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Tumour Review

Management of non-muscle invasive bladder cancer: A comprehensive analysis of guidelines from the United States, Europe and Asia

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ABSTRACT

Bladder cancer is the 8th most common cancer with 74,000 new cases in the United States in 2015. Non-muscle invasive bladder cancer (NMIBC) accounts for 75% of all bladder cancer cases. Transurethral resection and intravesical treatments remain the main treatment modality. Up to 31–78% of cases recur, hence the need for intensive treatment and surveillance protocols which makes bladder cancer one of the most expensive cancers to manage. The purpose of this review is to compare contemporary guidelines from Europe, (European Association of Urology), the United States (National Comprehensive Cancer Network), the United Kingdom (National Institute for Health and Care Excellence), Japan (Japanese Urological Association) and the International Consultation on Bladder Cancer (ICUD). We compare and contrast the different guidelines and the evidence on which their recommendations are based.

Introduction

Bladder cancer (BCa) is the 8th most common cancer and ranks 13th in terms of cancer mortality worldwide [1]. In 2015, there will be 74,000 new BCa cases in the United States with men 2.5 times more likely to develop BCa compared to women [2]. More than 75% of BCa cases are non-muscle invasive (NMIBC) where cancer is confined to the urothelium or lamina propria and do not invade the detrusor (pTa, carcinoma *in situ* (*CIS*), pT1) [3]. According to the European Organization for Research and Treatment of Cancer (EORTC) nomogram data, between 31% and 78% of cases recur and between 17 and 45% of cases will progress to muscle invasive bladder cancer (MIBC) within 5 years [4]. Due to the high recurrence rate, and a substantial risk of progression, intensive surveillance and treatment protocols are employed making BCa one of the most expensive cancers to manage [5].

Transurethral resection (TUR) surgery and intravesical treatment remains the main treatment modality for NMIBC. However, the exact surveillance protocol and treatment regime vary between countries according to which of the published guidelines are followed. In this report, we compare five guidelines: from Europe, (European Association of Urology, EAU-2015) [3], the United States (National Comprehensive Cancer Network, NCCN-2015) [6], the United Kingdom (National Institute for Health and Care Excellence, NICE-2015) [7], Japan (Japanese Urological Association, JUA-2010) [8] and the International Consultation on Bladder Cancer, ICUD-2012 [9]. We review these recommendations for diagnosis, TUR, intravesical treatment and surveillance protocols for this disease and discuss the evidence for these recommendations.

Imaging of the upper tracts at diagnosis and during surveillance

Should all newly diagnosed patients with bladder cancer have upper tract imaging?

All guidelines recommend upper tract imaging for either all or selected cases at first diagnosis. NCCN recommends upper tract imaging for all cases regardless of stage, grade, size, site or multiplicity, despite recognition that the incidence of synchronous upper tract tumours (UTT) is low at 0.8–1.8% [10,11]. The rationale for imaging in select cases, as proposed by EAU, NICE, and ICUD, is based on the low overall prevalence of synchronous UTT but proportionately higher risk in cases with certain clinico-pathological features, including disease at the ureteric orifice, bladder neck or trigone, or higher risk tumours. Using cancer registry data, Wright and colleagues showed that location within the bladder and high grade tumours were associated with up to 83.6% of UTT at diagnosis in patients investigated for haematuria [10]. In contrast to other guides, the JUA recognise that imaging is not necessary for all cases but did not specify who would benefit from imaging. The recom-

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mendation is that upper tract imaging should be performed for cases that clinically appear muscle invasive is supported by NCCN and JUA. The recommendations are summarised in Table 1 [10,11].

NICE and EAU suggest that high risk NMIBC should undergo upper tract imaging (Table 1). In addition, EAU also recommends imaging for all cases of BCa with trigonal or multifocal disease. The majority of BCa are detected following an initial presentation with haematuria and will undergo imaging as part of haematuria testing [12,13]. A consensus agreement across guides would be that as a minimum, for cases that do not have upper tract imaging at diagnosis, there is a requirement to image the upper tract based in patients with tumours at the ureteric orifice, bladder neck, trigone and all high grade tumours.

What is the most appropriate modality of upper tract imaging?

The variation across guidelines regarding the recommended modality of upper tract imaging reflecting a lack of level one evidence to support or refute guidance. NCCN recommends either one of the following: CT intravenous urogram (IVU), renal tract ultrasound, CT without contrast with retrograde pylogram, MRI IVU or ureteroscopy. NICE recommends CT/MRI IVU while EAU suggest that conventional IVU or renal tract ultrasound are alternatives to CT IVU for haematuria work up. ICUD and JUA do not specify a preference.

CT IVU has been shown to be the imaging modality of choice with a negative predictive value of 96% and a positive predictive value of 76% [14]. However, drawbacks include the use of ionising radiation, risk of contrast allergy and increased cost. Depending on the number of phases, effective dose values of CT IVU can vary between 16 and 35 mSv [15,16]. There have been two large observational studies on this. In a series of 1,903 patients evaluated for haematuria, renal tract ultrasound detected 57% (8/14) of UTT and has a limited role in detecting non-obstructive ureteric tumours [17]. Of the six tumours not detected with renal tract ultrasound, one patient had hydronephrosis which would normally trigger cross sectional imaging and identify the tumour although the remaining five patients had a normal finding. The other series of 4020 patients by Edwards et al. reported that renal tract ultrasound detected 94.3% of all upper tract tumours [18]. A Health Technology Assessment review in 2006 determined that there was insufficient evidence to draw conclusions regarding the accuracy of these imaging modalities but CT IVU is increasingly being used today [19]. Renal tract ultrasound is a good alternative for patients with a contraindication to intravenous contrast, or for younger patients who are keen to avoid ionising radiation given the low incidence of UTT although a low threshold for CT IVU is recommended.

Should urine cytology be performed at initial presentation?

EAU, NCCN and NICE supports the use of urine cytology in newly diagnosed BCa patients while ICUD recommends cytology during haematuria work-up. NICE supports the use of any of the following in replacement of cytology: narrow band imaging (NBI)/photodynamic diagnostic (PDD) cystoscopy or other urinary marker such as fluorescence *in situ* hybridization (FISH), ImmunoCyst or NMP22. None of the other guidelines support the use of novel urinary biomarkers in routine clinical practice and they cannot replace cystoscopy [20]. High grade BCa and *CIS* usually shed cells in urine and are more likely to be detected with urinary cytology. A positive urinary cytology indicates the possibility of BCa anywhere in the urinary tract including the upper tracts. It should be performed on fresh urine with adequate fixation and early morning voided specimens are not recommended due to significant cell lysis.

The role of urinary cytology in low grade BCa, however, is limited. In addition, there can be significant variability in reporting urinary cytology [21]. "Atypical" cytology which is reported in >20% of specimens remains a waste basket as results are often inconclusive [22]. The value of performing urinary cytology at initial cystoscopy is debateable but should be considered in patients with more adverse features such as multifocal disease or where non-specific erythematous lesions are seen raising the suspicion of *CIS*.

Transurethral resection

Transurethral resection of bladder tumour (TURBT) and bimanual examination under anaesthesia (EUA) should be performed under general anaesthetic. ICUD highlights the requirement for bimanual EUA to be performed after TURBT as a means of accurate clinical staging, with a preoperative EUA being optional. While EAU and NCCN do recommend bimanual EUA when performing TURBT, they do not stipulate whether it should be done preoperative or postoperatively. Following TURBT, if all visible tumour has been resected, a bladder wall that remains thickened with a mobile or fixed pelvic mass implies extravesical tumour, indicating clinical T3 and T4 disease respectively.

