking, have been implicated in determining response to BCG. Definitive conclusions regarding effectiveness across BCG strains are not reached. However, some strains could influence antitumor immune responses as suggested by clinical studies comparing BCG strains [LE:3]. Electro Motive Drug Administration (EMDA) and chemoradiation are effective alternative treatment options in NMIBC patients [43, 44]. The summary of recommendations discussed in this section is listed in the Table 3.

Management of positive urine cytology with negative white light cystoscopy

The management of positive cytology with negative white light cystoscopy involves: (1) confirmation of urine cytology through a second opinion review or repeat cytology, (2) utilization of PDD [45] or fluorescent cystoscopy to identify occult lesions in the bladder, (3) ruling out occult

disease in the prostatic urethra and the upper urinary tracts. If the workup is negative, patients with a positive cytology and an initial negative white light cystoscopy need to be informed that they may have a 76% chance of developing bladder cancer within 1 year [46] and that close surveillance is required for at least the next year. Random biopsies of normal appearing mucosa can be considered in patients at high risk of concomitant CIS, such as a positive cytology, but in the absence of a positive cytology there is little evidence to support random biopsies. [LE:3, GR:C]. An algorithm for management of positive voided urine cytology is available, and summarizes the idea in this setting as shown below [47].

1. Upper tract imaging (CT urography or intravenous pyelogram and renal ultrasound, MRI) and cystoscopy.
If findings are negative, perform cytological review and/or repeat cytology with bladder barbotage.
2. Cytological review and/or repeat cytology.
If positive, consider fluorescent cystoscopy.
3. Fluorescent cystoscopy.
If positive, biopsy abnormal areas.
If negative, consider prostatic urethral biopsies at the same time.
4. Bilateral retrograde ureteropyelograms with bilateral ureteroscopy, biopsies, and selective urine sampling.
5. Repeat cytology in 3–12 months if no abnormality is found.

Management of prostatic urethral involvement

There are several retrospective studies supporting the use of bladder preservation options for prostatic urethral mucosal disease. Intravesical BCG only without TURP has been reported to achieve complete responses in 54–80% of select cases of prostatic urethral disease [48, 49]. Complete response in the prostatic urethra of 65.7% for BCG only treated patients, which increases to 95.3% when TURP is performed prior to BCG [49]. It appears safe to initially manage high grade non-invasive disease of the prostatic urethral mucosa (Ta/T1, Tis) with TURP and BCG [LE:3]. There is very limited data to guide management of urothelial carcinoma of the prostate involving the prostatic acini and ducts [48]. More caution is needed for high grade disease involving the prostatic ducts (Tis), but TURP and BCG may be considered if ductal involvement is properly staged and found to be limited to the superficial ducts without invasion [LE:3]. Extensive ductal involvement or prostatic urethral recurrence after failed conservative treatment should be managed with radical cystoprostatectomy preferably with concurrent urethrectomy [LE:3]. Primary bladder tumors

Table 3 Summary of evidence and recommendation for high risk disease (HG Ta, T1, CIS)

Recommendation	LE	GR
A thorough examination should be performed on all patients with bladder tumors at the time of TURBT, including a bimanual exam and cystoscopic assessment of tumor characteristics	2	B
A complete TURBT should be performed on all patients with bladder tumors when safe, feasible, and bladder preservation is planned	3	C
A repeat TURBT should be performed within 6 weeks of initial resection for all patients with an incomplete initial resection and for patients with T1 disease after a complete initial resection	2	B
A repeat TURBT should be considered within 6 weeks of a complete initial resection for patients with high grade Ta tumors, particularly for patients with large or multifocal tumors	3	C
Patients with high risk NMIBC who are treated with intravesical BCG do not benefit from an immediate dose of intravesical chemotherapy	2	B
Patients with high risk NMIBC for whom bladder sparing is desired should be offered induction intravesical BCG after a complete TURBT	1	A
Patients with high risk NMIBC for whom bladder sparing is desired who are ineligible to receive intravesical BCG may be offered induction intravesical chemotherapy after a complete TURBT.	2	B
Patients who respond to induction intravesical BCG should be offered up to 3 years of maintenance	2	B
Patients who respond to induction intravesical chemotherapy should be offered maintenance therapy for 1 year	2	C
For patients who have intolerable side effects from BCG, dose reduction may be considered	2	B
Smoking is associated with increased risk of disease recurrence and progression. Patients should be advised to quit smoking	3	B
BCG refractory NMIBC is either 1) disease progression after one induction cycle of BCG or, 2) persistent high grade or worsening disease after two induction cycles or one induction cycle and one maintenance dose	3	B
BCG unresponsive includes both BCG refractory and BCG relapsing high risk disease within 6 months of last BCG exposure	4	C
Patients with BCG refractory high risk NMIBC who are unfit for or refuse cystectomy should be offered a clinical trial of salvage therapy	4	C
Patients with BCG refractory high risk NMIBC who are unfit for or refuse cystectomy for whom a clinical trial is unavailable may be offered salvage intravesical chemotherapy or immunotherapy	2	C
Patients with early relapsing high risk NMIBC within 12 months of induction therapy plus maintenance or two induction courses should be managed as BCG refractory NMIBC	3	C
Offer RF-induced CHT to NMIBC patients who failed on BCG treatment and are unfit or unwilling to undergo radical cystectomy	1b	B
Offer treatment with RF-induced CHT or EMDA-MMC in patients with intermediate to high risk NMIBC if BCG is not available	1b	B
Offer chemoradiation in patients with high risk NMIBC who are unfit or unwilling to undergo radical cystectomy, only if BCG is not available or contra-indicated	1b	B

