available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Guidelines

EAU Guidelines on Non–Muscle-invasive Urothelial Carcinoma of the Bladder: Update 2016

Marko Babjuk[a,*], *Andreas Böhle*[b], *Maximilian Burger*[c], *Otakar Capoun*[d,†], *Daniel Cohen*[e,f,†], *Eva M. Compérat*[g], *Virginia Hernández*[h,†], *Eero Kaasinen*[i], *Joan Palou*[j], *Morgan Rouprêt*[k,l], *Bas W.G. van Rhijn*[m], *Shahrokh F. Shariat*[n], *Viktor Soukup*[d,†], *Richard J. Sylvester*[o], *Richard Zigeuner*[p]

[a] *Department of Urology, Hospital Motol, Second Faculty of Medicine, Charles University, Praha, Czech Republic;* [b] *Department of Urology, HELIOS Agnes-Karll-Krankenhaus, Bad Schwartau, Germany;* [c] *Department of Urology, Caritas St. Josef Medical Centre, University of Regensburg, Regensburg, Germany;* [d] *Department of Urology, General University Hospital, First Faculty of Medicine, Charles University, Prague, Czech Republic;* [e] *Department of Surgery and Cancer, Imperial College London, UK;* [f] *Department of Urology, Lister Hospital, East and North Hertfordshire NHS Trust, Stevenage, UK;* [g] *Department of Pathology, Hôpital La Pitié-Salpétrière, UPMC, Paris, France;* [h] *Department of Urology, Hospital Universitario Fundación Alcorcón, Madrid, Spain;* [i] *Department of Urology, Hyvinkää Hospital, Hyvinkää, Finland;* [j] *Department of Urology, Fundació Puigvert, Universidad Autónoma de Barcelona, Barcelona, Spain;* [k] *AP-HP, Hôpital La Pitié-Salpétrière, Service d'Urologie, Paris, France;* [l] *UPMC University Paris 06, GRC5, ONCOTYPE-Uro, Institut Universitaire de Cancérologie, Paris, France;* [m] *Department of Surgical Oncology (Urology), Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands;* [n] *Medical University of Vienna, Vienna General Hospital, Vienna, Austria;* [o] *European Association of Urology Guidelines Office, Brussels, Belgium;* [p] *Department of Urology, Medical University of Graz, Graz, Austria*

Article info

Article history:
Accepted May 30, 2016

Associate Editor:
James Catto

Keywords:
Bacillus Calmette-Guérin (BCG)
Bladder cancer
Cystectomy
Diagnosis
Guidelines
Intravesical chemotherapy
Prognosis
Transurethral resection (TUR)
Urothelial carcinoma
European Association of Urology

Abstract

Context: The European Association of Urology (EAU) panel on Non–muscle-invasive Bladder Cancer (NMIBC) released an updated version of the guidelines on Non–muscle-invasive Bladder Cancer.
Objective: To present the 2016 EAU guidelines on NMIBC.
Evidence acquisition: A broad and comprehensive scoping exercise covering all areas of the NMIBC guidelines published between April 1, 2014, and May 31, 2015, was performed. Databases covered by the search included Medline, Embase, and the Cochrane Libraries. Previous guidelines were updated, and levels of evidence and grades of recommendation were assigned.
Evidence synthesis: Tumours staged as TaT1 or carcinoma *in situ* (CIS) are grouped as NMIBC. Diagnosis depends on cystoscopy and histologic evaluation of the tissue obtained by transurethral resection of the bladder (TURB) in papillary tumours or by multiple bladder biopsies in CIS. In papillary lesions, a complete TURB is essential for the patient's prognosis. If the initial resection is incomplete, there is no muscle in the specimen, or a high-grade or T1 tumour is detected, a second TURB should be performed within 2–6 wk. The risks of both recurrence and progression may be estimated for individual patients using the European Organisation for Research and Treatment of Cancer (EORTC) scoring system and risk tables. The stratification of patients into low-, intermediate-, and high-risk groups is pivotal to recommending adjuvant treatment. For patients with a low-risk tumour and intermediate-risk patients at a lower risk of recurrence, one immediate instillation of chemotherapy is recommended. Patients with an intermediate-risk tumour should receive 1 yr of full-dose bacillus Calmette-Guérin

† Guidelines associate.

* Corresponding author. Department of Urology, Hospital Motol, Second Faculty of Medicine, Charles University, V Úvalu 84, Praha 5, 15006, Czech Republic. Tel.: +420 224434801; fax: +420 224434821.
E-mail address: marek.babjuk@lfmotol.cuni.cz (M. Babjuk).

http://dx.doi.org/10.1016/j.eururo.2016.05.041

(BCG) intravesical immunotherapy or instillations of chemotherapy for a maximum of 1 yr. In patients with high-risk tumours, full-dose intravesical BCG for 1–3 yr is indicated. In patients at highest risk of tumour progression, immediate radical cystectomy (RC) should be considered. RC is recommended in BCG-refractory tumours. The long version of the guidelines is available at the EAU Web site (www.uroweb.org/guidelines).
Conclusions: These abridged EAU guidelines present updated information on the diagnosis and treatment of NMIBC for incorporation into clinical practice.
Patient summary: The European Association of Urology has released updated guidelines on Non–muscle-invasive Bladder Cancer (NMIBC). Stratification of patients into low-, intermediate-, and high-risk groups is essential for decisions about adjuvant intravesical instillations. Risk tables can be used to estimate risks of recurrence and progression. Radical cystectomy should be considered only in case of failure of instillations or in NMIBC with the highest risk of progression.

1. Introduction

This overview represents the updated European Association of Urology (EAU) guidelines for Non–muscle-invasive Bladder Cancer (NMIBC): TaT1 and carcinoma *in situ* (CIS). The information presented is limited to urothelial carcinoma, unless specified otherwise. The aim is to provide practical guidance on the clinical management of NMIBC with a focus on clinical presentation and recommendations.

Clinical guidelines present the best evidence available to the experts, but following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather they help to focus decisions, also taking personal values and preferences/individual circumstances of patients into account.

2. Evidence acquisition

A broad and comprehensive scoping exercise covering all areas of the NMIBC guidelines was performed. The search was limited to studies representing high levels of evidence (LE) only published in the English language. The search was restricted to articles published during the period from April 1, 2014, to May 31, 2015. Databases covered by the search included Medline, Embase, and the Cochrane Libraries. A total of 1040 unique records were identified, retrieved, and screened for relevance. A detailed search strategy is available online at https://uroweb.org/guideline/non-muscle-invasive-bladder-cancer/?type=appendices-publications.

Recommendations in this text are assessed according to their LE, and are given a grade of recommendation according to a classification system modified from the 2009 Oxford Centre for Evidence-Based Medicine Levels of Evidence. Additional methodology information can be found online at the EAU Web site: http://uroweb.org/guidelines/.

3. Epidemiology

Bladder cancer (BCa) is the seventh most commonly diagnosed cancer in the male population worldwide. It drops to 11th when both genders are considered [1]. The worldwide age-standardised incidence rate (per 100 000 person-years) is 9.0 for men and 2.2 for women [1]. In the European Union, the age-standardised incidence rate is 19.1 for men and 4.0 for women [1]. In Europe, the highest age-standardised incidence rate was reported in Belgium (31 in men and 6.2 in women) and the lowest in Finland (18.1 in men and 4.3 in women) [1,2].

Worldwide, the BCa age-standardised mortality rate (per 100 000 person-years) was 3.2 for men versus 0.9 for women in 2012 [1]. The incidence and mortality of BCa has decreased in some registries, possibly reflecting the decreased impact of causative agents [3].

Approximately 75% of patients with BCa present with a disease confined to the mucosa (stage Ta, CIS) or submucosa (stage T1) [2].

4. Risk factors

Tobacco smoking is the most important risk factor for BCa, accounting for approximately 50% of cases [2,4] (LE: 3). Occupational exposure to aromatic amines, polycyclic aromatic hydrocarbons, and chlorinated hydrocarbons accounts for about 10% of cases. This type of exposure occurs mainly in industrial plants processing paint, dye, metal, and petroleum products [2,5]. Genetic predisposition has an influence on susceptibility to other risk factors [2,6].

The chlorination of drinking water and subsequent levels of trihalomethanes are potentially carcinogenic, and exposure to arsenic in drinking water increases risk [2,7] (LE: 3). Exposure to ionising radiation is connected with increased risk; weak association was also suggested for cyclophosphamide and pioglitazone [2] (LE: 3). Schistosomiasis, based on recurrent infection with a parasitic trematode, is also a cause of BCa [2] (LE: 3).

5. Classification

5.1. Definition of non–muscle-invasive bladder cancer

Papillary tumours confined to the mucosa or invading the lamina propria are classified as stage Ta or T1, respectively, according to the TNM classification system. Flat high-grade (HG) tumours confined to the mucosa are classified as CIS (Tis). These tumours are grouped under the heading of NMIBC for therapeutic purposes. However, molecular biology techniques and clinical experience have demonstrated the

Please cite this article in press as: Babjuk M, et al. EAU Guidelines on Non–Muscle-invasive Urothelial Carcinoma of the Bladder: Update 2016. Eur Urol (2016), http://dx.doi.org/10.1016/j.eururo.2016.05.041

highly malignant potential of CIS and T1 lesions. Consequently, the terms *NMIBC* and *superficial BCa* are suboptimal descriptions.

5.2. TNM classification and definition of non–muscle-invasive bladder cancer

The 2002 TNM classification approved by the Union Internationale Contre le Cancer was updated in 2009 (7th edition) (Table 1) [8].

5.3. Grading

In 2004, the World Health Organisation (WHO) and the International Society of Urological Pathology published a new histologic classification of urothelial carcinomas that provides a different patient stratification compared with the older 1973 WHO classification (Table 2). A new update of the WHO grading classification was published recently, but the following guidelines are still based on the 1973 and 2004 WHO classifications [9,10].

5.4. Carcinoma in situ and its clinical classification

CIS is a flat HG/G3 noninvasive urothelial carcinoma. It can be missed at cystoscopy if it is not biopsied. CIS is often multifocal and can occur in the bladder but also in the upper urinary tract, prostatic ducts, and prostatic urethra [11].

Table 1 – 2009 TNM classification of urinary bladder cancer [8]

T: Primary tumour	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Ta	Noninvasive papillary carcinoma
Tis	Carcinoma *in situ:* "flat tumour"
T1	Tumour invades subepithelial connective tissue*
T2	Tumour invades muscle
	T2a Tumour invades superficial muscle (inner half)
	T2b Tumour invades deep muscle (outer half)
T3	Tumour invades perivesical tissue
	T3a Microscopically
	T3b Macroscopically (extravesical mass)
T4	Tumour invades any of the following: prostate, uterus, vagina, pelvic wall, abdominal wall
	T4a Tumour invades prostate, uterus, or vagina
	T4b Tumour invades pelvic wall or abdominal wall
N: Lymph nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single lymph node in the true pelvis (hypogastric, obturator, external iliac, or presacral)
N2	Metastasis in multiple lymph nodes in the true pelvis (hypogastric, obturator, external iliac, or presacral)
N3	Metastasis in common iliac lymph node(s)
M: Distant metastasis	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

* The WHO 2016 recommends pT1 substaging as clinically relevant without specific details on extent of invasion.