The resection specimen for all newly diagnosed BCa should include detrusor muscle, as this is essential for staging and planning further management. EAU and JUA guidelines recommend that tumours which are $\leqslant$1 cm should be resected *en bloc* while ICUD suggest that this is an option for tumours $\leqslant$3 cm. *En bloc* resection potentially allows for more accurate pathological assessment due to less diathermy artefact although there are no comparative studies to confirm this. Staged resection is the recommended technique for larger tumours, where the tumour is resected in phases beginning with the exophytic component, followed by the underlying tumour base, and the edges of the resection site. The requirement to submit different stages of resected tumour in separate containers for histopathological examination is stipulated by EAU although the other guidelines suggest that this is optional. Sending different stages of the resection separately aids the pathologist in identifying detrusor muscle especially if there is a considerable tumour tissue. However, this is not necessary if all tumour tissue is examined. Although biopsy of the base of resection site is practiced in some centres, this is not discussed in the guidelines and is not necessary in well performed TURBT.

When should mapping biopsies and prostatic biopsies be performed?

Mapping biopsies should be performed at the trigone, dome, right, left, anterior and posterior bladder wall. Prostatic urethra

Table 1
Comparison of recommendations for requirement and modality for upper tract imaging according to EAU, NCCN, NICE, ICUD and JUA guidelines.

	EAU, 2015 [3]	NCCN, 2015 [6]	NICE, 2015 [7]	ICUD, 2012 [9]	JUA, 2010 [8]
Upper tract imaging	CT IVU/IVU for tumours located in trigone. USS kidneys, ureters, bladder can be used at initial work up	All patients should have either CT intravenous urogram (IVU), renal tract ultrasound, CT without contrast with retrograde pylogram, MRI IVU or ureteroscopy	CT/MRI IVU in tumours suspicious of being muscle invasive pre-TURBT or new/recurrent high risk bladder tumours	Consider imaging in visible haematuria or unexplained positive urinary cytology	Not necessary in all patients. Consider CT IVU in tumours suspicious of being muscle invasive pre-TURBT

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biopsy should be performed with loop resection at the precollicular area between 5 and 7 o' clock. The indication to perform mapping bladder biopsies is to detect *CIS* or features relevant to urothelial field change such as dysplasia. The presence of concomitant *CIS* is a known risk factor for recurrence and subsequent disease progression [23,24]. NCCN recommend that in cases where the BCa which looks high grade, sessile (broad based) or where *CIS* is present, mapping biopsies should be performed. In addition to NCCN recommendations, EAU also suggest that mapping biopsies should be performed when urinary cytology is positive in the absence of tumour. The presence of *CIS* is the only indication for mapping biopsies according to JUA. ICUD suggest that mapping biopsies are required when there is discordance between urinary cytology and cystoscopic findings and for patients considered for a partial cystectomy while prostatic urethra biopsies are recommended in cases of multifocal disease, *CIS* or in the presence of abnormal prostatic urothelium.

The relevance of mapping biopsies was explored in two EORTC studies (308,911 and 30,863) [25]. Three hundred and ninety-three patients with low risk disease had a single random biopsy of normal looking urothelium and 602 patients with high risk disease had bladder mapping biopsies with prostatic urethra biopsies after TURBT. *CIS* was only observed in 1.5% of low risk tumours and 3.5% of high risk tumours suggesting that mapping biopsies do not change the management in the majority of cases [25]. Subsequently, May et al. reported that 12.4% of mapping biopsies performed in a series of 1033 predominantly intermediate and high risk NMIBC patients were positive for tumour and this changed management in 6.8% of patients [26]. Given the lack of level one evidence, the requirement for mapping biopsies remain controversial. Patients likely to benefit most are those with high risk disease, or where there is discordance between urinary cytology and cystoscopic findings. However, photodynamic cystoscopy is increasingly used instead of, or to guide the location of mapping biopsies.

What is the evidence for photodynamic (PDD)/narrow band (NBI) cystoscopy?

Recently, there has been an increased uptake of NBI and PDD cystoscopy as an adjunct to white light cystoscopy in order to improve the detection of bladder cancer. A meta-analysis of 1345 patients with NMIBC showed that patients treated with PDD cystoscopy had a higher BCa detection rate, as well as a lower risk of recurrence compared to white light cystoscopy alone [27]. In a prospective randomised trial of PDD cystoscopy vs white light cystoscopy, PDD cystoscopy detected more cases of *CIS*, although there was no difference in the rate of BCa recurrence in patients who received postoperative intravesical Mitomycin C (MMC) [28]. The comparable recurrence rates between white light and PDD cystoscopy in this study could be explained by the postoperative dose of MMC, which may be responsible for treating low volume BCa which might have been missed on white light cystoscopy.

Where PDD equipment is available, the EAU and ICUD advocate that patients with positive cytology but negative cystoscopy or high grade BCa should have PDD cystoscopy instead of mapping biopsies. NICE supports the use of PDD for all patients as a substitute for a urinary biomarker test as PDD may improve detection of cis by up to 20% [29]. NCCN states that PDD may be helpful in identifying lesions not visible by white light but similar to JUA, does not go as far as to recommend using PDD/NBI cystoscopy. Due to limited data on NBI, it has not been incorporated into most guidelines.

However, the guidelines differ where EAU recommends PDD cystoscopy in surveillance cystoscopy instead of random biopsies at 3–6 months after intravesical treatment in NMIBC patients, while ICUD suggest that PDD should be used in new cases of NMIBC, recurrent multifocal tumours or in TURBT training cases. All these recommendations are supported by level III evidence and have drawbacks. It is essential that PDD cystoscopy in patients treated with intravesical BCG should be delayed for at least 9 weeks to reduce false positive cases [30]. In addition, the benefit of PDD may be minimal in TURBT of new tumours by experienced surgeons, but may prove more useful in training cases, or for follow-up cases of known *CIS* or multifocal tumours where tumours might have been initially missed. Hence, results of PHOTO, a phase III multi-centre randomised controlled trial investigating the clinical outcome and cost-effectiveness of white light vs PDD cystoscopy are eagerly awaited (ISRCTN84013636).

When should repeat transurethral resection be performed?

Despite initial TURBT, residual tumour is present in up to 76% of NMIBC cases at second resection, while 29% of cases were upstaged to MIBC [31]. A prospective randomised trial looking at the effect of repeat resection on patients with pT1 BCa who had MMC after primary resection showed a significantly higher rate of recurrence (repeat resection: 25.6% vs single resection: 63.2%) as well as progression of disease (repeat resection: 4.05% vs single resection: 11.8%) in single resection cases which translated to worse overall survival (repeat resection: 91.9% vs. single resection: 89.7%) at a mean follow-up of 31.5 months [32].

All the guidelines support the role of repeat resection within 1–6 weeks after primary resection in cases of incomplete resection and in cases of high grade pTa where detrusor was not present. In addition, EAU, ICUD, NCCN and JUA recommend a repeat resection in all pT1 tumours. ICUD and NICE suggest a second resection in all high risk tumours even in cases with detrusor present in primary resection. EAU specifically stipulates that in cases of low grade pTa or primary *CIS*, a second resection is not necessary as muscle invasive disease is unlikely.

