

The management of non-muscle-invasive bladder cancer: A comparison of European and UK guidelines

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Abstract

Bladder cancer represents a significant health burden worldwide, with non-muscle-invasive tumours representing the majority of new bladder cancer diagnoses. Non-muscle-invasive bladder cancer (NMIBC) has a high prevalence and forms a large proportion of the caseload in urological practice, accounting for a significant cost in terms of urological healthcare. The last two decades have seen the development and refinement of guidelines from national and international organisations aiming to optimise management of NMIBC and bladder cancer in general. This review outlines the most recent European and United Kingdom guidelines on NMIBC, and in particular focuses on comparing and contrasting key recommendations from guidelines published by the European Association of Urology and the UK-based National Institute for Clinical Excellence.

Level of evidence: Not applicable for this multicentre audit.

Keywords

Bladder cancer, superficial, NMIBC, guidelines

Introduction

Bladder cancer is the seventh commonest cancer worldwide to affect men, and the 14th commonest cancer to affect women. Rates of bladder cancer appear to be higher in the developed world, where it represents the fourth commonest cancer in men.¹ The United Kingdom (UK) has the lowest incidence of bladder cancer in men in Europe and the 14th lowest for women.² Bladder cancer accounts for 3% of all cancer deaths in the UK, with a crude mortality rate of 8.2 cancer deaths per 100,00 individuals.³

Most (75%–80%) patients with bladder cancer present with disease confined to the mucosa. Non-muscle-invasive bladder cancer (NMIBC) has a higher prevalence than muscle-invasive tumours and a lower risk of cancer-specific mortality.^{2,4,5} Management of NMIBC is therefore a common and significant feature of secondary care urological practice.

This review outlines the most recent UK and European guidelines regarding the management of NMIBC, with a particular emphasis on comparing and contrasting

European Association of Urology (EAU)⁶ and National Institute of Clinical Excellence (NICE)⁷ guidelines.

Diagnosis and initial evaluation of NMIBC

There is consensus between the EAU and NICE guidance regarding initial evaluation of patients presenting with suspected bladder cancer. Both guidelines stress the

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importance of taking a comprehensive patient history and recommend cystoscopy for all patients with symptoms suggestive of bladder cancer. Both guidelines also suggest that the evidence for using urinary biomarkers in this setting is inadequate and they should not be substituted for cystoscopy to investigate suspected bladder cancer or for follow-up after treatment.

The EAU NMIBC guidelines suggest that a renal and bladder ultrasound may be valuable in the work-up of patients presenting with haematuria, but once a diagnosis of NMIBC is made computed tomography urography (CTU) should be performed only in selected cases (e.g. tumours located in the trigone, or multiple and/or high-risk tumours). This strategy is based on the observation that once a bladder tumour has been detected, the incidence of further significant findings on CT is low. The overall incidence of upper tract urothelial cancer is only about 1.8% in patients with newly diagnosed bladder cancer, although this increases to 7.5% in patients with trigone tumours. In contrast, NICE guidance recommends either CT or magnetic resonance imaging prior to transurethral resection of bladder tumour (TURBT) only if muscle-invasive disease is suspected at initial cystoscopy. In practice however it is commonplace for many patients in the UK to receive upper tract imaging as part of their initial assessment for haematuria.

EAU guidelines advocate collection of urine for cytological analysis to predict high-grade tumour before TURBT. This differs from NICE guidance, which suggests patients with suspected bladder cancer should be offered white light-guided TURBT along with photodynamic diagnosis, narrow-band imaging, urinary cytology or a urinary biomarker test such as UroVysion, ImmunoCyt or the nuclear matrix protein 22 test. Regarding urinary molecular markers (as opposed to cytology) the EAU guidelines comment that currently available tests are not sufficiently robust for routine clinical practice, because whilst many display greater sensitivity than cytology for detecting bladder cancer, they have lower specificity.

TURBT for NMIBC

In contrast to UK NICE guidelines, European guidelines provide a thorough step-wise description of optimum TURBT technique. NICE guidelines simply state that detrusor muscle should be obtained during TURBT, that the size and number of tumours should be recorded, and that random biopsies should be taken only if there is a specific clinical indication, e.g. investigation of positive urine cytology. EAU guidance concurs with these recommendations, but provides additional guidance regarding TURBT. This additional guidance includes recommendation for bimanual palpation under anaesthesia, which is not mentioned in NICE guidance. Furthermore, EAU guidelines recommend biopsy of the prostatic urethra in cases of

bladder neck tumour, when bladder carcinoma *in situ* (CIS) is present, or when there is positive cytology without obvious bladder tumour.^{8,9} These recommendations are absent from NICE guidelines.