Table 2 – 1973 and 2004/2016 World Health Organisation grading classifications

1973 WHO grading system
Urothelial papilloma
Grade 1: Well differentiated
Grade 2: Moderately differentiated
Grade 3: Poorly differentiated
2004/2016 WHO grading system [papillary lesions]
Urothelial papilloma (completely benign lesion)
PUNLMP
LG papillary urothelial carcinoma
HG papillary urothelial carcinoma
Flat lesions (2004 WHO grading system)
Urothelial proliferation of uncertain malignant potential (arcinia hyperplasia)
Reactive atypia (flat lesion with atypia)
Atypia of unknown significance
Urothelial dysplasia
Urothelial CIS (always HG)

CIS = carcinoma *in situ*; HG = high grade; LG = low grade; PUNLMP = papillary urothelial neoplasm of low malignant potential; WHO = World Health Organisation.

Classification of CIS into clinical type is as follows:

- Primary: isolated CIS with no previous or concurrent papillary tumours and no previous CIS
- Secondary: CIS detected during follow-up of patients with a previous tumour that was not CIS
- Concurrent: CIS in the presence of any other urothelial tumour in the bladder

5.5. Inter- and intraobserver variability in staging and grading

Pathologists vary significantly in their diagnosis of CIS, and agreement is achieved in 70–78% of cases [12] (LE: 2a). There is also interobserver variability in the classification of stage T1 versus Ta tumours and tumour grading in both the 1973 and 2004 classifications. The general conformity in staging and grading is between 50% and 60% [12–15] (LE: 2a). The published comparisons have not clearly confirmed that the WHO 2004 classification has better reproducibility than the 1973 classification [13,16].

5.6. Further promising pathology parameters

Lymphovascular invasion has been reported as an unfavourable prognostic factor in T1 tumours [17] (LE: 3). Some variants of urothelial carcinoma (micropapillary, plasmocytoid, nested, sarcomatoid, microcystic, squamous, and adeno variants of urothelial carcinoma) have a poor prognosis [18] (LE: 3). Table 3 lists recommendations for BCa classification.

6. Diagnosis

6.1. Patient history, signs, and symptoms

A comprehensive patient history is mandatory. Haematuria is the most common finding in NMIBC. CIS might be

Table 3 – Recommendations for non–muscle-invasive bladder cancer classification

Recommendation	GR
For classification of the depth of tumour invasion (staging), use the 2009 TNM system.	A
For histologic classification, use the 1973 and 2004/2016 WHO grading systems.	A
Do not use the term *superficial bladder cancer*.	A
Whenever you use the terminology NMIBC in individual cases, mention the tumour stage and grade.	A

GR = grade of recommendation; NMIBC = non–muscle-invasive bladder cancer; WHO = World Health Organisation.

suspected in patients with storage lower urinary tract symptoms.

6.2. Physical examination

Physical examination does not reveal NMIBC.

6.3. Imaging

Computed tomography (CT) urography is used to detect papillary tumours in the urinary tract that can be seen as filling defects or indicated by hydronephrosis. Intravenous urography (IVU) can be an alternative if CT is not available [19] (LE: 3), but particularly in muscle-invasive tumours of the bladder and in upper tract urothelial carcinomas (UTUCs), CT urography offers more information than IVU.

The necessity to perform a CT urography or IVU once a bladder tumour has been detected is questionable due to the low incidence of significant findings obtained [20] (LE: 2a). The incidence of UTUCs is low (1.8%) but increases to 7.5% in tumours located in the trigone [20] (LE: 2b). The risk of UTUC during follow-up increases in patients with multiple and high-risk tumours [21] (LE: 3).

Transabdominal ultrasound (US) permits characterisation of renal masses, detection of hydronephrosis, and visualisation of intraluminal masses in the bladder (LE: 3) Consequently, US is a useful tool in patients with haematuria. However, it cannot exclude the presence of UTUC and cannot replace CT urography.

The diagnosis of CIS cannot be made with imaging methods (LE: 4).

6.4. Urinary cytology

The examination of voided urine or bladder-washing specimens for exfoliated cancer cells has high sensitivity in HG tumours (84%) but low sensitivity in low-grade (LG) tumours (16%) [22]. The sensitivity for CIS detection is 28–100% [23] (LE: 2b). Cytology is useful, particularly as an adjunct to cystoscopy, if HG/CIS malignancy is present. Positive voided urinary cytology can indicate a urothelial tumour anywhere in the urinary tract; negative cytology, however, does not exclude the presence of a tumour.

Cytologic interpretation is user dependent [24]. Evaluation can be hampered by low cellular yield, urinary tract infections, stones, or intravesical instillations, but in experienced hands specificity exceeds 90% [25] (LE: 2b).

Table 4 – Recommendations for the primary assessment of non–muscle-invasive bladder cancer

Recommendation	GR
Patient history should be taken.	A
Renal and bladder US may be used during the initial work-up in patients with haematuria.	C
At the time of the initial diagnosis of NMIBC, CT urography (or IVU) should be performed in selected cases (eg, tumours located in the trigone, multiple or high-risk tumours).	B
Cystoscopy is recommended in all patients with symptoms suggestive of BCa. It cannot be replaced by cytology or by any other noninvasive test.	A
Cystoscopy should describe all macroscopic features of the tumour (site, size, number, and appearance) and mucosal abnormalities. A bladder diagram is recommended.	C
Voided urine cytology is advocated as an adjunct to cystoscopy to detect HG tumour.	C
Cytology should be performed on fresh urine with adequate fixation. Morning urine is not suitable because of the frequent presence of cytolysis.	C

BCa = bladder cancer; CT = computed tomography; GR = grade of recommendation; HG = high grade; IVU = intravenous urography; NMIBC = non–muscle-invasive bladder cancer; US = ultrasound.

Urine collection should be performed with respect to the recommendations provided in Table 4. One cytospin slide from the sample is usually sufficient. In patients with suspect cytology it is reasonable to repeat the investigation (LE: 3).

6.5. Urine molecular tests

Driven by the low sensitivity of urine cytology, numerous urinary tests were developed [25–27]. None of these markers have been accepted for diagnosis or follow-up in routine practice or clinical guidelines.

6.6. Cystoscopy

The diagnosis of papillary BCa depends on cystoscopic examination and histologic evaluation of the resected tissue. CIS is diagnosed by a combination of cystoscopy, urine cytology, and histologic evaluation of multiple bladder biopsies. Cystoscopy is initially performed in the office. A flexible instrument with intraurethral anaesthetic lubricant instillation results in better compliance compared with a rigid instrument, especially in men [28]. Table 4 lists recommendations for the primary assessment of BCa.

6.7. Transurethral resection of bladder cancer

6.7.1. Strategy of the procedure

The goal of transurethral resection of the bladder (TURB) in TaT1 BCa is to make the correct diagnosis and completely remove all visible lesions. TURB should be performed systematically in individual steps (Table 5). The strategy of resection depends on the size of the lesion. Separate resection of larger tumours provides good information about the extent of the tumour and helps improve completeness of resection [29,30] (LE: 3).

Please cite this article in press as: Babjuk M, et al. EAU Guidelines on Non–Muscle-invasive Urothelial Carcinoma of the Bladder: Update 2016. Eur Urol (2016), http://dx.doi.org/10.1016/j.eururo.2016.05.041

Table 5 – Recommendations for transurethral resection of the bladder and/or biopsies and pathology report

Recommendation	GR
In patients suspected of harbouring BCa, TURB followed by pathology investigation of the obtained specimen(s) is recommended as a diagnostic procedure and initial treatment step.	A
Perform TURB systematically in individual steps: • Bimanual palpation under anaesthesia • Insertion of the resectoscope under visual control with inspection of the whole urethra • Inspection of the whole urothelial lining of the bladder • Biopsy from prostatic urethra (if indicated) • Cold-cup bladder biopsies (if indicated) • Resection of the tumour • Surgical report formulation • Precise description of the specimen for pathology evaluation	C
Performance of individual steps:	
Perform resection in one piece for small papillary tumours (<1 cm) including part from the underlying bladder wall.	B
Perform resection in fractions including the exophytic part of the tumour, the underlying bladder wall with the detrusor muscle, and the edges of the resection area for tumours > 1 cm in diameter.	B
Avoid cauterisation as much as possible during TURB to avoid tissue deterioration.	C
Take biopsies from abnormal-looking urothelium. Biopsies from normal-looking mucosa (trigone, bladder dome, and right, left, and anterior and posterior bladder walls) are recommended when cytology is positive or when high-risk exophytic tumour is expected (nonpapillary appearance). If equipment is available, use fluorescence-guided (PDD) biopsies.	B
Take biopsy of the prostatic urethra in cases of bladder neck tumour, when bladder CIS is present or suspected, when there is positive cytology without evidence of tumour in the bladder, or when abnormalities of the prostatic urethra are visible. If biopsy is not performed during the initial procedure, it should be completed at the time of the second resection.	C
Take the biopsy from abnormal areas in the prostatic urethra and from the precollicular area (between 5 and 7 o'clock positions) using a resection loop. In primary non–muscle-invasive tumours when stromal invasion is not suspected, cold-cup biopsy with forceps can be used.	C
Refer the specimens from different biopsies and resection fractions to the pathologist in separate containers and label them separately.	C
TURB protocol must describe tumour appearance, all steps of the procedure, as well as the extent and completeness of resection.	C
In patients with positive cytology, but negative cystoscopy, exclude a UTUC, CIS in the bladder (random biopsies or PDD-targeted biopsies), and tumour in prostatic urethra (prostatic urethra biopsy).	C
Perform a second TURB in the following situations: • After incomplete initial TURB • If there is no muscle in the specimen after initial resection, with exception of TaG1 tumours and primary CIS • In all T1 tumours • In all HG/G3 tumours, except primary CIS	A
If indicated, perform a second TURB within 2–6 wk after initial resection. It should include the resection of primary tumour site.	C
Pathology report	
The pathology report should specify tumour location, tumour grade, depth of tumour invasion, presence of CIS, and whether the detrusor muscle is present in the specimen.	A
The pathology report should specify the presence of LVI or unusual (variant) histology.	C
In difficult cases, consider an additional review by an experienced genitourinary pathologist.	B

BCa = bladder cancer; CIS = carcinoma *in situ*; GR = grade of recommendation; HG = high grade; LVI = lymphovascular invasion; PDD = photodynamic diagnosis; TURB = transurethral resection of the bladder; UTUC = upper tract urothelial carcinoma.

A complete and correct TURB is essential to achieve a good prognosis [31]. The absence of detrusor muscle in the specimen is associated with a significantly higher risk of residual disease, early recurrence, and tumour understaging [30,32] (LE: 2b). Surgical experience can improve TURB results and thus supports the role of teaching programmes [33].

6.7.2. *Office-based fulguration*

In patients with a history of small Ta LG/G1 tumours, fulguration of small papillary recurrences on an outpatient basis can reduce the therapeutic burden and can be an option [34,35] (LE: 3).

6.7.3. *New resection techniques*

Compared with monopolar resection, the bipolar electrocautery system was introduced to reduce the risk of complications and produce better specimens for the pathologist [36] (LE: 3). The results currently remain controversial [37].