Risk classification

The risk classification of recurrence and progression of NMIBC is largely based on the European Organization for Research and Treatment of Cancer (EORTC) risk table derived from 2,596 patients from seven trials [33]. The other NMIBC scoring model is the Club Urológico Español de Tratamiento Oncológico (CUETO) model which is based on 1062 patients from four trials [34]. When these two nomograms were compared in an independent cohort of 4689 patients, both models were found to overestimate the risk of disease progression and recurrence especially in high risk patients [35]. This was unsurprising due to the low number of patients treated with intravesical BCG in the EORTC trails. A new EORTC nomogram derived from 1812 patients treated with 1–3 year BCG maintenance has recently been published [36]. Although this updated risk table reflects current practice as all patients received maintenance BCG, care should be taken when interpreting these risk tables as patients with *CIS* were not included and no high risk patients underwent repeat resection which is recommended by guidelines. In addition, low risk patients were treated with intravesical BCG which was not recommended in clinical practice. Hence, this risk tables may underestimate recurrence and progression in low risk NMIBC but overestimate recurrence and progression in high risk disease. In addition, there was no distinction made between patients receiving one or three year BCG maintenance. Table 2 describes key predictors for recurrence, progression, cancer specific survival (CSS) and overall survival (OS) from multivariate analysis.

Risk groups adopted by the guidelines are based on the old EORTC tables. EAU and NICE were the only two to define risk groups (Table 3). Although NCCN, ICUD and JUA provided

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Table 2
Variables predicting early and late recurrence, progression, cancer specific survival and overall survival.

	EORTC, 2006 [33]	CUETO, 2009 [34]	EORTC, 2016 [36]
Early Recurrence	– Number of tumours: 2-7, ⩾8 – Prior recurrence rate: ⩽1/yr, >1/yr – Tumour size: ⩾3 cm – Grade: G2, G3 – Presence of CIS – T Category: T1	– Tumour status: recurrent – Gender: Female – Grade: G2, G3 – Tumour size: ⩾3 cm – Presence of CIS – Age: 60–70, >70 yr	– Prior recurrence rate: ⩽1/yr, >1/yr – Number of tumours: ⩾4 – Grade: G2–G3
Late recurrence			– Prior recurrence rate: ⩽1/yr, >1/yr – Number of tumours: ⩾4
Progression	– Presence of CIS – Grade: G3 – T Category: T1 – Number of tumours: 2–7, ⩾8 – Tumour size: ⩾3 cm – Prior recurrence rate: ⩽1/yr, >1/yr	– Grade: G2, G3 – Age: >70 yr – Tumour status: recurrent – T Category: T1 – Presence of CIS	– Stage: T1 – Grade: G2, G3
Cancer specific survival			– Stage: T1 – Grade: G2, G3
Overall survival			– Increasing age (continuous) – Grade: G2, G3

Yr: year; CIS: carcinoma *in situ*.

Table 3
Risk groups of non-muscle invasive bladder cancer stratified by EAU and NICE guidelines.

Risk groups	EAU, 2015 [3]	NICE, 2015 [7]
Low	– New solitary pTa low grade (G1/2) < 3 cm	– Solitary pT1 low grade (G1/2) <3 cm – Papillary urothelial neoplasm of low malignant potential
Intermediate	– All others	– Solitary pTa low grade (G1/2) >3 cm – Multifocal pTa low grade (G1/2) – pTa high grade (G2) – Any pTaG2 (unspecified) – Any low risk with recurrence <12 months
High	– Any pT1 – pTa high grade (G3) – p*CIS* – Multiple/recurrent AND >3 cm Ta low grade (G1/2)	– Any pT1 – pTa high grade (G3) – p*CIS* – Aggressive variants – nested/micropapillary

CIS: carcinoma *in situ*.

recommendations based on risk groups, they did not specify what constituents the different risk groups. The key difference between EAU and NICE is that EAU categorises patients with multiple or recurrent low grade >3 cm Ta tumours as high risk disease while it would be under intermediate risk disease according to NICE. NICE has also acknowledge that aggressive variants such as micropapillary tumours are high risk regardless of stage as this is reflected in their poor prognosis and this should be adopted by all guidelines [37].

Management

Intravesical chemotherapy

Intravesical chemotherapy serves to either prophylactically reduce the risk of BCa recurrence or as an adjuvant treatment after TURBT. MMC is the most common form of chemotherapy used although other chemotherapeutic agents such as doxorubicin and epirubicin have been shown to be as effective although no direct comparison in efficacy has been reported [38].

What is the evidence for immediate postoperative intravesical chemotherapy?

All guidelines support the use of an immediate instillation (or ⩽24 h) of intravesical chemotherapy postTURBT. Delaying instillation by >24 h was found to increase recurrence rates by nearly two fold [39]. The rational of adjuvant intravesical chemotherapy is to destroy intravesical circulating tumour cells after TURBT and low volume unidentified BCa. To maximise the chemotherapeutic properties, increasing drug concentration by minimising fluid intake 8 h prior to treatment, urinary alkalisation and complete bladder draining prior to chemotherapy instillation have been shown to be advantageous [40].

The use of immediate postTURBT chemotherapy is supported by a meta-analysis of 1476 patients where a single postoperative instillation of chemotherapy reduced the recurrent rate by 39% (HR: 0.61, 95% CI 0.49–0.75) compared to TURBT alone in pT1 and pTa patients [41]. However, an up to date meta-analysis of 2278 patients treated with postTURBT chemotherapy showed that patients with ⩾1 recurrence/year or with a 2006 EORTC recurrence score ⩾5 (Supplementary section Table 1) did not achieve a lower recurrence rate [42]. In addition, the instillation had no effect on bladder cancer specific mortality but significantly increased the risk of death (HR: 1.26; 95% CI: 1.05–1.51) [42]. However, conclusions on survival from this meta-analysis should be interpreted with caution as survival was not a primary end point in the study and survival might be influenced by subsequent treatments received by patients.

The NCCN provides the option of omitting the immediate chemotherapy instillation especially in low grade tumours. However, level I evidence has shown that all patients with the exception of those with ⩾1 recurrence/year or with a EORTC score ⩾5 will benefit from this, it would be prudent to consider an immediate instillation of chemotherapy in all cases [42]. Immediate postoperative chemotherapy has also been shown to be effective in high grade tumours (HR: 0.58; 95% CI: 0.39–0.86) and pT1 tumours (HR0.67; 95% CI: 0.53–0.84) and resulted in a significantly longer time to first recurrence [42]. Despite this, ICUD does not support the use of a single dose of chemotherapy in high risk disease (pTa high grade, *CIS* or pT1). Evaluating the evidence, all patients should have immediate intravesical chemotherapy unless there is any suspicion of bladder perforation or significant bleeding, requiring bladder irrigation.

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A phase III multicentre randomised trial comparing pre-TURBT electromotive MMC (eMMC) against standard postTURBT MMC reported a significantly lower recurrence rate (pre-TURBT eMMC: 38% vs postTURBT MMC: 59% vs TURBT alone: 64%; $p < 0.0001$) and a higher median recurrence free interval (pre-TURBT eMMC: 52 months vs. post-TURBT MMC: 16 months vs TURBT alone: 12 months; $p < 0.0001$) (NCT01149174) in the preTURBT eMMC arm [43]. The use of neo-adjuvant MMC has the benefit of improving compliance with the administration of MMC which might be omitted in cases of bladder perforation or significant haematuria. Validating these results with further trails would be essential before adoption in clinical practice. Another phase II trial Investigating Bladder Chemotherapy Instead of Surgery for Low Risk Bladder Cancer (CALIBER) (NCT02070120) is currently underway.

Who should have induction intravesical chemotherapy and what is the evidence for maintenance intravesical chemotherapy?