Both EAU and NICE guidelines recommend that a single dose of intravesical Mitomycin C should be given as soon as possible after initial TURBT, based on strong evidence that this is associated with a significant reduction in tumour recurrence. Three large meta-analyses have demonstrated that postoperative intravesical chemotherapy after TURBT reduces the risk of recurrence from 24.7% to 13.0% compared with TURBT alone.^{8,10–12}

Risk stratification of NMIBC

Tumours should be stratified into low-, intermediate- and high-risk groups based on histological analysis, tumour size and number. Such risk stratification provides prognostic information and guides ongoing management. The precise criteria used for risk stratification are similar between sets of guidelines (Table 1), although one important difference is the inclusion within the intermediate-risk group of the NICE guidance of 'any recurrent low-risk NMIBC recurring within 12 months of the last tumour occurrence'. This stipulation does not exist within EAU guidelines, and hence early recurrences would not necessarily be classified as intermediate risk.

Re-do TURBT

NICE and EAU guidelines assess the value of repeat TURBT within six weeks due to the risk of residual tumour after initial TURBT.¹³ Guidance is consistent that repeat TURBT should be performed if muscle is absent from the initial TURBT specimen (except CIS and low-grade Ta). However, there remain subtle differences between NICE and EAU guidelines regarding criteria that mandate repeat TURBT. For instance, NICE recommend repeat TURBT on all NMIBC patients with high-risk tumours, whereas EAU guidance advocates re-resection in all T1 tumours and all high-grade lesions.^{14–16} According to NICE risk stratification (see Table 1), G2pTa (high-grade) tumours are intermediate risk and thus repeat TURBT is not necessary, whereas EAU guidelines advocate re-resection of all high-grade lesions (except CIS). Both guidelines assert that repeat TURBT should be performed within six weeks of the initial resection.

Disease management

Additional treatment for NMIBC after initial TURBT depends on tumour risk-stratification, with treatment options ranging from single-dose intravesical chemotherapy to radical cystectomy (RC). EAU treatment recommendations for NMIBC are summarised in Table 2. NICE

Table 1. Risk stratification of NMIBC according to EAU and NICE guidelines.

Risk group stratification	EAU guidelines	NICE guidelines
Low-risk tumours	Primary, solitary, Ta, G1 (PUNLMP, LG), <3 cm, no CIS	Solitary pTaG1 < 3 cm, solitary pTaG2 (LG) <3 cm, PUNLMP
Intermediate-risk tumours	All tumours not defined in the two adjacent categories	Any cancer that is not high or low risk, including: <ul style="list-style-type: none"> solitary pTaG1 > 3 cm multifocal pTaG1 solitary pTaG2 (LG) >3 cm multifocal pTaG2 (high grade) pTaG2 (high grade) Any low-risk NMIBC recurring within 12 months of last tumour occurrence
High-risk tumours	Any of the following: <ul style="list-style-type: none"> T1 tumour G3 (high-grade) tumour CIS Multiple and recurrent and large (>3 cm) TaG1/2 tumours 	Urothelial cancer with any: <ul style="list-style-type: none"> pTaG3 pT1G2 pT1G3 pTis (CIS) Aggressive variants of urothelial carcinoma, for example. micropapillary or nested variants

CIS: carcinoma *in situ*; EAU: European Association of Urology; LG: low-grade; NICE: National Institute of Clinical Excellence; NMIBC: non-muscle-invasive bladder cancer; PUNLMP: papillary urothelial neoplasm of low malignant potential.

Table 2. EAU treatment recommendations for NMIBC according to risk stratification.

Risk category	Definition	Treatment recommendation
Low-risk	Primary, solitary, Ta, LG/G1, <3 cm, no CIS	One immediate instillation of chemotherapy post-TURBT
Intermediate-risk	All cases between categories of low and high risk	One immediate instillation of chemotherapy followed by further instillations, with chemotherapy for a maximum of one year or one year full-dose BCG
High-risk	T1 tumours; HG/G3 tumours; CIS; multiple and recurrent and large (>3 cm) Ta G1/2 tumours	Intravesical full-dose BCG instillations for one to three years or cystectomy (in highest-risk tumours)
Subgroup of highest risk tumours	G3T1 associated with concurrent CIS; multiple and/or large G3T1 and/or recurrent G3T1; G3T1 with CIS in prostatic urethra/ unusual histology of urothelial carcinoma/ lympho-vascular invasion; BCG failures	Radical cystectomy (RC) should be considered for all patients; For patients who refuse or are unsuitable for RC, intravesical full-dose BCG installations for one to three years; RC is recommended for BCG failures