invading into the prostatic stroma (T4) have a 5-year survival rate of 21% with increased risk of nodal metastasis [50]. Patients with stromal invasion should be considered for cisplatin-based neoadjuvant chemotherapy followed by radical cystoprostatectomy preferably with concurrent urethrectomy [LE:1]. Extended pelvic lymph node dissection should also be strongly considered given the rates of node positive disease when stromal invasion is present [LE:4].

Indications for timely cystectomy

NMIBC unfortunately has an estimated 10–20% chance of progressing to muscle invasive disease during follow-up [23]. Depth of invasion, lymphovascular invasion (LVI), concomitant CIS, increased size and pure variant histologies (micropapillary, sarcomatoid or plasmacytoid) place patients at higher risk for recurrence, progression and disease-related mortality [51]. In patients who are operative candidates and have T1 disease with these high risk features, or persistent/

recurrent T1 disease at re-resection, clinicians should consider initial radical cystectomy (RC) [LE:3, GR:C]. Early RC improves survival rates; 15-year cancer-specific survival was improved in patients who had RC within 2 years of BCG initiation (69%) compared to those after 2 years (26%) [52]. There is enough data to suggest potential mortality benefits in patients with aggressive NMIBC that consensus exists to consider early cystectomy with lymph node dissection for these patients.

Surveillance strategies for NMIBC

Most protocols include this combination every 3–6 months for 2 years after the initial diagnosis, then every 6–12 months for the following 2 years, and then annually thereafter, resetting the clock with each newly identified tumor [18, 19]. In addition to cystoscopy, use of urine cytology plays an important role in the surveillance of NMIBC. The urine cytology has been found to have a high sensitivity for detecting

HG lesions (84%) but low sensitivity for LG tumors (16%) [53]. It also has a high specificity (> 90%) for both low and high grade tumors, including CIS [54]. The first surveillance cystoscopy for patients with NMIBC should be performed 3 months following TURBT, as it is an important prognostic indicator of recurrence and progression [LE:1a, GR:A] [18]. The frequency and duration of cystoscopy and imaging, however, should be risk-adjusted. Surveillance strategies following a negative 3 months surveillance cystoscopy should be: (1) for low risk disease, cystoscopy 6–9 months later and annually thereafter; consider cessation following five recurrence-free years. No upper tract imaging necessary unless hematuria present; (2) for intermediate risk, cystoscopy with cytology every 3–6 months for 2 years; then every 6–12 months during years 3 and 4; then annually for lifetime. Upper tract imaging every 1–2 years; (3) for high risk, cystoscopy with cytology every 3 months for 2 years; then every 6 months during years 3 and 4; then annually for lifetime. Upper tract imaging every 1–2 years [LE:3,GR:C] [18, 19].

Conclusion

NMIBC remains a common and challenging malignancy to manage. Accurate staging, grading, and risk stratification are critical determinants needed to convey prognosis to patients and to guide management decisions. Improvements in risk stratification, identification of high risk patients and tumor characteristics, and development of new technologies will further improve our prognostic accuracy and management strategies in the future. Current tools for risk stratification are limited but informative, and should be used in clinical practice when determining diagnosis, surveillance, and treatment of NMIBC. High risk NMIBC (high grade Ta, T1, CIS) present risk for progression, close surveillance and timely radical cystectomy may improve oncological outcomes after initial diagnosis. The third ICUD covered the entire spectrum of NMIBC. For missing sections such as prognostic factors, management of complications of intravesical therapy, new treatment strategies from ongoing and future clinical trials, refer to the ICUD chapter on NMIBC [55].

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Compliance with ethical standards

Conflict of interest Author JA Witjes has relationship with Sanofi Pasteur, MEL Amsterdam (Synergo), Cepheid, Nucleix, BMS, Taris, BioCancel and Spectrum. Author SS Chang has relationship with Mdx Health, BioCancel, Bristol Myers Squibb, and Altor. Author GS Kulkarni has received research funds from Biosyent Canada. Author MA O'Donnell has relationship with Abbot Molecular, Roche, Photocure, Urogen, Medical Enterprises, Viventia, Spectrum, Fidia Pharmaceuticals, Vaxiion Pharmaceuticals, and Therlasae. The other authors declare that they have no conflict of interest.

Research involving human participants and/or animals For this type of study formal consent is not required. This article does not contain any studies with human participants or animals performed by any of the authors.

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