6.7.4. *Bladder and prostatic urethral biopsies*

CIS can present as an area indistinguishable from inflammation, or it may not be visible at all. For this reason, the strategy of taking biopsies from abnormal urothelium and biopsies from normal-looking mucosa (random/mapping biopsies) is recommended (Table 5). The indication for random biopsies reflects the fact that the likelihood of detecting CIS, especially in low-risk tumours, is extremely low (<2%) [38] (LE: 2a). The risk increases in patients with high-risk tumours and with positive cytology [39]. If equipment is available, photodynamic diagnosis (PDD) is a useful tool to target the biopsy.

Involvement of the prostatic urethra and ducts in men with NMIBC has been reported (11.7% in one study) (LE: 2b) [40]. The risk is higher if the tumour is located on the trigone or bladder neck in the presence of bladder CIS and multiple tumours [41] (LE: 3). Based on this observation, a biopsy from the prostatic urethra is necessary in some cases [40].

6.7.5. *New methods of tumour visualisation*

As a standard procedure, cystoscopy and TURB are performed using white light (WL). However, the use of WL can lead to missing lesions that are not visible, which is why new technologies are being developed.

6.7.5.1. Photodynamic diagnosis (fluorescence cystoscopy). PDD is performed using violet light after intravesical instillation of 5-aminolaevulinic acid (ALA) or hexaminolaevulinic acid (HAL). Fluorescence-guided biopsy and resection are more sensitive than conventional procedures for the detection of malignant tumours, particularly for CIS [42] (LE: 2a). In a systematic review and meta-analysis, PDD had higher sensitivity than WL endoscopy in the pooled estimates for analyses at both the patient level (92% vs71%) and biopsy level (93% vs 65%) [42]. A prospective randomised trial did not confirm a higher detection rate in patients with known positive cytology before TURB [43].

Please cite this article in press as: Babjuk M, et al. EAU Guidelines on Non–Muscle-invasive Urothelial Carcinoma of the Bladder: Update 2016. Eur Urol (2016), http://dx.doi.org/10.1016/j.eururo.2016.05.041

PDD had lower specificity than WL endoscopy (63% vs 81%) [42].

False positivity can be induced by inflammation or recent TURB and during the first 3 mo after bacillus Calmette-Guérin (BCG) instillation [44] (LE: 3). Prospective randomised studies evaluating the impact of ALA fluorescence cystoscopy (FC)-guided TURB on disease-recurrence rate provided controversial results [42,45,46].

The beneficial effect of HAL FC on recurrence rate in patients with TURB was confirmed by a multicentre prospective randomised trial and by a meta-analysis based on raw data of controlled trials. A meta-analysis reported an increase in detection of tumour lesions in HAL arms and an absolute reduction $< 10\%$ in recurrence rates within 12 mo [47] (LE: 1a). The beneficial effect of HAL FC on recurrence rates in patients with TURB and early intravesical instillation of chemotherapy was not confirmed by prospective randomised trials [48]. The value of FC for improvement of outcome in relation to progression rate and survival remains to be demonstrated.

6.7.5.2. Narrow-band imaging. In narrow-band imaging (NBI), the contrast between normal urothelium and hypervascular cancer tissue is enhanced. Initial studies have demonstrated improved cancer detection by NBI-guided biopsies and resection [49] (LE: 3).

6.8. Second resection

The significant risk of residual tumour after initial TURB of TaT1 lesions was demonstrated [31] (LE: 2a). Persistent disease after resection of T1 tumours was observed in 33–55% of patients, and after resection of TaG3 tumour in 41.4% [50,51]. The tumour is often understaged by initial resection. The likelihood that muscle-invasive disease is detected by second resection of initially T1 tumour ranges from 4% to 25%, and it increases to 45% if there was no muscle in the initial resection [30]. This risk increased to 50% in some radical cystectomy (RC) series, although these studies only enrolled selected patients [52] (LE: 2a). It has been demonstrated that a second TURB can increase recurrence-free survival [50] (LE: 2a), improve outcomes after BCG treatment [53] (LE: 3), and provide prognostic information [54] (LE: 3). Based on these arguments, a second TURB is recommended in selected cases (Table 5).

6.9. Pathology report

Pathologic investigation of the specimen(s) obtained by TURB is an essential step in the diagnosis and treatment of BCa. Close cooperation between urologists and pathologists is recommended. A high quality of resected and submitted tissue is essential for correct pathologic assessment. The presence of sufficient muscle is necessary for the correct assignment of T category. The specimen collection, handling, and evaluation should respect the recommendations [55]. Table 5 presents the recommendations for TURB and/or biopsies and pathology report.

7. Predicting recurrence and progression

7.1. Prognosis of TaT1 tumours

To predict separately the short- and long-term risks of disease recurrence and progression in individual patients, the European Organisation for the Research and Treatment of Cancer-Genito-Urinary Cancer Group (EORTC-GUCG) developed a scoring system and risk tables [56]. These tables are based on individual patient data from 2596 patients with TaT1 tumours who were randomised into seven EORTC trials and did not undergo a second TURB or receive maintenance BCG.

The scoring system is based on the six most significant clinical and pathologic factors: number of tumours, tumour size, prior recurrence rate, T category, presence of concurrent CIS, and tumour grade (WHO 1973).

Scoring models for BCG-treated patients that predict the short- and long-term risks of recurrence and progression have been developed by the Club Urológico Español de Tratamiento Oncológico (CUETO) and the EORTC.

Using the CUETO tables, the calculated risk of recurrence is lower than that obtained by the EORTC tables. For progression probabilities, it is lower only in high-risk patients [57]. The lower risks in the CUETO tables may be attributable to using BCG, which is a more effective instillation therapy. The CUETO risk calculator is available at http://www.aeu.es/Cueto.html.

In 1812 intermediate- and high-risk patients without CIS treated with 1–3 yr of maintenance BCG, the EORTC developed new BCG risk tables. The prior disease-recurrence rate and number of tumours were the most important prognostic factors for disease recurrence, stage and grade were the most important prognostic factors for disease progression and disease-specific survival, and age and grade were the most important prognostic factors for overall survival (OS). T1G3 patients do poorly, with 1- and 5-yr disease-progression rates of 11.4% and 19.8%, respectively [58] (LE: 2a).

Further prognostic factors have been described in selected patient populations. Female sex and CIS in the prostatic urethra are important prognostic factors in T1G3 patients treated with an induction course of BCG, and age, tumour size, and concurrent CIS in BCG-treated patients [40,59] (LE: 2b). Attention must be given to patients with T1G3 tumours in the bladder (pseudo)diverticulum because of an absence of muscle layer in the diverticular wall [60] (LE: 3). In patients with high-risk disease, the tumour stage at the time of the second TURB is an unfavourable prognostic factor [54] (LE: 3). Recurrence at 3 mo was the most important predictor of progression in T1G2 tumours treated with TURB [61] (LE: 2b).

7.2. Prognosis of carcinoma in situ

Without any treatment, approximately 54% of patients with CIS progress to muscle-invasive disease [62] (LE: 3). No reliable prognostic factors are available to predict the course of the disease. Some studies have reported a worse

Table 6 – Risk group stratification

Low-risk tumours	Primary, solitary, Ta, LG/G1, < 3 cm, no CIS
Intermediate-risk tumours	All tumours not defined in the two adjacent categories (between the category of low and high risk)
High-risk tumours	Any of the following: • T1 tumour • HG/G3 tumour • CIS • Multiple and recurrent and large (>3 cm) Ta G1G2 tumours (all conditions must be present in this point)

CIS = carcinoma *in situ*; HG = high grade; LG = low grade.

Table 7 – Recommendations for stratification of non–muscle-invasive bladder cancer

Recommendation	GR
Stratify patients into three risk groups according to Table 6.	B
Apply EORTC risk tables and calculator for individual prediction of the risk of tumour recurrence and progression in different intervals after TURB.	B
For individual prediction of the risk of tumour recurrence and progression in patients treated with BCG, use the CUETO risk tables and the new EORTC risk tables.	B

BCG = bacillus Calmette-Guérin; CUETO = Club Urológico Español de Tratamiento Oncológico; EORTC = European Organisation for Research and Treatment of Cancer; GR = grade of recommendation; TURB = transurethral resection of the bladder.

prognosis in concurrent CIS and T1 tumours compared with primary CIS [63], in extended CIS [64], and in CIS in the prostatic urethra [40] (LE: 3).

The response to intravesical treatment with BCG or chemotherapy is an important prognostic factor for subsequent progression and death caused by BCa [57,61]. Approximately 10–20% of complete responders eventually progress to muscle-invasive disease, compared with 66% of nonresponders [65] (LE: 2a).

7.3. *Patient stratification into risk groups*

To facilitate treatment recommendations, it is important to categorise patients into risk groups. Table 6 provides a definition of risk groups that takes into account the EORTC risk tables' probabilities of recurrence and especially progression. Table 7 lists recommendations for NMIBC patient stratification.

8. Disease management

8.1. *Counselling of smoking cessation*

It has been confirmed that smoking increases the risk of tumour recurrence and progression [66,67] (LE: 3).

8.2. *Adjuvant treatment*

8.2.1. *Intravesical chemotherapy*

Although TURB by itself can eradicate a TaT1 tumour completely, these tumours commonly recur and can progress to muscle-invasive BCa. It is therefore necessary to consider adjuvant therapy in all patients.

8.2.1.1. Single immediate postoperative intravesical instillation. Immediate single instillation (SI) acts by destroying circulating tumour cells after TURB and by an ablative effect (chemoresection) on residual tumour cells at the resection site and on small overlooked tumours. Four large meta-analyses showed that after TURB, SI significantly reduces the recurrence rate compared with TURB alone [68–71] (LE: 1a). In the most recent systematic review and individual patient data meta-analysis of 2278 eligible patients [68], SI reduced the 5-yr recurrence rate from 59% to 45%. The number to treat (NNT) to prevent one recurrence within 5 yr was seven eligible patients. Only low-risk patients and intermediate-risk patients with a prior recurrence rate of less than or equal to one recurrence per year and an EORTC recurrence score < 5 benefitted from SI. Mitomycin C (MMC), epirubicin, and pirarubicin have all shown a beneficial effect [68] (LE: 1a).

Prevention of tumour cell implantation should be initiated within the first few hours after TURB. After that, tumour cells are firmly implanted and are covered by extracellular matrix [72] (LE: 3). To maximise the efficacy of SI, flexible practices should be devised that allow the instillation to be given as soon as possible after TURB, preferably within the first 2 h. Because severe complications have been reported in patients with drug extravasation [73], safety measures should be maintained.

8.2.1.2. Additional intravesical chemotherapy instillations. In low-risk patients, an SI reduces the risk of recurrence and is considered the standard and complete treatment. For other patients, however, a SI remains an incomplete treatment because of the considerable likelihood of recurrence and/or progression. Evidence from several studies indicated that in intermediate-risk patients, SI might have an impact on recurrence even when further adjuvant instillations are given; however, they do not take into account the EORTC recurrence score [74] (LE: 2a). In one study [75], further chemotherapy instillations after SI improved recurrence-free survival in intermediate-risk patients (LE: 2a). Conversely, a sufficient number of delayed repeat chemotherapy instillations without SI can also reduce recurrences [74].