Although low risk BCa patients would only require a single instillation of intravesical chemotherapy, this is sub-therapeutic for intermediate risk disease and an induction course 3–4 weeks after TURBT is recommended by all guidelines. The exact induction regime and the need for maintenance instillation are uncertain. EAU does not support the use of intravesical chemotherapy >12 months while ICUD and JUA did not specify the duration of a maintenance regime. NICE and NCCN supports the use of an induction course of at least six instillations of MMC which is similar to the MMC arm in the SWOG 8795 protocol [44]. NCCN advocates that a maximum of two induction instillations should be used where there was incomplete response. A randomised trial comparing three different regime of intravesical chemotherapy failed to show any difference between a 6 month and a 1 year regime in a predominantly intermediate risk cohort indicating that maintenance MMC has no benefit [45]. Similarly, data from two EORTC trails concur with this [46]. Intravesical BCG can be used as an alternative, especially in cases of intravesical chemotherapy failure based on a phase III randomised control trial showing that BCG resulted in significantly lower recurrence compared to intravesical MMC with the drawback of higher toxicity [44].

A further phase IV trial of 495 patients with intermediate and high risk disease randomised to either 6 weeks MMC, 6 weeks BCG or 6 weeks MMC with a 36 month maintenance regime. The results showed that maintenance MMC was superior at reducing the risk of recurrence when compared to induction MMC and induction BCG ($p = 0.001$) (maintenance MMC: HR: 0.86; 95% CI: 77.9–91.4 vs MMC: HR: 0.65; 95% CI: 55.9–73.5 vs BCG: HR: 0.69; 95% CI: 59.9–75.7) [47]. A criticism of this trial was that a lower dose of MMC (20 mg) was used compared to the conventional 40 mg and an immediate postTURBT MMC instillation was not given. However, the result that maintenance MMC was superior to induction BCG in reducing recurrence was unexpected. It is plausible that an immediate instillation with an intensive regime might negate the need for a maintenance regime as suggested by Hendricksen et al. [45].

Currently, hyperthermia for intermediate risk bladder cancer (HIVEC-II) (ISRCTN: 23639415), a phase II randomised trial comparing hyperthermia and MMC against MMC alone for 6 weeks has started recruiting intermediate risk patients to determine disease free survival at 24 months.

Who should have intravesical BCG?

All guidelines advocate the use of intravesical BCG >1 week after TURBT in high risk BCa. This recommendation is supported by five meta-analyses confirming the superiority of intravesical BCG over intravesical MMC in both high risk papillary and *CIS* tumours [48–52]. However, a reduction of 32–59% in tumour recurrence only when maintenance BCG was used as opposed to induction alone [48–52]. However, data regarding the effect of intravesical BCG on the risk of progression is conflicting. Two meta-analysis comparing intravesical BCG and MMC reported a 27–34% reduction in progression rates in patients treated with BCG with a lower progression rate in patients receiving maintenance BCG [53,54]. A more recent meta-analysis with individual patient data suggests that there is no difference in disease progression between groups [55]. However, this study has been criticised because of the heterogenous MMC and BCG regimes used in different trials.

What is the optimum duration for intravesical BCG treatment?

The BCG induction regime of once a week for six weeks, which was first described by Morales et al. in 1976 is still advocated today by EAU, ICUD, NCCN and NICE [56]. JUA recommends once a week instillation for 6–8 weeks however, the exact dose of BCG and duration of maintenance regime is unknown. EAU, ICUD and NCCN advocate maintenance regime of 1–3 years while JUA and NICE specify a 3 year maintenance regime.

While different maintenance protocol exist ranging from 6 once weekly instillations every 6 months for 2 years [57] to monthly instillations for 2 years [58], the most commonly used protocol is based on the Southwest Oncology Group (SWOG) regime [59]. In this study, 550 patients who received the six once weekly induction instillation of BCG were randomised to either a maintenance regime of 3 once weekly BCG at 3 and 6 months followed by 3 once weekly BCG every 6 months for up to 3 years or no maintenance. A significant difference in recurrence free survival favouring the BCG maintenance arm (maintenance: 76.8 months vs no maintenance: 35.7 months, $p \leqslant 0.001$) was observed with an absolute 5 year survival advantage of 5% (maintenance: 83% vs no maintenance: 78%, $p = 0.08$) confirming the superiority of maintenance BCG [59].

Are there any options to reduce toxicity from intravesical BCG treatment?

EAU and NICE do not advocate the use of antibiotics prophylaxis in patients treated with BCG while NCCN, ICUD and JUA does not comment on this. Efforts to reduce BCG toxicity have led investigators to investigate if a lower dose of BCG will reduce toxicity while maintaining efficacy. Two randomised controlled trials have shown no difference in systemic or local toxicity between full dose and 1/3 dose BCG [60,61].

The CUETO study showed that when using an 18 week BCG induction regime, there was no difference in efficacy between full dose and 1/3 dose BCG [61]. The EORTC trail randomised 1316 patients to four BCG treatment arms: full dose (81 mg) for 1 year, full dose for 3 years, 1/3 dose (27 mg) for 1 year and 1/3 dose for 3 years reporting 5 year RFS rates of 58.8%, 64.2%, 54.5% and 62.6% respectively [60]. This trial report that high risk patients treated with full dose 3 year maintenance had significantly better RFS compared to 3 year 1/3 dose was used ($p = 0.009$). There was no difference noted between 3 year and 1 year maintenance for intermediate risk disease when full dose was used. Comparing RFS for patients treated with full dose BCG for 3 years with 1/3 dose for 3 years, the absolute 5 year RFS advantage of 1.6% would not be of clinical significance. However, given that the adverse events were not BCG dose dependent, high risk patients in particular should be treated with a 3 year full dose maintenance regime.

Are there any alternatives for patients intolerant of intravesical BCG?

Several trails have compared device assisted chemotherapy such as hyperthermic MMC and electromotive MMC with intraves-

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ical BCG. However, to date the use of device assisted chemotherapy is not recommended by any guidelines. A randomised trial comparing radiofrequency induced hyperthermic MMC against BCG in 190 intermediate to high risk patients treated with 1 year of maintenance treatment showed that 24 month RFS in patients with papillary disease was significantly better in the hyperthermic MMC arm in per-protocol analysis (hyperthermic MMC: 81.8% vs BCG: 64.8%; $p = 0.008$) (NCT00384891) [62]. However, complete response rates for *CIS* between the two groups were similar. Another randomised control trail of 212 pT1 BCa patients randomised to either BCG or sequential BCG and electromotive MMC (BCG/MMC) for a total maintenance duration of 1 year showed that BCG/MMC had significantly lower recurrence rate (BCG/MMC: 41.9% vs BCG: 57.9%; $p = 0.0012$), disease progression (BCG/MMC: 9.3% vs BCG: 21.9; $p = 0.004$) and overall mortality (BCG/MMC:21.5% vs BCG:32.4%; $p = 0.045$) [63]. These results are promising and device assisted chemotherapy may play a role in in the management of high risk NMIBC in the future.

In cases of intravesical BCG failure, what is the evidence for repeating an induction course of intravesical BCG?

Although BCG is an effective treatment for high risk NMIBC, up to 41.3% of patients with develop recurrence and 19.8% of patients will progress to MIBC within 5 years despite maintenance BCG [36]. EAU describes BCG failure as the development of MIBC, recurrence of high grade NMIBC or *CIS* during or after BCG treatment and recommends cystectomy in these cases. Early cystectomy has been shown to improve survival in patients with high risk NMIBC who have failed intravesical BCG [64,65].

