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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 were 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* (pCIS), pT1) [3]. According to the European Organization for Research and Treatment of Cancer (EORTC) nomogram data, between 31–78% of cases recur and between 17–45% of cases 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 tumours at these sites and higher grade tumours were associated with an up to two fold higher risk of having of UTT at diagnosis [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 recommendation is

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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 reflect the 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 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 4,020 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 the reporting of 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 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 biopsy should be performed with loop resection at the precollicular

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