A meta-analysis of 3703 patients from 11 randomised trials showed a highly significant 44% reduction in the odds of recurrence (corresponding to an absolute difference of approximately 14%) at 1 yr in favour of chemotherapy over TURB alone, but no effect on tumour progression [76]. The length and frequency of chemotherapy instillations is still controversial [74]. The available evidence does not support treatment > 1 yr (LE: 3).

8.2.1.3. Optimising intravesical chemotherapy. Adapting urinary pH, decreasing urinary excretion, and buffering the intravesical solution of MMC reduced the recurrence rate [77] (LE: 1b). A 1-h instillation of MMC was more effective than a 30-min instillation, but no efficacy comparisons are available for 1- and 2-h instillations [78] (LE: 3). Another

Please cite this article in press as: Babjuk M, et al. EAU Guidelines on Non–Muscle-invasive Urothelial Carcinoma of the Bladder: Update 2016. Eur Urol (2016), http://dx.doi.org/10.1016/j.eururo.2016.05.041

randomised controlled trial (RCT) using epirubicin documented that concentration is more important than treatment duration [79] (LE: 1b).

Promising data have been presented on enhancing the efficacy of MMC using microwave-induced hyperthermia or the efficacy of MMC using electromotive drug administration in patients with mainly high-risk tumours. The current evidence, however, is limited [80,81], and both treatment modalities are considered experimental (LE: 2b).

8.2.2. Intravesical bacillus Calmette-Guérin immunotherapy

8.2.2.1. Efficacy of bacillus Calmette-Guérin. Five meta-analyses have confirmed that BCG after TURB is superior to TURB alone or TURB plus chemotherapy for preventing the recurrence of NMIBC [82–86] (LE: 1a). Three RCTs of intermediate- and high-risk tumours compared BCG with epirubicin plus interferon [87], MMC [88], or epirubicin alone [89] and confirmed the superiority of BCG for the prevention of tumour recurrence (LE: 1a). The effect is long lasting [88,89] and was also observed in a separate analysis of patients with intermediate-risk tumours [89].

Two meta-analyses demonstrated that BCG therapy prevents, or at least delays, the risk of tumour progression [90,91] (LE: 1a). A meta-analysis carried out by the EORTC-GUCG evaluated data from 4863 patients enrolled in 24 RCTs. Five different BCG strains were used, and in 20 of the trials, some form of BCG maintenance was used. Based on a median follow-up of 2.5 yr, in 9.8% of patients treated with BCG, tumours progressed compared with 13.8% in the control groups. The size of the reduction was similar in patients with TaT1 papillary tumours, and in those with CIS [91]. A recent RCT with long-term observation demonstrated significantly fewer distant metastases and better OS and disease-specific survival in patients treated with BCG compared with epirubicin [89] (LE: 1b). On the contrary, a meta-analysis of individual patient data was not able to confirm any statistically significant difference between MMC and BCG for progression, survival, and cause of death [82].

A meta-analysis suggested a possible bias in favour of BCG arising from the inclusion of patients previously treated with intravesical chemotherapy [92]. In the most recent meta-analysis, however, BCG maintenance was more effective than MMC, both in patients previously treated and not previously treated with chemotherapy [82] (LE: 1a). It was demonstrated that BCG was less effective in patients > 70 yr of age, but it was still more effective than epirubicin [93] (LE: 1a).

8.2.2.2. Bacillus Calmette-Guérin strain. The EORTC meta-analysis suggested no large differences in efficacy between various BCG strains [91]. Smaller studies without maintenance demonstrated some differences between strains. This clearly needs further evaluation in prospective trials [94,95] (LE: 2a).

8.2.2.3. Bacillus Calmette-Guérin toxicity. BCG intravesical treatment is associated with more side effects compared with intravesical chemotherapy. However, serious side effects are encountered in < 5% of patients and can be treated effectively. Side effects requiring treatment stoppage were seen more often in the first year of therapy [96].

Major complications can appear after systemic absorption of the drug. Thus contraindications of BCG intravesical instillation should be respected (Table 8).

The presence of leukocyturia, nonvisible haematuria, or asymptomatic bacteriuria is not a contraindication for BCG

Table 8 – Recommendations for adjuvant therapy in TaT1 tumours and for therapy of carcinoma *in situ*

Recommendations	GR
Smokers with confirmed NMIBC should be counselled to stop smoking.	B
The type of further therapy after TURB should be based on the risk groups shown in Table 6.	A
In patients with tumours presumed to be at low risk and in those presumed to be at intermediate risk with previous low recurrence rate (less than or equal to one recurrence per year) and expected EORTC recurrence score < 5, one immediate chemotherapy instillation is recommended.	A
In patients with intermediate-risk tumours (with or without immediate instillation), 1-yr full-dose BCG treatment (induction plus once weekly instillations for 3 wk at 3, 6, and 12 mo), or instillations of chemotherapy (the optimal schedule is not known) for a maximum of 1 yr is recommended. The final choice should reflect the individual patient's risk of recurrence and progression as well as the efficacy and side effects of each treatment modality.	A
In patients with high-risk tumours, full-dose intravesical BCG for 1–3 yr (induction plus instillations once weekly for 3 wk at 3, 6, 12, 18, 24, 30, and 36 mo) is indicated. The additional beneficial effect of the second and third years of maintenance should be weighed against its added costs and inconveniences.	A
In patients with CIS in the epithelial lining of the prostatic urethra, TUR of the prostate followed by intravesical instillation of BCG can be offered.	C
In patients at highest risk of tumour progression (sect. 7.1; Table 10), immediate RC should be considered.	C
In patients with BCG failure, RC is indicated.	B
Intravesical chemotherapy	
When given, one immediate instillation of chemotherapy should be administered within 24 h after TURB, preferably within 2 h.	C
One immediate instillation of chemotherapy should be omitted in any case of overt or suspected intra- or extraperitoneal perforation (after extensive TURB or bleeding requiring bladder irrigation).	C
Give clear instructions to the nursing staff to control the free flow of the bladder catheter at the end of the immediate instillation.	C
The optimal schedule of further intravesical chemotherapy instillation and its duration is not known; it should not exceed 1 yr.	C
If intravesical chemotherapy is given, it is advised to use the drug at its optimal pH and to maintain the concentration of the drug by reducing fluid intake before and during instillation.	B
The length of individual instillation should be 1–2 h.	C
BCG intravesical immunotherapy	
Absolute contraindications of BCG intravesical instillation: • During the first 2 wk after TURB • In patients with visible haematuria • After traumatic catheterisation • In patients with symptomatic urinary tract infection	C
The management of side effects after BCG intravesical instillation should reflect their type and grade.	C

BCG = bacillus Calmette-Guérin; CIS = carcinoma *in situ*; EORTC = European Organisation for Research and Treatment of Cancer; GR = grade of recommendation; NMIBC = non–muscle-invasive bladder cancer; RC = radical cystectomy; TUR = transurethral resection; TURB = transurethral resection of the bladder.

application, and antibiotic prophylaxis is not necessary in these cases [97] (LE: 3).

BCG should be used with caution (relative contraindication) in immunocompromised patients (LE: 3). The management of side effects after BCG should reflect their type and grade [98,99].

8.2.2.4. Optimal bacillus Calmette-Guérin schedule. Induction BCG instillations are given according to the empirical schedule of once weekly for 6 wk. For optimal efficacy, BCG must be given in a maintenance schedule [82,86,90,91] (LE: 1a). Many different maintenance schedules have been used; it is not possible, however, to determine which BCG maintenance schedule is the most effective [91,100]. At least 1 yr of maintenance BCG is required to obtain superiority of BCG over MMC for prevention of recurrence or progression [90] (LE: 1a).

The optimal number of induction instillations and optimal frequency and duration of maintenance instillations is not fully known. In an RCT of 1355 patients, the EORTC showed that when BCG is given at full dose, 3 yr of maintenance reduces the recurrence rate compared with 1 yr in high-risk but not in intermediate-risk patients [101] (LE: 1b). In an RCT of 397 patients, CUETO suggested that in high-risk tumours, the maintenance schedule with only one instillation every 3 mo for 3 yr may be suboptimal [102] (LE: 1b).

8.2.2.5. Optimal dose of bacillus Calmette-Guérin. To reduce BCG toxicity, instillation of a reduced dose was proposed. The CUETO study compared a one-third dose with full-dose BCG and found no overall difference in efficacy. However, it was suggested that a full dose of BCG is more effective in multifocal tumours [103] (LE: 1b). A further reduction to a one-sixth dose resulted in a decrease in efficacy with no decrease in toxicity [104] (LE: 1b).

The EORTC did not find any difference in toxicity between one-third and full-dose BCG [96,101] (LE: 1b).

8.2.2.6. Indications for bacillus Calmette-Guérin. Table 8 lists the recommendations for individual risk groups. A statement by the panel on BCG shortage can be accessed online at https://uroweb.org/guideline/non-muscle-invasive-bladder-cancer/?type=appendices-publications.

8.2.3. Combination therapy

In one RCT, a combination of MMC and BCG reduced recurrences but was more toxic compared with BCG monotherapy [105]. In frequently recurrent NMIBC, another RCT demonstrated a significantly higher efficacy of weekly MMC followed by monthly BCG in reduction of the recurrence rate when compared with BCG and interferon [106].

8.2.4. Specific aspects of treatment of carcinoma in situ

8.2.4.1. Treatment strategy. Histologic diagnosis of CIS must be followed by further treatment, either intravesical BCG instillations or RC (LE: 4). Tumour-specific survival rates after immediate RC for CIS are excellent, but as many as 40–50% of patients may be overtreated [62] (LE: 3).

8.2.4.2. Intravesical treatment of bladder carcinoma in situ. A meta-analysis of clinical trials comparing intravesical BCG with intravesical chemotherapy in patients with CIS showed a significantly increased response rate after BCG and a reduction of 59% in the odds of treatment failure with BCG [107] (LE: 1a).

In an EORTC-GUCG meta-analysis (a subgroup of 403 patients with CIS), BCG reduced the risk of progression by 35% compared with intravesical chemotherapy or different immunotherapy [91] (LE: 1b). The combination of BCG and MMC was not superior to BCG alone [108].

8.2.4.3. Treatment of carcinoma in situ in prostatic urethra and upper urinary tract. Patients with CIS are at high risk of extravesical involvement in the upper urinary tract (UUT) and in the prostatic urethra. Patients with extravesical involvement had worse survival than those with bladder CIS alone [109] (LE: 3).

Patients with CIS in the epithelial lining of the prostatic urethra can be treated by intravesical instillation of BCG. Transurethral resection of the prostate can improve contact of BCG with the prostatic urethra [110] (LE: 3).

In patients with prostatic duct involvement, there are promising results after BCG instillation, but the data are insufficient to provide clear treatment recommendations, and radical surgery should be considered [110] (LE: 3).

Treatment of CIS that involves the UUT is discussed in the EAU guidelines on urothelial carcinomas of the upper urinary tract (http://uroweb.org/wp-content/uploads/06-UTUC_druk_LR.pdf).