NCCN, NICE, ICUD and JUA however advocate that patients can either consider re-challenging with a further induction intravesical BCG and maintenance protocol or proceed to early cystectomy. This is supported by a retrospective analysis of 104 patients which reported that the first 6 weekly course of BCG had a response rate of 34% and re-challenging those who failed BCG with a further 6 weekly induction course resulted in a 53% response rate [66]. Although there is no level one evidence to support a second induction course of BCG, it should be an option especially in patients who are reluctant to have a cystectomy. All guidelines recommend cystectomy failing two induction courses as a third induction course of BCG only has a response rate of 20% [67].

Which patients should be considered for early cystectomy?

High risk MIBC is a heterogeneous disease. EAU, NICE, NCCN, ICUD and JUA suggest that high risk tumours can be treated with early cystectomy as an alternative to intravesical BCG. ICUD specifically specify this includes young patients with T1 disease with at least one adverse prognostic factor such as multifocality, concurrent *CIS*, prostatic involvement, difficult to resect tumour and non-compliance to intravesical BCG treatment. In addition to the above characteristics, EAU suggest that patients with large tumours (>3 cm) and micropapillary variants are also candidates of early cystectomy.

This is consistent with evidence that high grade T1 BCa with concurrent *CIS* is associated with an increased risk of recurrence and progression [4]. EORTC nomograms also suggest that in patients treated with maintenance BCG, previous recurrence rate and multifocal disease were associated with progression and death [36]. In addition, micropapillary BCa has been reported to be refractory to BCG as it has a 67% risk of disease progression and early cystectomy is advocated [68].

What treatment options are available for NMIBC patients who are unfit for cystectomy?

EAU, NCCN and ICUD suggest that patients unfit for a cystectomy should consider further salvage intravesical therapy. NICE recommends further management plan should be discussed at a specialist multidisciplinary team setting. There is however limited data on intravesical salvage therapy. Valrubicin has been approved by the Food and Drug Administration for the treatment of *CIS* refractory to intravesical BCG with a 21% complete response rate although NCCN does not support its use [69]. In a SWOG phase II study, intravesical gemcitabine showed a 28% recurrence free survival rate in high risk patients who had failed two courses of intravesical BCG [70]. BCG with interferon-α reported a RFS rate of 42% at a median follow-up of 2 years in a phase II multicentre trial [71]. The first phase III randomised controlled trial comparing hyperthermia with MMC to a second course of BCG or institutional standard in high risk NMIBC (HYMN) (NCT01094964) showed that hyperthermia with MMC was effective in reducing recurrence in papillary disease (HR: 0.40; 95% CI: 0.16–0.98; $p = 0.05$) but not in *CIS* (HR: 2.17; 95% CI: 1.15–4.08; $p = 0.02$) [72].

Surveillance

Surveillance of NMIBC with a combination of cystoscopy, upper tract imaging and urinary test is recommended due to the risk of recurrence and progression of disease [4]. However, there is no standardised follow-up protocol with all the guidelines adopting a risk stratified approach. Differences in guidelines are described in Table 4. The three month cystoscopy is essential as it has prognostic implications for tumour progression and should be performed in all patients regardless of stage and grade of disease [4,73].

EAU and ICDU support the use of outpatient fulguration of recurrent low grade pTa NMIBC although NICE specify that fulguration should only be an option in low risk solitary tumours $\leqslant$3 mm which have been disease free for at least 6 months. Flexible cystoscopy with fulguration is well tolerated and has the advantage of avoiding morbidity of general anaesthesia, lower cost and shorter operating time [74].

What is the recommended surveillance interval for low risk bladder cancer patients?

EAU recommendation is that patients who are recurrence free at 5 years can be discharged. This is based on a cohort study of 115 low risk patients followed up for a mean duration of 19.4 years where 98% of patients who did not develop recurrence after 5 years remained recurrence free at 20 years [75]. NCCN, ICUD and JUA did not specify a surveillance interval. The new NICE guidelines advocate discharging low risk patients after 1 year of no recurrence.

There is no evidence that intensive cystoscopic surveillance in low risk NMIBC will actually improve overall survival. In addition, cystoscopy is not without morbidity with up to 5.5% of patients developing a urinary tract infection and a long surveillance protocol has significant healthcare cost implications [76,77]. A cohort study reported that in patients who developed disease progression, nearly all were observed in their first year postTURBT supporting NICE recommendations [75].

There is increasing evidence that low grade NMIBC infrequently progress and some have even recommended watchful waiting for small recurrent low grade pTa tumours and tumours were only resected when there was a change in tumour morphology or size [78]. A cohort of 32 patients with a mean tumour observation duration of 10 months had a 6.7% of disease progression rate

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Table 4
Comparison of surveillance protocol of EAU, NCCN, NICE, ICUD and JUA guidelines.

	EAU, 2015 [3]	NCCN, 2015 [6]	NICE, 2015 [7]	ICUD, 2012 [9]	JUA, 2010 [8]
Low	3 months cystoscopy, then at 12 months and yearly for 5 years then discharge	3 months cystoscopy then increase interval	3 months cystoscopy then at 12 months then discharge No urinary markers/cytology	Periodic cystoscopy No upper tract imaging	3 months follow up then risk adapted
Intermediate	Adapted to personal/subjective factors		Cystoscopy at 3, 9, 18, 30 months then yearly for 5 years in total then discharge		
High	3 monthly cystoscopy and urinary cytology for 2 years, then 6 monthly for 5 years and then yearly indefinitely Yearly upper tract imaging with IVU/CT IVU	Cystoscopy and urinary cytology every 3–6 months for 2 years then increase interval Consider upper tract imaging every 1–2 years Urinary markers optional	3 monthly cystoscopy for 2 years then 6 monthly for 2 years then yearly indefinitely	Cystoscopy and urinary cytology 3 monthly for 2 years then 4 monthly for 3rd year then 6 monthly for 4th and 5th year then yearly. If no recurrence, imaging of upper tracts by renal tract ultrasound/IVU, CT IVU periodically	

IVU, intravenous urogram; CT IVU, CT intravenous urogram.