CIS: carcinoma *in situ*; EAU: European Association of Urology; BCG: Bacillus Calmette-Guerin; LG: low-grade; NMIBC: non-muscle-invasive bladder cancer; TURBT: transurethral resection of bladder tumour.

and EUA guidance are very similar regarding disease management, with both recommending that treatment should be based on risk-stratification. Low-risk tumours require no further treatment beyond a single dose of Mitomycin C following initial TURBT. NICE guidance recommends that patients with intermediate-risk NMIBC should be offered a six-dose course of intravesical Mitomycin C, but these recommendations do not mention any role for Bacillus Calmette-Guerin (BCG) therapy in the management of intermediate-risk disease. In contrast the EAU

guidance advocates either intravesical chemotherapy for up to a year or a one-year course of BCG therapy. Both NICE and EAU guidance recommend offering either BCG therapy (for one to three years) or RC to patients with high-risk disease. A key difference between EAU and NICE guidelines is that, unlike the EAU guidelines, NICE does not sub-stratify high-risk disease to include a subgroup of highest risk tumours for whom RC should strongly be considered over BCG. The choice of treatment should be based on a full discussion with the patient,

covering advantages and disadvantages of each treatment modality and the risk of progression.

Follow-up of patients with NMIBC

Given the risk of recurrence and progression in patients with NMIBC, regular follow-up with cystoscopy is mandated by both EAU and NICE guidelines. In general there is agreement that patients with NMIBC require regular cystoscopy surveillance to check for intravesical recurrence, but the optimal frequency and length of follow-up is contentious, and NICE and EAU guidelines differ with respect to follow-up of low-risk NMIBC. The risk of recurrence or progression of NMIBC may be predicted through use of risk tables, and cystoscopy follow-up strategies may be tailored accordingly to enable follow-up to be safely reduced for low-risk groups whilst ensuring that high-risk groups are monitored closely.^{17,18} Whilst both advise cystoscopy at three months post-TURBT and a further cystoscopy at 12 months post-TURBT, if the cystoscopy at 12 months demonstrates no recurrence then NICE recommends discharge back to primary care. This particular guidance is based on evidence suggesting that if a low-risk NMIBC tumour recurs after the first year then it typically does so with the same low-risk stage and grade, and the patient would usually present with recurrent symptoms such as haematuria. However, this aspect of NICE guidance regarding discharge to primary care differs markedly from EAU recommendations, which advise annual-check cystoscopies for five years before discharge. There is no clear consensus between the EAU and NICE guidelines regarding the timing of discharge from follow-up for patients with low-risk disease, although the literature suggests that the risk of progression is low and that most recurrences are low grade and non-life-threatening.^{19–22} The available evidence also indicates that the risk of recurrence after five recurrence-free years is low,²³ suggesting that discharge at five years can be considered safe.

NICE guidelines advise cystoscopy follow-up for patients with intermediate-risk NMIBC at a schedule of three, nine and 18 months, with annual-check cystoscopies thereafter. Discharge to primary care for this group of patients can be considered after five years of disease-free follow-up. This contrasts with EAU guidance, which simply recommends a follow-up schedule for patients with intermediate-risk Ta tumours to be somewhere between the surveillance schedule for low- and high- risk disease, with scheduling adapted according to personal and subjective factors.

The follow-up of high-risk NMIBC differs between the two sets of guidelines. NICE recommend check cystoscopies at a schedule of every three months for the first two years, then every six months for the next two years, and annually thereafter. In contrast, EAU guidance recommends cystoscopy and urine cytology at three-monthly intervals for the first two years and then every six months thereafter for five years, followed by annual-check cystoscopy. EAU

guidance also advises annual upper tract imaging (either CTU or intravenous urogram) for high-risk tumours, whereas NICE guidance does not mention this.

Conclusion

The EAU and NICE guidelines for NMIBC provide considerable consensus regarding the management of this common malignancy, which is often difficult to manage. However, there are key differences between the guidelines, and there are a small number of areas that are open to interpretation. These guidelines have been developed in order to optimise the management of patients with NMIBC and equip urologists with a set of standards with which to guide their practice. We recommend that urologists actively involved in the management of NMIBC should be familiar with both sets of guidelines and incorporate their key recommendations into their clinical practice.

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