8.3. Treatment of failure of intravesical therapy

8.3.1. Failure of intravesical chemotherapy

Patients with NMIBC recurrence after a chemotherapy regimen can benefit from BCG instillations. Prior intravesical

Table 9 – Categories of unsuccessful treatment with intravesical bacillus Calmette-Guérin

BCG failure
Whenever a MIBC is detected during follow-up.
BCG-refractory tumour: 1. If HG non–muscle-invasive papillary tumour is present at 3 mo. Further conservative treatment with BCG is associated with increased risk of progression (LE: 3). 2. If CIS (without concomitant papillary tumour) is present at both 3 and 6 mo. If patients with CIS present at 3 mo, an additional BCG course can achieve a complete response in > 50% of cases [11] (LE: 3). 3. If HG tumour appears during BCG therapy.*
HG recurrence after BCG. Recurrence of HG/grade 3 (WHO 2004/1973) tumour after completion of BCG maintenance, despite an initial response (LE: 3).
BCG intolerance
Severe side effects that prevent further BCG instillation before completing induction.

BCG = bacillus Calmette-Guérin; CIS = carcinoma *in situ*; HG = high grade; LE = level of evidence; MIBC = muscle-invasive bladder cancer; WHO = World Health Organisation.
* Patients with low-grade recurrence during or after BCG treatment are not considered a BCG failure.

Table 10 – Treatment recommendations in TaT1 tumours and carcinoma *in situ* according to risk stratification

Risk category	Definition	Treatment recommendation
Low-risk tumours	Primary, solitary, Ta, G1/PUNLMP/LG, < 3 cm, no CIS	One immediate instillation of intravesical chemotherapy after TURB.
Intermediate-risk tumours	All cases between categories of low and high risk	In patients with previous low recurrence rate (less than or equal to one recurrence per year) and expected EORTC recurrence score < 5, one immediate instillation of intravesical chemotherapy after TURB. In all patients either 1-yr full-dose BCG treatment (induction plus weekly instillations for 3 wk at 3, 6, and 12 mo), or instillations of chemotherapy (the optimal schedule is not known) for a maximum of 1 yr.
High-risk tumours	Any of the following: • T1 tumours • HG/G3 tumours • CIS • Multiple and recurrent and large (>3 cm) Ta G1G2 tumours (all these conditions must be present)	Intravesical full-dose BCG instillations for 1–3 yr or cystectomy (in highest risk tumours; see below).
	Subgroup of highest risk tumours	
	T1G3/HG associated with concurrent bladder CIS, multiple and/or large T1G3/HG and/or recurrent T1G3/HG, T1G3/HG with CIS in the prostatic urethra, unusual histology of urothelial carcinoma, LVI (sect. 5.6 and 7.1).	RC should be considered. In those who refuse RC, intravesical full-dose BCG instillations for 1–3 yr.
	BCG failures	RC is recommended.

BCG = bacillus Calmette-Guérin; CIS = carcinoma *in situ*; EORTC = European Organisation for Research and Treatment of Cancer; HG = high grade; LG = low grade; LVI = lymphovascular invasion; PUNLMP = papillary urothelial neoplasm of low malignant potential; RC = radical cystectomy; TURB = transurethral resection of the bladder.

chemotherapy has no impact on the effect of BCG instillation [82] (LE: 1a).

8.3.2. *Recurrence and failure after intravesical bacillus Calmette-Guérin immunotherapy*

Table 9 lists the categories of unsuccessful treatment with intravesical BCG. Patients with BCG failure are unlikely to respond to further BCG therapy; therefore, RC is the preferred option. Several bladder preservation strategies are also now available that can be categorised as immunotherapy [111], chemotherapy, device-assisted therapy, and combination therapy [112]. Changing from BCG to these options can yield responses in selected cases with BCG treatment failure [113–116] (LE: 3).

However, at the present time, treatments other than RC must be considered oncologically inferior in patients with BCG failure (LE: 3).

Little is known about the optimal treatment in patients with high-risk tumours who could not complete BCG instillations because of intolerance.

Non-HG recurrence after BCG is not considered as BCG failure. Treatment decisions should be individualised according to tumour characteristics.

8.4. *Radical cystectomy for non–muscle-invasive bladder cancer*

If RC is indicated before progression to muscle-invasive tumour, it can be performed as an immediate procedure (right after NMIBC diagnosis) or early procedure (after BCG failure).

There are two reasons to consider immediate RC for selected patients with NMIBC: (1) The staging accuracy for T1 tumours by TURB is low with 27–51% of patients upstaged to MIBC at RC [52,117,118] (LE: 3), and (2) some patients with NMIBC experience disease progression to muscle-invasive disease.

The potential benefit of RC must be weighed against the risk, morbidity, and impact on quality of life. It is reasonable to propose immediate RC in those patients with NMIBC who are at highest risk of progression based on prognostic tables and additional prognostic factors mentioned in section 7.1 (Table 10) (LE: 3).

Early RC is strongly recommended in patients with BCG-refractory tumours. A delay in RC might lead to decreased disease-specific survival [119] (LE: 3).

Recommendations for adjuvant therapy in TaT1 tumours and for therapy of CIS are presented in Table 8.

Treatment principles for NMIBC and for BCG failures are summarised in Tables 10 and 11.

Table 11 – Treatment recommendations for bacillus Calmette-Guérin (BCG) failure and recurrences after BCG

Category	Treatment recommendation	GR
BCG-refractory tumour	1. RC 2. Bladder-preserving strategies in patients not suitable for RC	B
HG/G3 recurrence after BCG	1. RC 2. Repeat BCG course 3. Bladder-preserving strategies	C
Non-HG/G3 recurrence after BCG for primary intermediate-risk tumour	1. Repeat BCG or intravesical chemotherapy 2. RC	C

BCG = bacillus Calmette-Guérin; GR = grade of recommendation; HG = high grade; RC = radical cystectomy.

9. Follow-up of patients with non–muscle-invasive bladder cancer

As a result of the risk of recurrence and progression, patients with NMIBC need to be followed up. However, the frequency and duration of cystoscopy and imaging should reflect the individual patient's degree of risk. When planning the follow-up schedule and methods, the following aspects should be considered:

- The prompt detection of muscle-invasive and HG/G3 NMIBC recurrence is crucial because a delay in diagnosis and therapy can be life threatening.
- Tumour recurrence in the low-risk group is nearly always low stage and LG/G1. Small Ta LG/G1 papillary recurrence does not present an immediate danger to the patient, and early detection is not essential for successful therapy [120,121] (LE: 2b). Fulguration of small papillary recurrences on an outpatient basis could be a safe option that reduces the therapeutic burden [40,41] (LE: 3). Some authors have even defended temporary surveillance in selected cases [121] (LE: 3).
- The first cystoscopy after TURB at 3 mo is an important prognostic indicator for recurrence and progression [61,65,122,123] (LE: 1a); therefore, the first cystoscopy should always be performed 3 mo after TURB in all patients with TaT1 tumours and CIS.
- In tumours at low risk, the risk of recurrence after 5 recurrence-free years is low [122] (LE: 3). Discontinuation of cystoscopy or its replacement with less invasive methods can be considered [123].
- In tumours originally intermediate or high risk, recurrences after 10 yr tumour free are not unusual [124] (LE: 3); therefore, lifelong follow-up is recommended [123].
- The follow-up strategy must reflect the risk of extravesical recurrence (prostatic urethra in men and UUT).
- The risk of UUT recurrence increases in patients with multiple- and high-risk tumours [21] (LE: 3).
- Positive urine test results have a positive impact on the quality of performed follow-up cystoscopy [27] (LE: 1b). It supports the adjunctive role of urine tests during follow-up.

No noninvasive method can replace endoscopy; therefore, follow-up is based on regular cystoscopy. There is a lack of randomised studies that have investigated the possibility of safely reducing the frequency of follow-up cystoscopy.

Multiple biopsies may be necessary in selected cases to confirm the efficacy of intravesical treatment in patients treated for CIS.

Table 12 lists recommendations for the NMIBC follow-up schedule.

Table 12 – Recommendations for follow-up in patients after transurethral resection of the bladder of non–muscle-invasive bladder cancer

Recommendation	GR
The follow-up of TaT1 tumours and CIS is based on regular cystoscopy.	A
Patients with low-risk Ta tumours should undergo cystoscopy at 3 mo. If negative, subsequent cystoscopy is advised 9 mo later, and then yearly for 5 yr.	C
Patients with high-risk tumours should undergo cystoscopy and urinary cytology at 3 mo. If negative, subsequent cystoscopy and cytology should be repeated every 3 mo for a period of 2 yr, and every 6 mo thereafter until 5 yr, and then yearly.	C
Patients with intermediate-risk Ta tumours should have an in-between follow-up scheme using cystoscopy, which is adapted according to personal and subjective factors.	C
Regular (yearly) upper tract imaging (CT-IVU) is recommended for high-risk tumours.	C
Endoscopy under anaesthesia and bladder biopsies should be performed when office cystoscopy shows suspicious findings or if urinary cytology is positive.	B
Consider R-biopsies or biopsies with PDD after intravesical treatment (at 3 or 6 mo) in patients with CIS.	C
During follow-up in patients with positive cytology and no visible tumour in the bladder, R-biopsies or biopsies with PDD (if equipment is available) and investigation of extravesical locations (CT urography, prostatic urethra biopsy) are recommended.	B

CIS = carcinoma *in situ*; CT-IVU = computed tomography intravenous urography; GR = grade of recommendation; PDD = photodynamic diagnosis; R-biopsies = random biopsies.

Author contributions: Marko Babjuk had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Babjuk.
Acquisition of data: Babjuk, Böhle, Burger, Capoun, Cohen, Compérat, Hernández, Kaasinen, Palou, Rouprêt, van Rhijn, Shariat, Soukup, Sylvester, Zigeuner.
Analysis and interpretation of data: Babjuk, Böhle, Burger, Capoun, Cohen, Compérat, Hernández, Kaasinen, Palou, Rouprêt, van Rhijn, Shariat, Soukup, Sylvester, Zigeuner.
Drafting of the manuscript: Babjuk.
Critical revision of the manuscript for important intellectual content: Babjuk, Böhle, Burger, Capoun, Cohen, Compérat, Hernández, Kaasinen, Palou, Rouprêt, van Rhijn, Shariat, Soukup, Sylvester, Zigeuner.
Statistical analysis: Sylvester.
Obtaining funding: None.
Administrative, technical, or material support: None.
Supervision: Babjuk.
Other (specify): None.
Financial disclosures: Marko Babjuk certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: Marko Babjuk received speaker honoraria from Astellas and Janssen and participates on trials for Sotio. Andreas Böhle has nothing to disclose. Maximilian Burger is a company consultant and receives speaker honoraria for Astellas, Ipsen, Janssen, Pfizer, Springer and Thieme. Eva Compérat has nothing to disclose. Eero Kaasinen receives grants/research support from the Pfizer Foundation and Pfizer (for a research group). Joan Palou is a company consultant for: Olympus, Ipsen and Inibsa; and participates in trials for Inibsa, Combat Medical and Presurgery. Morgan Rouprêt is a company consultant for Lilly, GSK, Ipsen, Astellas, Takeda, and Sanofi Pasteur. He participates in