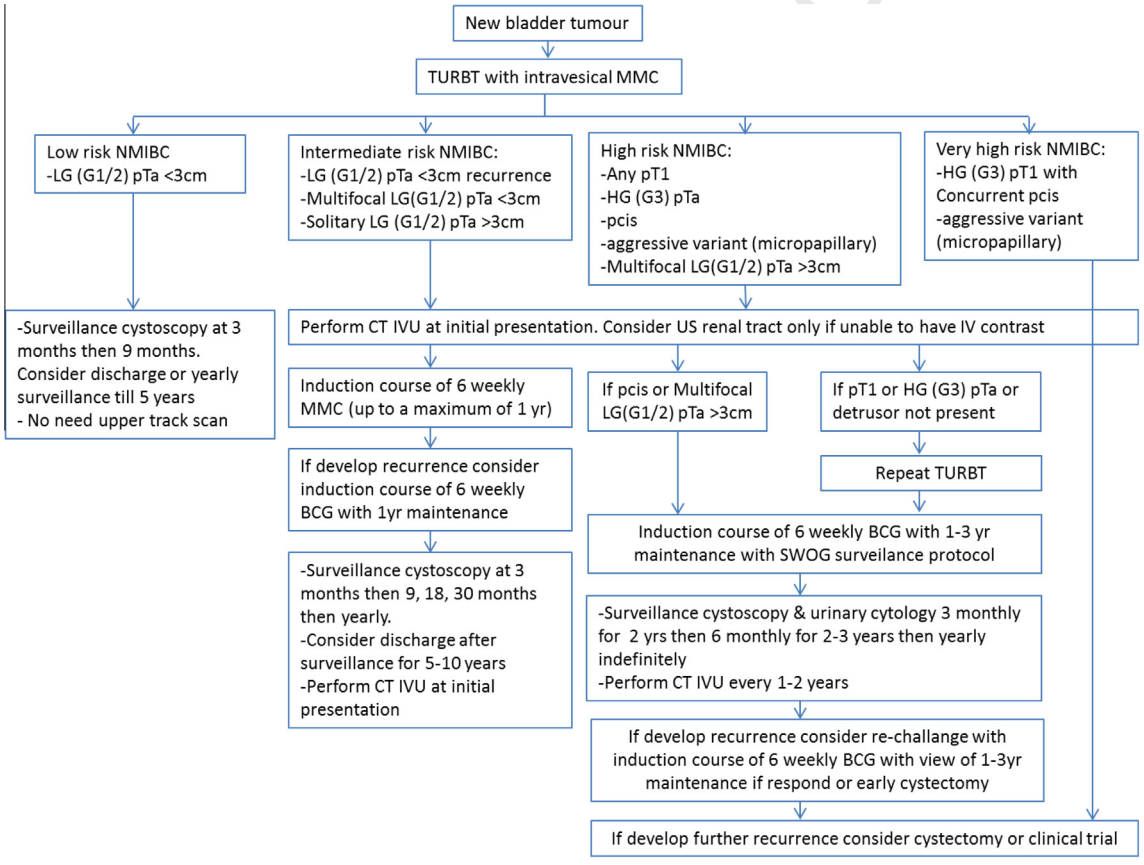

Fig. 1. Proposed management and surveillance protocol based on EAU, NCCN, NICE, ICUD and JUA guidelines.

although no patients developed MIBC [79]. However, another retrospective analysis of 152 low grade pTa patients reported that 55% of all recurrence occurred within 12 months, 13% within 12–24 months and 27% within 24–60 months [80]. Hence, given the rarity of low grade NMIBC patients progressing to MIBC, discharging patient after one year follow-up can be considered an option however there should be a very low threshold of repeating cystoscopy.

All guidelines do not support surveillance upper tract imaging, urinary cytology or any other urinary biomarker for low risk BCa patients. This is supported by patient registry data of 99,338 BCa patients which showed that only 0.7% of low grade BCa patients developed UTT at a median duration of 33 months [10].

What is the recommended surveillance interval for high risk bladder cancer patients?

In high risk NMIBC, EAU, NCCN, NICE and ICUD recommend performing yearly surveillance cystoscopy even beyond 5 years. In high risk BCa patients treated with maintenance BCG, disease progression at 5 years occurred in 19.8% of patients with a cancer specific survival of 88.7% at 5 years [81]. In addition, up to 12%

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(5/43) of high risk patients developed recurrence beyond 10 years [82]. The role of urinary cytology was not specified by NICE although it is of significant value especially in high risk disease [83]. It is worth considering that given the high sensitivity of urinary cytology in high grade BCa, its use during surveillance of high risk NMIBC should be recommended in coherence with EAU, NCCN, ICUD and JUA recommendations [84]. Only NCCN specified that FDA approved urinary biomarkers such as FISH and NMP22 are options in the surveillance setting. No other guidelines support the use of novel urinary biomarkers. Cost analysis performed by NICE suggested that the use of urinary cytology or FISH was cost effective when coupled with a reduce cystoscopy follow-up strategy although there is a lack of comparative evidence and more research is required. EAU recommends that bladder mapping/PDD cystoscopy, prostatic urethra biopsy and CT IVU should be performed when urinary cytology is positive in the absence of BCa recurrence. The need for upper tract surveillance is recommended by EAU, NCCN and ICUD every 1–2 years indefinitely. Retrospective analysis of 193 high risk NMIBC patients treated with BCG with a median follow-up of 86 months report that 9.8% (19/193) of patients develop upper tract tumours emphasising the need for continuous intermittent upper tract surveillance in high risk NMIBC [85].

Conclusion

The EAU, NCCN, NICE, ICUD and JUA guidelines are largely consistent with minor variation regarding the need for upper tract imaging, second resection and intravesical treatment. In Fig. 1, we propose a management and surveillance protocol for NMIBC based on the cumulative recommendations of EAU, NCCN, NICE, ICUD and JUA guidelines. NICE, which is the most recently updated guideline, has issued guidance for the use of PDD/NBI cystoscopy, which is welcomed. The key difference between the guidelines is in the recommended surveillance protocol, particularly for the low-risk group. In the absence of recurrence, NICE guidelines advocate discharging low-risk patients after one year, which is in contrast to the 5-year follow-up suggested by EAU. This difference reflects the lack of level one evidence on which recommendations are made. Instead recommendations for surveillance protocols are based on data from cohort studies. With regards to intravesical treatment, there are currently no options beyond MMC and BCG which are recommended by guidelines. Device assisted intravesical treatment are promising although further trials are needed before they can be incorporated into guidelines. Novel biomarkers are clearly needed to help with diagnosis, prognosis and predicting response to treatment, which will allow a more personalised approach to treating patients with BCa.

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Appendix A. Supplementary data

