Dear Author,

Please, note that changes made to the HTML content will be added to the article before publication, but are not reflected in this PDF.

Note also that this file should not be used for submitting corrections.
Management of non-muscle invasive bladder cancer: A comprehensive analysis of guidelines from the United States, Europe and Asia

Wei Shen Tan a,b,⁎, Simon Rodney a,b, Benjamin Lamb b, Mark Feneley b, John Kelly a,b

⁎Division of Surgery and Interventional Science, University College London, 74 Huntley Street, London WC1E 6AU, UK
Division of Surgery, University College London Hospital, 16-18 Westmoreland Street, London W1G 8PH, UK

A R T I C L E  I N F O

Article history:
Received 29 March 2016
Received in revised form 3 May 2016
Accepted 4 May 2016
Available online xxxx

Keywords:
Bladder cancer
Consensus guidelines
Recommendations
Non-muscle invasive bladder cancer
Review

A B S T R A C T

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 treatment remains 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.

© 2016 Published by Elsevier Ltd.

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-
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 pyelogram, 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 hydrenephrosis 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), Immuno-Cyst 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 debatable 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 <1 cm should be resected en bloc while ICUD suggest that this is an option for tumours <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 it 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.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Upper tract imaging</strong></td>
<td><strong>CT IVU/IVU for tumours located in trigone. USS kidneys, ureters, bladder can be used at initial work up</strong></td>
<td><strong>All patients should have either CT intravenous urogram (IVU), renal tract ultrasound, CT without contrast with retrograde pyelogram, MRI IVU or ureteroscopy</strong></td>
<td><strong>CT/MRI IVU in tumours suspicious of being muscle invasive pre-TURBT or new/recurrent high risk bladder tumours</strong></td>
<td><strong>Consider imaging in visible haematuria or unexplained positive urinary cytology</strong></td>
</tr>
</tbody>
</table>

Please cite this article in press as: Tan WS et al. Management of non-muscle invasive bladder cancer: A comprehensive analysis of guidelines from the United States, Europe and Asia. Cancer Treat Rev (2016), http://dx.doi.org/10.1016/j.ctrv.2016.05.002
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 in the absence of the 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 cystoscopice 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 20X [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: 4.0% 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 second 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 trials. 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
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 rationale 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 (HR: 0.67; 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.

Table 2

<table>
<thead>
<tr>
<th>Variables predicting early and late recurrence, progression, cancer specific survival and overall survival.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EORTC, 2006</strong></td>
</tr>
<tr>
<td>Early Recurrence</td>
</tr>
<tr>
<td>- Prior recurrence rate: ≤1/yr, &gt;1/yr</td>
</tr>
<tr>
<td>- Tumour size: &gt;3 cm</td>
</tr>
<tr>
<td>- Grade: G2, G3</td>
</tr>
<tr>
<td>- Presence of CIS</td>
</tr>
<tr>
<td>- T Category: T1</td>
</tr>
<tr>
<td>Late recurrence</td>
</tr>
<tr>
<td>- Grade: G2, G3</td>
</tr>
<tr>
<td>- T Category: T1</td>
</tr>
<tr>
<td>- Tumour size: &gt;3 cm</td>
</tr>
<tr>
<td>- Prior recurrence rate: ≤1/yr, &gt;1/yr</td>
</tr>
<tr>
<td>Cancer specific survival</td>
</tr>
<tr>
<td>- Number of tumours: &gt;4</td>
</tr>
<tr>
<td>Overall survival</td>
</tr>
</tbody>
</table>

Yr: year; CIS: carcinoma in situ.

Table 3

<table>
<thead>
<tr>
<th>Risk groups</th>
<th>EAU, 2015</th>
<th>NICE, 2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>- New solitary pTa low grade (G1/2) &lt; 3 cm</td>
<td>- Solitary pT1 low grade (G1/2) &lt; 3 cm</td>
</tr>
<tr>
<td>Intermediate</td>
<td>- All others</td>
<td>- Papillary urothelial neoplasms of low malignant potential</td>
</tr>
<tr>
<td>High</td>
<td>- Any pT1</td>
<td>- Solitary pTa low grade (G1/2) &lt; 3 cm</td>
</tr>
<tr>
<td>- pTa high grade (G3)</td>
<td>- Multifocal pTa low grade (G1/2)</td>
<td></td>
</tr>
<tr>
<td>- pCIS</td>
<td>- pTa high grade (G2)</td>
<td></td>
</tr>
<tr>
<td>- Multiple/recurrent AND &gt;3 cm Ta low grade (G1/2)</td>
<td>- Any pTaC2 (unspecified)</td>
<td></td>
</tr>
<tr>
<td>- Aggressive variants</td>
<td>- Any low risk with recurrence &lt;12 months</td>
<td></td>
</tr>
<tr>
<td>- Nested/micropapillary</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CIS: carcinoma in situ.

recommendations based on risk groups, they did not specify what constitutes 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].
A phase III multicentre randomised trial comparing pre-TURB T electromotive MMC (eMMC) against standard post-TURB T MMC reported a significantly lower recurrence rate (pre-TURB T eMMC: 38% vs post-TURB T MMC: 59% vs TURB T alone: 64%; \( p < 0.0001 \)) and a higher median recurrence free interval (pre-TURB T eMMC: 52 months vs. post-TURB T MMC: 16 months vs. TURB T alone: 12 months; \( p < 0.0001 \) (NCT01149174) in the preTURB T eMMC arm [43]. The use of neo-adjvant 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 trials 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 TURB T 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 trials 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 postTURB T 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 Hendrickse 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 TURB T 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 protocols 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, \( p < 0.001 \)) 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?

EUA 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 trial 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.
ical BCG. However, due to the use of device assisted chemotherapy it 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%; \( p = 0.008 \)) [62]. However, complete response rates for CIS between the two groups were similar.

Another randomised control trial 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 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 NMIBC 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 BCG 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-\( \alpha \) 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].

**Survveillance**

Survveillance 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 ICUD 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 <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

Please cite this article in press as: Tan WS et al. Management of non-muscle invasive bladder cancer: A comprehensive analysis of guidelines from the United States, Europe and Asia. Cancer Treat Rev (2016), http://dx.doi.org/10.1016/j.ctrv.2016.05.002
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%
(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 EUA, 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. EUA 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 EUA, 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 EUA, 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 EUA, 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 EUA. 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 is 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.

Funding support

No specific funding to be disclosed.

Conflict of interest disclosures

No conflict of interest to disclose.

Acknowledgments

We are grateful to the Urology Foundation & UCLH Biomedical Research Centre for funding our work.

Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.ctrv.2016.05.002.

References