trials for GSK. Bas W.G. van Rhijn is a company consultant for Astellas. Shahrokh F. Shariat holds various patents as follows: Shariat S, Slawin K. Methods to determine prognosis after therapy for prostate cancer. US patent application serial number: docket 60/266,976. Filed May 31, 2001; Shariat S, Lerner S, Slawin K. Methods to determine prognosis after therapy for bladder cancer. US patent application serial number: docket 675.003US1. Filed June 1, 2001; Shariat S, Slawin K, Kattan M, Scardino P. Pre- and posttreatment nomograms for predicting recurrence in patients with clinically localized prostate cancer that includes the blood markers interlukin-6 soluble receptor and transforming growth; Slawin K, Kattan M, Shariat S, Stephenson A, Scardino P. Nomogram for predicting outcome of salvage radiotherapy for suspected local recurrence of prostate cancer after radical prostatectomy. Shariat S. Solube Fas: a promising novel urinary marker for the detection of bladder transitional cell carcinoma (UTSD:1666). US patent application serial in process. He is a company consultant for Astellas, Olympus, and Wolff. He receives company speaker honoraria from Lilly, Astellas, and Ipsen. He participates in trials for Alere Inc. on NMP22. He is a company consultant for Ipsen, Cepheid, Olympus, and Wolff and receives company speaker honoraria from Janssen. Richard Sylvester has nothing to disclose. Richard Zigeuner receives company speaker honoraria from Pfizer, Bayer Healthcare, Roche, and Novartis. He receives fellowships and travel grants from Bayer Healthcare, Pfizer, Amgen, Novartis, and GSK. He receives grants/research supports from Bayer Healthcare and company speaker honoraria from GSK and Amgen. He receives fellowships and travel grants from Astellas and Takeda, and is a company consultant for Pfizer. Otakar Capoun receives company honoraria or consultation fees from Janssen, Ipsen, Astellas and Bayer. Daniel Cohen, Virginia Hernández, and Viktor Soukup have nothing to disclose.

Funding/Support and role of the sponsor: None.

References

[1] Ferlay J, Soerjomataram I, Dikshit R, et al. GLOBOCAN 2012 v.1.0, estimated cancer incidence, mortality and prevalence worldwide in 2012.. Lyon, France: International Agency for Research on Cancer; 2013.

[2] Burger M, Catto JW, Dalbagni G, et al. Epidemiology and risk factors of urothelial bladder cancer. Eur Urol 2013;63:234–41.

[3] Chavan S, Bray F, Lortet-Tieulent J, Goodman M, Jemal A. International variations in bladder cancer incidence and mortality. Eur Urol 2014;66:59–73.

[4] Freedman ND, Silverman DT, Hollenbeck AR, Schatzkin A, Abnet CC. Association between smoking and risk of bladder cancer among men and women. JAMA 2011;306:737–45.

[5] Rushton L, Hutchings SJ, Fortunato L, et al. Occupational cancer burden in Great Britain. Br J Cancer 2012;107(Suppl 1):S3–7.

[6] Corral R, Lewinger JP, Van Den Berg D, et al. Comprehensive analyses of DNA repair pathways, smoking and bladder cancer risk in Los Angeles and Shanghai. Int J Cancer 2014;135:335–47.

[7] Ros MM, Bas Bueno-de-Mesquita HB, Buchner FL, et al. Fluid intake and the risk of urothelial cell carcinomas in the European Prospective Investigation into Cancer and Nutrition (EPIC). Int J Cancer 2011;128:2695–708.

[8] TNM classification of malignant tumors. In: Sobin LH, Gospodarowicz M, Wittekind C, editors. UICC International Union Against Cancer. ed 7. Hoboken, NJ: Wiley-Blackwell; 2009. p. 262–5.

[9] Mostofi FK, Sobin LH, Torloni H. Histologic typing of urinary bladder tumors. International Histological Classification of Tumors, No. 10.. Geneva, Switzerland: World Health Organization; 1973.

[10] Eble JN, Sauter G, Epstein JI, Sesterhenn IA, editors. Pathology and genetics of tumours of the urinary system and male genital organs. World Health Organization classification of tumours.. Lyon, France: IARC Press; 2004.

[11] Sylvester RJ, van der Meijden A, Witjes JA, et al. High-grade Ta urothelial carcinoma and carcinoma in situ of the bladder. Urology 2005;66(Suppl 1):90–107.

[12] Murphy WM, Takezawa K, Maruniak NA. Interobserver discrepancy using the 1998 World Health Organization/International Society of Urologic Pathology classification of urothelial neoplasms: practical choices for patient care. J Urol 2002;168:968–72.

[13] May M, Brookman-Amissah S, Roigas J, et al. Prognostic accuracy of individual uropathologists in noninvasive urinary bladder carcinoma: a multicentre study comparing the 1973 and 2004 World Health Organisation classifications. Eur Urol 2010;57:850–8.

[14] van Rhijn BW, van der Kwast TH, Kakiashvili DM, et al. Pathological stage review is indicated in primary pT1 bladder cancer. BJU Int 2010;106:206–11.

[15] Compérat E, Egevad L, Lopez-Beltran A, et al. An interobserver reproducibility study on invasiveness of bladder cancer using virtual microscopy and heatmaps. Histopathology 2013;63:756–66.

[16] Mangrud OM, Waalen R, Gudlaugsson E, et al. Reproducibility and prognostic value of WHO1973 and WHO2004 grading systems in TaT1 urothelial carcinoma of the urinary bladder. PLoS One 2014; 9:e83192.

[17] Cho KS, Seo HK, Joung JY, et al. Lymphovascular invasion in transurethral resection specimens as predictor of progression and metastasis in patients with newly diagnosed T1 bladder urothelial cancer. J Urol 2009;182:2625–30.

[18] Wasco MJ, Daignault S, Zhang Y, et al. Urothelial carcinoma with divergent histologic differentiation (mixed histologic features) predicts the presence of locally advanced bladder cancer when detected at transurethral resection. Urology 2007;70:69–74.

[19] Nolte-Ernsting C, Cowan N. Understanding multislice CT urography techniques: many roads lead to Rome. Eur Radiol 2006;16:2670–86.

[20] Palou J, Rodriguez-Rubio F, Huguet J, et al. Multivariate analysis of clinical parameters of synchronous primary superficial bladder cancer and upper urinary tract tumor. J Urol 2005;174:859–61, discussion 861.

[21] Millan-Rodriguez F, Chechile-Toniolo G, Salvador-Bayarri J, Huguet-Perez J, Vicente-Rodriguez J. Upper urinary tract tumors after primary superficial bladder tumors: prognostic factors and risk groups. J Urol 2000;164:1183–7.

[22] Yafi FA, Brimo F, Steinberg J, Aprikian AG, Tanguay S, Kassouf W. Prospective analysis of sensitivity and specificity of urinary cytology and other urinary biomarkers for bladder cancer. Urol Oncol 2015;33, 66 e25-31.

[23] Tetu B. Diagnosis of urothelial carcinoma from urine. Mod Pathol 2009;22(Suppl 2):S53–9.

[24] Raitanen MP, Aine R, Rintala E, et al. Differences between local and review urinary cytology in diagnosis of bladder cancer. An interobserver multicenter analysis. Eur Urol 2002;41:284–9.

[25] Lokeshwar VB, Habuchi T, Grossman HB, et al. Bladder tumor markers beyond cytology: international consensus panel on bladder tumor markers. Urology 2005;66(Suppl 1):35–63.

[26] Hajdinjak T. UroVysion FISH test for detecting urothelial cancers: meta-analysis of diagnostic accuracy and comparison with urinary cytology testing. Urol Oncol 2008;26:646–51.

[27] van der Aa MN, Steyerberg EW, Bangma C, van Rhijn BW, Zwarthoff EC, van der Kwast TH. Cystoscopy revisited as the gold standard for detecting bladder cancer recurrence: diagnostic review bias in the randomized, prospective CEFUB trial. J Urol 2010;183:76–80.

[28] Aaronson DS, Walsh TJ, Smith JF, Davies BJ, Hsieh MH, Konety BR. Meta-analysis: does lidocaine gel before flexible cystoscopy provide pain relief? BJU Int 2009;104:506–9, discussion 509–10.

[29] Richterstetter M, Wullich B, Amann K, et al. The value of extended transurethral resection of bladder tumour (TURBT) in the treatment of bladder cancer. BJU Int 2012;110:E76–9.

Please cite this article in press as: Babjuk M, et al. EAU Guidelines on Non–Muscle-invasive Urothelial Carcinoma of the Bladder: Update 2016. Eur Urol (2016), http://dx.doi.org/10.1016/j.eururo.2016.05.041