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References

[1] Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015;136:E359–86.
[2] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA Cancer J Clin 2015;65:5–29.
[3] Babjuk M, Burger M, Zigeuner R, Shariat SF, van Rhijn BW, Compérat E, et al. EAU guidelines on non-muscle-invasive urothelial carcinoma of the bladder: update 2013. Eur Urol 2013;64:639–53.
[4] Sylvester RJ, van der Meijden AP, Oosterlinck W, Witjes JA, Bouffioux C, Denis L, 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;49:466–77.
[5] Svatek RS, Hollenbeck BK, Holmang S, Lee R, Kim SP, Stenzl A, et al. The economics of bladder cancer: costs and considerations of caring for this disease. Eur Urol 2014;66:253–62.
[6] Network NCC. NCCN clinical practice guidelines in oncology. Bladder Cancer 2015.
[7] Excellence NIfHaC. Bladder cancer: diagnosis and management; 2015.
[8] Committee for Establishment of the Clinical Practice Guidelines for the Management of Bladder Cancer and the Japanese Urological Association. Evidence-based clinical practice guidelines for bladder cancer (summary – JUA 2009 Edition). Int J Urol 2010;17:102–24.
[9] Burger M, Oosterlinck W, Konety B, Chang S, Gudjonsson S, Pruthi R, et al. ICUD-EAU International Consultation on Bladder Cancer 2012: non-muscle-invasive urothelial carcinoma of the bladder. Eur Urol 2013;63:36–44.
[10] Wright JL, Hotaling J, Porter MP. Predictors of upper tract urothelial cell carcinoma after primary bladder cancer: a population based analysis. J Urol 2009;181:1035–9 [discussion 9].
[11] Palou J, Rodriguez-Rubio F, Huguet J, Segarra J, Ribal MJ, Alcaraz A, 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 61].
[12] Anderson MJ, Fawcett MD, Feehally J, Goldberg L, Kelly MJ, MacTier R, et al. Joint consensus statement on the initial assessment of haematuria. BAUS/RA Guidelines 2008;2008:p. 1–5
[13] Davis R, Jones JS, Barocas DA, Castle EP, Lang EK, Leveillee RJ, et al. Diagnosis, evaluation and follow-up of asymptomatic microhematuria (AMH) in adults: AUA guideline. J Urol 2012;188:2473–81.
[14] Sudakoff GS, Dunn DP, Guralnick ML, Hellman RS, Eastwood D, See WA. Multidetector computerized tomography urography as the primary imaging modality for detecting urinary tract neoplasms in patients with asymptomatic hematuria. J Urol 2008;179:862–7.
[15] Nawfel RD, Judy PF, Schleipman AR, Silverman SG. Patient radiation dose at CT urography and conventional urography 1. Radiology 2004;232:126–32.
[16] Caoili EM, Cohan RH, Korobkin M, Platt JF, Francis IR, Faerber GJ, et al. Urinary tract abnormalities: initial experience with multi-detector row CT urography. Radiology 2002;222:353–60.
[17] Khadra M, Pickard R, Charlton M, Powell P, Neal D. A prospective analysis of 1930 patients with hematuria to evaluate current diagnostic practice. J Urol 2000;163:524–7.
[18] Edwards TJ, Dickinson AJ, Natale S, Gosling J, McGrath JS. A prospective analysis of the diagnostic yield resulting from the attendance of 4020 patients at a protocol-driven haematuria clinic. BJU Int 2006;97:301–5.
[19] Rodgers M, Nixon J, Hempel S, Aho T, Kelly J, Neal D, et al. Diagnostic tests and algorithms used in the investigation of haematuria: systematic reviews and economic evaluation. Health Technol Assess 2006 [10:xi-259].
[20] Chou R, Gore JL, Buckley D, Fu R, Gustafson K, Griffin JC, et al. Urinary biomarkers for diagnosis of bladder cancer: a systematic review and meta-analysis. Ann Intern Med 2015;163:922–31.
[21] Raitanen MP, Aine R, Rintala E, Kallio J, Rajala P, Juusela H, et al. Differences between local and review urinary cytology in diagnosis of bladder cancer. An interobserver multicenter analysis. Eur Urol 2002;41:284–9.
[22] Brimo F, Vollmer RT, Case B, Aprikian A, Kassouf W, Auger M. Accuracy of urine cytology and the significance of an atypical category. Am J Clin Pathol 2009;132:785–93.
[23] Jones TD, Wang M, Eble JN, MacLennan GT, Lopez-Beltran A, Zhang S, et al. Molecular evidence supporting field effect in urothelial carcinogenesis. Clin Cancer Res 2005;11:6512–9.
[24] Kiemeney LALM, Witjes JA, Heijbroek RP, Koper NP, Verbeek ALM, Debruyne FMJ, et al. Should random urothelial biopsies be taken from patients with primary superficial bladder cancer? a decision analysis. Br J Urol 1994;73:164–71.
[25] van der Meijden A, Oosterlinck W, Brausi M, Kurth KH, Sylvester R, deBalincourt C, et al. Significance of bladder biopsies in Ta, T1 bladder tumors: a report from the EORTC genito-urinary tract cancer cooperative group. Eur Urol 1999;35:267–71.

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[26] May F, Treiber U, Hartung R, Schwaibold H. Significance of random bladder biopsies in superficial bladder cancer. Eur Urol 2003;44:47–50.
[27] Burger M, Grossman HB, Droller M, Schmidbauer J, Hermann G, Dragoescu O, 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.
[28] 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.
[29] Witjes JA, Redorta JP, Jacqmin D, Sofras F, Malmstrom PU, Riedl C, et al. Hexaminolevulinate-guided fluorescence cystoscopy in the diagnosis and follow-up of patients with non-muscle-invasive bladder cancer: review of the evidence and recommendations. Eur Urol 2010;57:607–14.
[30] 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–Guerin immunotherapy and mitomycin C intravesical therapy. Eur Urol 2010;57:655–60.
[31] Herr HW. The value of a second transurethral resection in evaluating patients with bladder tumors. J Urol 1999;162:74–6.
[32] 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.
[33] Sylvester RJ, van der Meijden AP, Oosterlinck W, Witjes JA, Bouffioux C, Denis L, 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 [466–5].
[34] Fernandez-Gomez J, Madero R, Solsona E, Unda M, Martinez-Pineiro L, Gonzalez M, et al. Predicting nonmuscle invasive bladder cancer recurrence and progression in patients treated with bacillus Calmette–Guerin: the CUETO scoring model. J Urol 2009;182:2195–203.
[35] Xylinas E, Kent M, Kluth L, Pycha A, Comploj E, Svatek RS, et al. Accuracy of the EORTC risk tables and of the CUETO scoring model to predict outcomes in non-muscle-invasive urothelial carcinoma of the bladder. Br J Cancer 2013;109:1460–6.
[36] Cambier S, Sylvester RJ, Collette L, Gontero P, Brausi MA, van Andel G, 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–Guerin. Eur Urol 2015;22 [00556-4].
[37] Kamat AM, Gee JR, Dinney CP, Grossman HB, Swanson DA, Millikan RE, et al. The case for early cystectomy in the treatment of nonmuscle invasive micropapillary bladder carcinoma. J Urol 2006;175:881–5.
[38] Sylvester RJ, Oosterlinck W, van der Meijden AP. 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.
[39] Kaasinen E, Rintala E, Hellström P, Viitanen J, Juusela H, Rajala P, et al. Factors explaining recurrence in patients undergoing chemoimmunotherapy regimens for frequently recurring superficial bladder carcinoma. Eur Urol 2002;42:167–74.
[40] Au JL, Badalament RA, Wientjes MG, Young DC, Warner JA, Venema PL, 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.
[41] 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 435.
[42] Sylvester RJ, Oosterlinck W, Holmang S, Sydes MR, Birtle A, Gudjonsson 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 2015;16:050.
[43] Di Stasi SM, Valenti M, Verri C, Liberati E, Giurioli A, Leprini G, et al. Electromotive instillation of mitomycin immediately before transurethral resection for patients with primary urothelial non-muscle invasive bladder cancer: a randomised controlled trial. Lancet Oncol 2011;12:871–9.
[44] Lamm DL, Blumenstein BA, David Crawford E, Crissman JD, Lowe BA, Smith Jr JA, et al. Randomized intergroup comparison of bacillus calmette–guerin immunotherapy and mitomycin C chemotherapy prophylaxis in superficial transitional cell carcinoma of the bladder a southwest oncology group study. Urol Oncol 1995;1:119–26.
[45] Hendricksen K, Witjes WP, Idema JG, Kums JJ, van Vierssen Trip OB, de Bruin MJ, et al. Comparison of three schedules of intravesical epirubicin in patients with non-muscle-invasive bladder cancer. Eur Urol 2008;53:984–91.
[46] Bouffioux C, Kurth K, Bono A, Oosterlinck W, Kruger CB, De Pauw M, et al. Original articles: bladder cancer: intravesical adjuvant chemotherapy for superficial transitional cell bladder carcinoma: results of 2 European organization for research and treatment of cancer randomized trials with mitomycin C and doxorubicin comparing early versus delayed instillations and short-term versus long-term treatment. J Urol 1995;153:934–41.
[47] Friedrich MG, Pichlmeier U, Schwaibold H, Conrad S, Huland H. Long-term intravesical adjuvant chemotherapy further reduces recurrence rate compared with short-term intravesical chemotherapy and short-term therapy with bacillus Calmette–Guérin (BCG) in patients with non-muscle-invasive bladder carcinoma. Eur Urol 2007;52:1123–30.
[48] Bohle A, Jocham D, Bock PR. Intravesical bacillus Calmette–Guerin versus mitomycin C for superficial bladder cancer: a formal meta-analysis of comparative studies on recurrence and toxicity. J Urol 2003;169:90–5.
[49] Shelley MD, Wilt TJ, Court J, Coles B, Kynaston H, Mason MD. Intravesical bacillus Calmette–Guerin 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.
[50] Malmström P-U, Sylvester RJ, Crawford DE, Friedrich M, Krege S, Rintala E, 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.
[51] 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.
[52] Sylvester RJ, van der Meijden AP, Witjes JA, Kurth K. Bacillus calmette–guerin 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.
[53] Sylvester RJ, van der MA, Lamm DL. Intravesical bacillus Calmette–Guerin 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.
[54] Bohle A, Bock PR. Intravesical bacille Calmette–Guerin versus mitomycin C in superficial bladder cancer: formal meta-analysis of comparative studies on tumor progression. Urology 2004;63:682–6.
[55] Malmstrom PU, Sylvester RJ, Crawford DE, Friedrich M, Krege S, Rintala E, et al. An individual patient data meta-analysis of the long-term outcome of randomised studies comparing intravesical mitomycin C versus bacillus Calmette–Guerin for non-muscle-invasive bladder cancer. Eur Urol 2009;56:247–56.
[56] Morales A, Eidinger D, Bruce AW. Intracavitary Bacillus Calmette–Guerin in the treatment of superficial bladder tumors. J Urol 1976;116:180–3.
[57] Palou J, Laguna P, Millan-Rodriguez F, Hall RR, Salvador-Bayarri J, Vicente-Rodriguez J. Control group and maintenance treatment with bacillus Calmette–Guerin for carcinoma in situ and/or high grade bladder tumors. J Urol 2001;165:1488–91.
[58] Badalament RA, Herr HW, Wong GY, Gnecco C, Pinsky CM, Whitmore Jr WF, et al. A prospective randomized trial of maintenance versus nonmaintenance intravesical bacillus Calmette–Guerin therapy of superficial bladder cancer. J Clin Oncol 1987;5:441–9.
[59] Lamm DL, Blumenstein BA, Crissman JD, Montie JE, Gottesman JE, Lowe BA, et al. Maintenance bacillus Calmette–Guerin 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.
[60] Oddens J, Brausi M, Sylvester R, Bono A, van de Beek C, van Andel G, et al. Final results of an EORTC-GU cancers group randomized study of maintenance bacillus Calmette–Guerin 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.
[61] Ojea A, Nogueira JL, Solsona E, Flores N, Gomez JM, Molina JR, et al. A multicentre, randomised prospective trial comparing three intravesical adjuvant therapies for intermediate-risk superficial bladder cancer: low-dose bacillus Calmette–Guerin (27 mg) versus very low-dose bacillus Calmette–Guerin (13.5 mg) versus mitomycin C. Eur Urol 2007;52:1398–406.
[62] Arends TJ, Nativ O, Maffezzini M, de Cobelli O, Canepa G, Verweij F, et al. Results of a randomised controlled trial comparing intravesical chemohyperthermia with mitomycin C Versus Bacillus Calmette–Guerin for adjuvant treatment of patients with intermediate- and high-risk non-muscle-invasive bladder cancer. Eur Urol 2016.
[63] Di Stasi SM, Giannantoni A, Giurioli A, Valenti M, Zampa G, Storti L, 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.
[64] Herr HW, Sogani PC. Does early cystectomy improve the survival of patients with high risk superficial bladder tumors? J Urol 2001;166:1296–9.
[65] Hautmann RE, Volkmer BG, Gust K. Quantification of the survival benefit of early versus deferred cystectomy in high-risk non-muscle invasive bladder cancer (T1 G3). World J Urol 2009;27:347–51.
[66] Coplen DE, Marcus MD, Myers JA, Ratliff TL, Catalona WJ. Long-term followup of patients treated with 1 or 2, 6-week courses of intravesical bacillus Calmette–Guerin: analysis of possible predictors of response free of tumor. J Urol 1990;144:652–7.
[67] Catalona WJ, Hudson MA, Gillen DP, Andriole GL, Ratliff TL. Risks and benefits of repeated courses of intravesical bacillus Calmette–Guerin therapy for superficial bladder cancer. J Urol 1987;137:220–4.
[68] Kamat AM, Gee JR, Dinney CP, Grossman HB, Swanson DA, Millikan RE, et al. The case for early cystectomy in the treatment of nonmuscle invasive micropapillary bladder carcinoma. J Urol 2006;175:881–5.