[30] Herr HW, Donat SM. Quality control in transurethral resection of bladder tumours. BJU Int 2008;102:1242–6.
[31] Brausi M, Collette L, Kurth K, et al. Variability in the recurrence rate at first follow-up cystoscopy after TUR in stage Ta T1 transitional cell carcinoma of the bladder: a combined analysis of seven EORTC studies. Eur Urol 2002;41:523–31.
[32] Mariappan P, Zachou A, Grigor KM. Detrusor muscle in the first, apparently complete transurethral resection of bladder tumour specimen is a surrogate marker of resection quality, predicts risk of early recurrence, and is dependent on operator experience. Eur Urol 2010;57:843–9.
[33] Mariappan P, Finney SM, Head E, et al. Good quality white-light transurethral resection of bladder tumours (GQ-WLTURBT) with experienced surgeons performing complete resections and obtaining detrusor muscle reduces early recurrence in new non-muscle-invasive bladder cancer: validation across time and place and recommendation for benchmarking. BJU Int 2012;109:1666–73.
[34] Herr HW, Donat SM, Reuter VE. Management of low grade papillary bladder tumors. J Urol 2007;178:1201–5, discussion 1205.
[35] Sabir EF, Holmäng S. TaG1 bladder cancer: a third of all primary tumors and 80% of all recurrences can be treated in the office using local anesthesia. Urol Pract 2014;1:184–8.
[36] Gupta NP, Saini AK, Dogra PN, Seth A, Kumar R. Bipolar energy for transurethral resection of bladder tumours at low-power settings: initial experience. BJU Int 2011;108:553–6.
[37] Venkatramani V, Panda A, Manojkumar R, Kekre NS. Monopolar versus bipolar transurethral resection of bladder tumors: a single center, parallel arm, randomized, controlled trial. J Urol 2014;191:1703–7.
[38] van der Meijden A, Oosterlinck W, Brausi M, Kurth KH, Sylvester R, de Balincourt C. Significance of bladder biopsies in Ta,T1 bladder tumors: a report from the EORTC Genito-Urinary Tract Cancer Cooperative Group. EORTC-GU Group Superficial Bladder Committee. Eur Urol 1999;35:267–71.
[39] Hara T, Takahashi M, Gondo T, et al. Risk of concomitant carcinoma in situ determining biopsy candidates among primary non-muscle-invasive bladder cancer patients: retrospective analysis of 173 Japanese cases. Int J Urol 2009;16:293–8.
[40] Palou J, Sylvester RJ, Faba OR, et al. Female gender and carcinoma in situ in the prostatic urethra are prognostic factors for recurrence, progression, and disease-specific mortality in T1G3 bladder cancer patients treated with bacillus Calmette-Guérin. Eur Urol 2012;62:118–25.
[41] Mungan MU, Canda AE, Tuzel E, Yorukoglu K, Kirkali Z. Risk factors for mucosal prostatic urethral involvement in superficial transitional cell carcinoma of the bladder. Eur Urol 2005;48:760–3.
[42] Mowatt G, N'Dow J, Vale L, , et al. Aberdeen Technology Assessment Review (TAR) Group. Photodynamic diagnosis of bladder cancer compared with white light cystoscopy: systematic review and meta-analysis. Int J Technol Assess Health Care 2011;27:3–10.
[43] Neuzillet Y, Methorst C, Schneider M, et al. Assessment of diagnostic gain with hexaminolevulinate (HAL) in the setting of newly diagnosed non-muscle-invasive bladder cancer with positive results on urine cytology. Urol Oncol 2014;32:1135–40.
[44] Draga RO, Grimbergen MC, Kok ET, Jonges TN, van Swol CF, Bosch JL. Photodynamic diagnosis (5-aminolevulinic acid) of transitional cell carcinoma after bacillus Calmette-Guérin immunotherapy and mitomycin C intravesical therapy. Eur Urol 2010;57:655–60.
[45] Schumacher MC, Holmang S, Davidsson T, Friedrich B, Pedersen J, Wiklund NP. Transurethral resection of non-muscle-invasive bladder transitional cell cancers with or without 5-aminolevulinic acid under visible and fluorescent light: results of a prospective, randomised, multicentre study. Eur Urol 2010;57:293–9.
[46] Stenzl A, Penkoff H, Dajc-Sommerer E, et al. Detection and clinical outcome of urinary bladder cancer with 5-aminolevulinic acid-induced fluorescence cystoscopy: a multicenter randomized, double-blind, placebo-controlled trial. Cancer 2011;117:938–47.
[47] Burger M, Grossman HB, Droller M, et al. Photodynamic diagnosis of non-muscle-invasive bladder cancer with hexaminolevulinate cystoscopy: a meta-analysis of detection and recurrence based on raw data. Eur Urol 2013;64:846–54.
[48] O'Brien T, Ray E, Chatterton K, Khan MS, Chandra A, Thomas K. Prospective randomized trial of hexylaminolevulinate photodynamic-assisted transurethral resection of bladder tumour (TURBT) plus single-shot intravesical mitomycin C vs conventional white-light TURBT plus mitomycin C in newly presenting non-muscle-invasive bladder cancer. BJU Int 2013;112:1096–104.
[49] Zheng C, Lv Y, Zhong Q, Wang R, Jiang Q. Narrow band imaging diagnosis of bladder cancer: systematic review and meta-analysis. BJU Int 2012;110:E680–7.
[50] Divrik RT, Yildirim U, Zorlu F, Ozen H. The effect of repeat transurethral resection on recurrence and progression rates in patients with T1 tumors of the bladder who received intravesical mitomycin: a prospective, randomized clinical trial. J Urol 2006;175:1641–4.
[51] Lazica DA, Roth S, Brandt AS, Bottcher S, Mathers MJ, Ubrig B. Second transurethral resection after Ta high-grade bladder tumor: a 4.5-year period at a single university center. Urol Int 2014;92:131–5.
[52] Fritsche HM, Burger M, Svatek RS, et al. Characteristics and outcomes of patients with clinical T1 grade 3 urothelial carcinoma treated with radical cystectomy: results from an international cohort. Eur Urol 2010;57:300–9.
[53] Sfakianos JP, Kim PH, Hakimi AA, Herr HW. The effect of restaging transurethral resection on recurrence and progression rates in patients with nonmuscle invasive bladder cancer treated with intravesical bacillus Calmette-Guérin. J Urol 2014;191:341–5.
[54] Bishr M, Lattouf JB, Latour M, Saad F. Tumour stage on re-staging transurethral resection predicts recurrence and progression-free survival of patients with high-risk non-muscle invasive bladder cancer. Can Urol Assoc J 2014;8:E306–10.
[55] Lopez-Beltran A, Bassi P, Pavone-Macaluso M, Montironi R. Handling and pathology reporting of specimens with carcinoma of the urinary bladder, ureter, and renal pelvis. Eur Urol 2004;45:257–66.
[56] Sylvester RJ, van der Meijden AP, Oosterlinck W, et al. Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: a combined analysis of 2596 patients from seven EORTC trials. Eur Urol 2006;49:466–75, discussion 475–7.
[57] Fernandez-Gomez J, Madero R, Solsona E, et al. Predicting nonmuscle invasive bladder cancer recurrence and progression in patients treated with bacillus Calmette-Guérin: the CUETO scoring model. J Urol 2009;182:2195–203.
[58] Cambier S, Sylvester RJ, Collette L, et al. EORTC nomograms and risk groups for predicting recurrence, progression, and disease-specific and overall survival in non–muscle-invasive stage Ta-T1 urothelial bladder cancer patients treated with 1-3 years of maintenance bacillus Calmette-Guérin. Eur Urol 2016;69:60–9.
[59] Gontero P, Sylvester R, Pisano F, et al. Prognostic factors and risk groups in T1G3 non–muscle-invasive bladder cancer patients initially treated with bacillus Calmette-Guérin: results of a retrospective multicenter study of 2451 patients. Eur Urol 2015;67:74–82.
[60] Golijanin D, Yossepowitch O, Beck SD, Sogani P, Dalbagni G. Carcinoma in a bladder diverticulum: presentation and treatment outcome. J Urol 2003;170:1761–4.
[61] Palou J, Rodriguez-Rubio F, Millan F, et al. Recurrence at three months and high-grade recurrence as prognostic factor of progression in multivariate analysis of T1G2 bladder tumors. Urology 2009;73:1313–7.

[62] Lamm DL. Carcinoma in situ. Urol Clin North Am 1992;19:499–508.
[63] Griffiths TR, Charlton M, Neal DE, Powell PH. Treatment of carcinoma in situ with intravesical bacillus Calmette-Guérin without maintenance. J Urol 2002;167:2408–12.
[64] Takenaka A, Yamada Y, Miyake H, Hara I, Fujisawa M. Clinical outcomes of bacillus Calmette-Guérin instillation therapy for carcinoma in situ of urinary bladder. Int J Urol 2008;15:309–13.
[65] Solsona E, Iborra I, Dumont R, Rubio-Briones J, Casanova J, Almenar S. The 3-month clinical response to intravesical therapy as a predictive factor for progression in patients with high risk superficial bladder cancer. J Urol 2000;164:685–9.
[66] Lammers RJ, Witjes WP, Hendricksen K, Caris CT, Janzing-Pastors MH, Witjes JA. Smoking status is a risk factor for recurrence after transurethral resection of non–muscle-invasive bladder cancer. Eur Urol 2011;60:713–20.
[67] Rink M, Xylinas E, Babjuk M, et al. Smoking reduces the efficacy of intravesical bacillus Calmette-Guérin immunotherapy in non-muscle-invasive bladder cancer. Eur Urol 2012;62:1204–6.
[68] Sylvester RJ, Oosterlinck W, Holmang S, et al. Systematic review and individual patient data meta-analysis of randomized trials comparing a single immediate instillation of chemotherapy after transurethral resection with transurethral resection alone in patients with stage pTa-pT1 urothelial carcinoma of the bladder: which patients benefit from the instillation? Eur Urol 2016;69:231–44.
[69] Sylvester RJ, Oosterlinck W, van der Meijden AP. A single immediate postoperative instillation of chemotherapy decreases the risk of recurrence in patients with stage Ta T1 bladder cancer: a meta-analysis of published results of randomized clinical trials. J Urol 2004;171:2186–90, quiz 2435.
[70] Abern MR, Owusu RA, Anderson MR, Rampersaud EN, Inman BA. Perioperative intravesical chemotherapy in non-muscle-invasive bladder cancer: a systematic review and meta-analysis. J Natl Compr Canc Netw 2013;11:477–84.
[71] Perlis N, Zlotta AR, Beyene J, Finelli A, Fleshner NE, Kulkarni GS. Immediate post-transurethral resection of bladder tumor intravesical chemotherapy prevents non–muscle-invasive bladder cancer recurrences: an updated meta-analysis on 2548 patients and quality-of-evidence review. Eur Urol 2013;64:421–30.
[72] Bohle A, Jurczok A, Ardelt P, et al. Inhibition of bladder carcinoma cell adhesion by oligopeptide combinations in vitro and in vivo. J Urol 2002;167:357–63.
[73] Oddens JR, van der Meijden AP, Sylvester R. One immediate postoperative instillation of chemotherapy in low risk Ta,T1 bladder cancer patients. Is it always safe? Eur Urol 2004;46:336–8.
[74] Sylvester RJ, Oosterlinck W, Witjes JA. The schedule and duration of intravesical chemotherapy in patients with non–muscle-invasive bladder cancer: a systematic review of the published results of randomized clinical trials. Eur Urol 2008;53:709–19.
[75] Tolley DA, Parmar MK, Grigor KM, et al. The effect of intravesical mitomycin C on recurrence of newly diagnosed superficial bladder cancer: a further report with 7 years of follow up. J Urol 1996;155:1233–8.
[76] Huncharek M, McGarry R, Kupelnick B. Impact of intravesical chemotherapy on recurrence rate of recurrent superficial transitional cell carcinoma of the bladder: results of a meta-analysis. Anticancer Res 2001;21:765–9.
[77] Au JL, Badalament RA, Wientjes MG, et al. Methods to improve efficacy of intravesical mitomycin C: results of a randomized phase III trial. J Natl Cancer Inst 2001;93:597–604.
[78] Giesbers AA, Van Helsdingen PJ, Kramer AE. Recurrence of superficial bladder carcinoma after intravesical instillation of mitomycin-C. Comparison of exposure times. Br J Urol 1989;63:176–9.
[79] Kuroda M, Niijima T, Kotake T, Akaza H, Hinotsu S. Effect of prophylactic treatment with intravesical epirubicin on recurrence of superficial bladder cancer–the 6th Trial of the Japanese Urological Cancer Research Group (JUCRG): a randomized trial of intravesical epirubicin at dose of 20 mg/40 ml, 30 mg/40 ml, 40 mg/40 ml. Eur Urol 2004;45:600–5.
[80] Lammers RJ, Witjes JA, Inman BA, et al. The role of a combined regimen with intravesical chemotherapy and hyperthermia in the management of non–muscle-invasive bladder cancer: a systematic review. Eur Urol 2011;60:81–93.
[81] Di Stasi SM, Giannantoni A, Giurioli A, et al. Sequential BCG and electromotive mitomycin versus BCG alone for high-risk superficial bladder cancer: a randomised controlled trial. Lancet Oncol 2006;7:43–51.
[82] Malmstrom PU, Sylvester RJ, Crawford DE, et al. An individual patient data meta-analysis of the long-term outcome of randomised studies comparing intravesical mitomycin C versus bacillus Calmette-Guérin for non–muscle-invasive bladder cancer. Eur Urol 2009;56:247–56.
[83] Shelley MD, Kynaston H, Court J, et al. A systematic review of intravesical bacillus Calmette-Guérin plus transurethral resection vs transurethral resection alone in Ta and T1 bladder cancer. BJU Int 2001;88:209–16.
[84] Han RF, Pan JG. Can intravesical bacillus Calmette-Guérin reduce recurrence in patients with superficial bladder cancer?. A meta-analysis of randomized trials. Urology 2006;67:1216–23.
[85] Shelley MD, Wilt TJ, Court J, Coles B, Kynaston H, Mason MD. Intravesical bacillus Calmette-Guérin is superior to mitomycin C in reducing tumour recurrence in high-risk superficial bladder cancer: a meta-analysis of randomized trials. BJU Int 2004;93:485–90.
[86] Bohle A, Jocham D, Bock PR. Intravesical bacillus Calmette-Guérin versus mitomycin C for superficial bladder cancer: a formal meta-analysis of comparative studies on recurrence and toxicity. J Urol 2003;169:90–5.
[87] Duchek M, Johansson R, Jahnson S, et al. Bacillus Calmette-Guérin is superior to a combination of epirubicin and interferon-alpha2b in the intravesical treatment of patients with stage T1 urinary bladder cancer. A prospective, randomized, Nordic study. Eur Urol 2010;57:25–31.
[88] Jarvinen R, Kaasinen E, Sankila A, Rintala E. Long-term efficacy of maintenance bacillus Calmette-Guérin versus maintenance mitomycin C instillation therapy in frequently recurrent TaT1 tumours without carcinoma in situ: a subgroup analysis of the prospective, randomised FinnBladder I study with a 20-year follow-up. Eur Urol 2009;56:260–5.
[89] Sylvester RJ, Brausi MA, Kirkels WJ, et al. Long-term efficacy results of EORTC Genito-Urinary Group randomized phase 3 study 30911 comparing intravesical instillations of epirubicin, bacillus Calmette-Guérin, and bacillus Calmette-Guérin plus isoniazid in patients with intermediate- and high-risk stage Ta T1 urothelial carcinoma of the bladder. Eur Urol 2010;57:766–73.
[90] Bohle A, Bock PR. Intravesical bacille Calmette-Guérin versus mitomycin C in superficial bladder cancer: formal meta-analysis of comparative studies on tumor progression. Urology 2004;63:682–6, discussion 686–7.
[91] Sylvester RJ, van der Meijden A, Lamm DL. Intravesical bacillus Calmette-Guérin reduces the risk of progression in patients with superficial bladder cancer: a meta-analysis of the published results of randomized clinical trials. J Urol 2002;168:1964–70.
[92] Huncharek M, Kupelnick B. The influence of intravesical therapy on progression of superficial transitional cell carcinoma of the bladder: a metaanalytic comparison of chemotherapy versus bacilli Calmette-Guérin immunotherapy. Am J Clin Oncol 2004;27:522–8.

Please cite this article in press as: Babjuk M, et al. EAU Guidelines on Non–Muscle-invasive Urothelial Carcinoma of the Bladder: Update 2016. Eur Urol (2016), http://dx.doi.org/10.1016/j.eururo.2016.05.041

[93] Oddens JR, Sylvester RJ, Brausi MA, et al. The effect of age on the efficacy of maintenance bacillus Calmette-Guérin relative to maintenance epirubicin in patients with stage Ta T1 urothelial bladder cancer: results from EORTC Genito-Urinary Group Study 30911. Eur Urol 2014;66:694–701.
[94] Rentsch CA, Birkhauser FD, Biot C, et al. Bacillus Calmette-Guérin strain differences have an impact on clinical outcome in bladder cancer immunotherapy. Eur Urol 2014;66:677–88.
[95] Sengiku A, Ito M, Miyazaki Y, Sawazaki H, Takahashi T, Ogura K. A prospective comparative study of intravesical bacillus Calmette-Guérin therapy with the Tokyo or Connaught strain for nonmuscle invasive bladder cancer. J Urol 2013;190:50–4.
[96] Brausi M, Oddens J, Sylvester R, et al. Side effects of bacillus Calmette-Guérin (BCG) in the treatment of intermediate- and high-risk Ta, T1 papillary carcinoma of the bladder: results of the EORTC Genito-Urinary Cancers Group randomised phase 3 study comparing one-third dose with full dose and 1 year with 3 years of maintenance BCG. Eur Urol 2014;65:69–76.
[97] Herr HW. Intravesical bacillus Calmette-Guérin outcomes in patients with bladder cancer and asymptomatic bacteriuria. J Urol 2012;187:435–7.
[98] Rodriguez F, Palou J, Martinez R, et al. Practical guideline for the management of adverse events associated with BCG installations [in Spanish]. Arch Esp Urol 2008;61:591–6.
[99] Witjes JA, Palou J, Soloway M, et al. Clinical practice recommendations for the prevention and management of intravesical therapy–associated adverse events. Eur Urol Suppl 2008;7:667–74.
[100] Lamm DL, Blumenstein BA, Crissman JD, et al. Maintenance bacillus Calmette-Guérin immunotherapy for recurrent TA, T1 and carcinoma in situ transitional cell carcinoma of the bladder: a randomized Southwest Oncology Group Study. J Urol 2000;163:1124–9.
[101] Oddens J, Brausi M, Sylvester R, et al. Final results of an EORTC-GU cancers group randomized study of maintenance bacillus Calmette-Guérin in intermediate- and high-risk Ta, T1 papillary carcinoma of the urinary bladder: one-third dose versus full dose and 1 year versus 3 years of maintenance. Eur Urol 2013;63:462–72.
[102] Martinez-Pineiro L, Portillo JA, Fernandez JM, et al. Maintenance therapy with 3-monthly bacillus Calmette-Guérin for 3 years is not superior to standard induction therapy in high-risk non–muscle-invasive urothelial bladder carcinoma: final results of randomised CUETO study 98013. Eur Urol 2015;68:256–62.
[103] Martinez-Pineiro JA, Martinez-Pineiro L, Solsona E, et al. Has a 3-fold decreased dose of bacillus Calmette-Guérin the same efficacy against recurrences and progression of T1G3 and Tis bladder tumors than the standard dose? Results of a prospective randomized trial. J Urol 2005;174:1242–7.
[104] Ojea A, Nogueira JL, Solsona E, et al. A multicentre, randomised prospective trial comparing three intravesical adjuvant therapies for intermediate-risk superficial bladder cancer: low-dose bacillus Calmette-Guérin (27 mg) versus very low-dose bacillus Calmette-Guérin (13.5 mg) versus mitomycin C. Eur Urol 2007;52:1398–406.
[105] Solsona E, Madero R, Chantada V, et al. Sequential combination of mitomycin C plus bacillus Calmette-Guérin (BCG) is more effective but more toxic than BCG alone in patients with non–muscle-invasive bladder cancer in intermediate- and high-risk patients: final outcome of CUETO 93009, a randomized prospective trial. Eur Urol 2015;67:508–16.
[106] Jarvinen R, Marttila T, Kaasinen E, et al. Long-term outcome of patients with frequently recurrent non-muscle-invasive bladder carcinoma treated with one perioperative plus four weekly instillations of mitomycin c followed by monthly bacillus Calmette-Guérin (BCG) or alternating BCG and interferon-alpha2b instillations: prospective randomised FinnBladder-4 Study. Eur Urol 2015;68:611–7.
[107] Sylvester RJ, van der Meijden AP, Witjes JA, Kurth K. Bacillus Calmette-Guérin versus chemotherapy for the intravesical treatment of patients with carcinoma in situ of the bladder: a meta-analysis of the published results of randomized clinical trials. J Urol 2005;174:86–91, discussion 92.
[108] Kaasinen E, Wijkstrom H, Malmstrom PU, et al. Alternating mitomycin C and BCG instillations versus BCG alone in treatment of carcinoma in situ of the urinary bladder: a Nordic study. Eur Urol 2003;43:637–45.
[109] Solsona E, Iborra I, Ricos JV, Monros JL, Dumont R, Almenar S. Extravesical involvement in patients with bladder carcinoma in situ: biological and therapy implications. J Urol 1996;155:895–9, discussion 899–900.
[110] Palou J, Baniel J, Klotz L, et al. Urothelial carcinoma of the prostate. Urology 2007;69(Suppl):50–61.
[111] Morales A, Herr H, Steinberg G, et al. Efficacy and safety of MCNA in patients with nonmuscle invasive bladder cancer at high risk for recurrence and progression after failed treatment with bacillus Calmette-Guérin. J Urol 2015;193:1135–43.
[112] Yates DR, Brausi MA, Catto JW, et al. Treatment options available for bacillus Calmette-Guérin failure in non–muscle-invasive bladder cancer. Eur Urol 2012;62:1088–96.
[113] Barlow L, McKiernan J, Sawczuk I, Benson M. A single-institution experience with induction and maintenance intravesical docetaxel in the management of non-muscle-invasive bladder cancer refractory to bacille Calmette-Guérin therapy. BJU Int 2009;104:1098–102.
[114] Nativ O, Witjes JA, Hendricksen K, et al. Combined thermo-chemotherapy for recurrent bladder cancer after bacillus Calmette-Guérin. J Urol 2009;182:1313–7.
[115] Joudi FN, Smith BJ, O'Donnell MA. Final results from a national multicenter phase II trial of combination bacillus Calmette-Guérin plus interferon alpha-2B for reducing recurrence of superficial bladder cancer. Urol Oncol 2006;24:344–8.
[116] Di Lorenzo G, Perdona S, Damiano R, et al. Gemcitabine versus bacille Calmette-Guérin after initial bacille Calmette-Guérin failure in non-muscle-invasive bladder cancer: a multicenter prospective randomized trial. Cancer 2010;116:1893–900.
[117] Turker P, Bostrom PJ, Wroclawski ML, et al. Upstaging of urothelial cancer at the time of radical cystectomy: factors associated with upstaging and its effect on outcome. BJU Int 2012;110:804–11.
[118] Shariat SF, Palapattu GS, Karakiewicz PI, et al. Discrepancy between clinical and pathologic stage: impact on prognosis after radical cystectomy. Eur Urol 2007;51:137–49, discussion 149–51.
[119] Raj GV, Herr H, Serio AM, et al. Treatment paradigm shift may improve survival of patients with high risk superficial bladder cancer. J Urol 2007;177:1283–6, discussion 1286.
[120] Holmang S, Andius P, Hedelin H, Wester K, Busch C, Johansson SL. Stage progression in Ta papillary urothelial tumors: relationship to grade, immunohistochemical expression of tumor markers, mitotic frequency and DNA ploidy. J Urol 2001;165:1124–8, discussion 1128–30.
[121] Gofrit ON, Pode D, Lazar A, Katz R, Shapiro A. Watchful waiting policy in recurrent Ta G1 bladder tumors. Eur Urol 2006;49:303–6, discussion 306–7.
[122] Mariappan P, Smith G. A surveillance schedule for G1Ta bladder cancer allowing efficient use of check cystoscopy and safe discharge at 5 years based on a 25-year prospective database. J Urol 2005;173:1108–11.
[123] Soukup V, Babjuk M, Bellmunt J, et al. Follow-up after surgical treatment of bladder cancer: a critical analysis of the literature. Eur Urol 2012;62:290–302.
[124] Holmang S, Strock V. Should follow-up cystoscopy in bacillus Calmette-Guérin-treated patients continue after five tumour-free years? Eur Urol 2012;61:503–7.

Please cite this article in press as: Babjuk M, et al. EAU Guidelines on Non–Muscle-invasive Urothelial Carcinoma of the Bladder: Update 2016. Eur Urol (2016), http://dx.doi.org/10.1016/j.eururo.2016.05.041