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[69] Steinberg G, Bahnson R, Brosman S, Middleton R, Wajsman Z, Wehle M, et al. Efficacy and safety of valrubicin for the treatment of bacillus Calmette–Guerin refractory carcinoma in situ of the bladder. J Urol 2000;163:761–7.
[70] Skinner EC, Goldman B, Sakr WA, Petrylak DP, Lenz H-J, Lee CT, et al. SWOG S0353: phase II trial of intravesical gemcitabine in patients with nonmuscle invasive bladder cancer and recurrence after 2 prior courses of intravesical bacillus Calmette–Guerin. J Urol 2013;190:1200–4.
[71] O'Donnell MA, Lilli K, Leopold C, Group NBC-GIPI. Interim results from a national multicenter phase II trial of combination bacillus Calmette–Guerin plus interferon alfa-2b for superficial bladder cancer. J Urol 2004;172:888–93.
[72] Kelly J, Buckley L, Devall A, Loubiere L, Barnwell J, Mostafid H, et al. HYMN: a randomised controlled phase III trial comparing hyperthermia plus mitomycin to a second course of BCG or institutional standard in patients with recurrence of non-muscle invasive bladder cancer (NMIBC) following induction or maintenance BCG therapy. 111 RIVER ST, HOBOKEN 07030-5774, NJ USA: BJU Int: WILEY-BLACKWELL; 2015. p. 12.
[73] Palou J, Rodríguez-Rubio F, Millán F, Algaba F, Rodríguez-Faba O, Huguet J, 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.
[74] Herr HW, Schneider M. Outpatient flexible cystoscopy in men: a randomized study of patient tolerance. J Urol 2001;165:1971–2.
[75] 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.
[76] Burke D, Shackley D, O'reilly P. The community-based morbidity of flexible cystoscopy. BJU Int 2002;89:347–9.
[77] Botteman MF, Pashos CL, Redaelli A, Laskin B, Hauser R. The health economics of bladder cancer. PharmacoEconomics 2003;21:1315–30.
[78] Gofrit ON, Pode D, Lazar A, Katz R, Shapiro A. Watchful waiting policy in recurrent Ta G1 bladder tumors. Eur Urol 2006;49:303–7.
[79] Soloway MS, Bruck DS, Kim SS. Expectant management of small, recurrent, noninvasive papillary bladder tumors. J Urol 2003;170:438–41.
[80] Leblanc B, Duclos A, Benard F, Côté J, Valiquette L, Paquin J, et al. Long-term followup of initial Ta grade 1 transitional cell carcinoma of the bladder. J Urol 1999;162:1946–50.
[81] Cambier S, Sylvester RJ, Collette L, Gontero P, Brausi MA, van Andel G, 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 2015.
[82] Cookson MS, Herr HW, Zhang ZF, Soloway S, Sogani PC, Fair WR. The treated natural history of high risk superficial bladder cancer: 15-year outcome. J Urol 1997;158:62–7.
[83] Van Rhijn BW, Van der Poel HG, van Der Kwast TH. Urine markers for bladder cancer surveillance: a systematic review. Eur Urol 2005;47:736–48.
[84] Lotan Y, Roehrborn CG. Sensitivity and specificity of commonly available bladder tumor markers versus cytology: results of a comprehensive literature review and meta-analyses. Urology 2003;61:109–18.
[85] Hurle R, Losa A, Manzetti A, Lembo A. Upper urinary tract tumors developing after treatment of superficial bladder cancer: 7-year follow-up of 591 consecutive patients. Urology 1999;53:1144–8.

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