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TOPIC PAPER

Epidemiology, prevention, screening, diagnosis, and evaluation: update of the ICUD–SIU joint consultation on bladder cancer

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Abstract

Purpose To update current recommendations on prevention, screening, diagnosis, and evaluation of bladder cancer (BC) based on a thorough assessment of the most recent literature on these topics.

Methods A non-systematic review was performed, including articles until June 2017. A variety of original articles, reviews, and editorials were selected according to their epidemiologic, demographic, and clinical relevance. Assessment of the level of evidence and grade of recommendations was performed according to the International Consultation on Urological Diseases grading system.

Results BC is the ninth most common cancer worldwide with 430,000 new cases in 2012. Currently, approximately 165,000 people die from the disease annually. Absolute incidence and prevalence of BC are expected to rise significantly during the next decades because of population ageing. Tobacco smoking is still the main risk factor, accounting for about 50% of cases. Smoking cessation is, therefore, the most relevant recommendation in terms of prevention, as the risk of developing BC drops almost 40% within 5 years of cessation. BC screening is not recommended for the general population. BC diagnosis remains mainly based on cystoscopy, but development of new endoscopic and imaging technologies may rapidly change the diagnosis algorithm. The same applies for local, regional, and distant staging modalities.

Conclusions A thorough understanding of epidemiology, risk factors, early detection strategies, diagnosis, and evaluation is essential for correct, evidence-based management of BC patients. Recent developments in endoscopic techniques and imaging raise the hope for providing better risk-adopted approaches and thereby improving clinical outcomes.

Keywords Neoplasm, urinary bladder · Risk factor · Primary prevention · Early detection of cancer · Cystoscopy · Neoplasm staging

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Introduction

Bladder cancer (BC) is a heterogeneous disease with a variable natural history. Knowledge of its epidemiology, risk factors, and screening strategies is crucial to improve early detection and to promote prevention. The addition of new technologies in endoscopic evaluation and treatment of lower urinary tract tumors during the last years hold the promise of improving BC diagnosis and initial management. New imaging modalities are also impacting preoperative evaluation of newly diagnosed bladder tumors. The present review is based on the recommendations made by the respective committee at the SIU–ICUD Joint Consultation held in Lisbon in 2017 and focuses on current indications and modalities of prevention, screening, and diagnosis of BC.

Evidence acquisition

A non-systematic MEDLINE/PubMed© literature search was performed with different combinations of terms such as "bladder cancer", "bladder carcinoma", "bladder tumor", bladder urothelial carcinoma", "bladder transitional cell carcinoma", "epidemiology", "prevention", "screening", "detection", "diagnosis", "cystoscopy", "transurethral resection", and "imaging". Time period included relevant articles until May 2018. Cited references from selected articles were analyzed to find and include significant papers previously excluded from our search. Readers should consider data in the context of the geographic location, patient demographics, and scope of practice investigated to ensure that the recommendations provided are truly relevant to the respective individuals and populations. A summary of conclusions and recommendations is provided in Table 1. It has to be noted that very few studies with level of evidence (LOE) one have been published on these issues since the last SIU–ICUD Guidelines.

Evidence synthesis

Epidemiology: general statistics and trends

Bladder cancer ranks ninth in worldwide cancer incidence (7th among men and 17th among women) with 430,000 new cases in 2012. Approximately 165,000 people die from the disease annually [1]. About 75% of BC occur in men which, for the most part, is a reflection of differences between men and women in historical smoking prevalence and exposure to occupational carcinogens [2].

Differences in registration practices among cancer registries make it difficult to compare BC incidence between different world regions, especially when incidence rates are not stratified by disease stage as some registries include TNM Ta tumors, while others do not. This also complicates the comparison of survival estimates [3]. In addition, differences exist in the registration of metachronous BC, especially in situations, where muscle-invasive bladder cancer (MIBC) is diagnosed in patients who were treated previously for non-muscle-invasive bladder cancer (NMIBC). Some registries report only the first diagnosis of BC, while others also report a second diagnosis when MIBC appears during follow-up of an NMIBC or even when a T1 tumor appears after a Ta tumor. It is, therefore, important to realize that differences in BC burden parameters may partly be artificial.

The age-standardized incidence and mortality rates (world standard population), as derived from GLOBOCAN, are listed in Fig. 1 [1]. There is a large geographic variation in occurrence, especially among men, with more than 20/100,000 men being diagnosed each year in Southern Europe and only 2–3/100,000 in some parts of Africa (Fig. 1). More than half of all BC cases occur among the 20% of the world population living in very high Human Development Index (HDI, based on health, education, and income) countries, while only 5% of all diagnoses occur in low HDI countries [4]. In terms of mortality, about 3.2/100,000 men and 0.9/100,000 women die from BC each year with somewhat less variation between different parts of the world.

As BC survival hardly changed in the past decades, the future burden of BC is mainly determined by the number of new cases. This depends heavily on demographic changes and the prevalence of risk factors. Western countries will experience a 'double ageing' phenomenon during the next few decades: more elderly with a higher life expectancy. The less developed regions will experience even faster ageing over a much shorter period. Therefore, both the absolute incidence and prevalence as well as the risk of the disease in low HDI countries will increase enormously, also due to a higher tobacco smoking prevalence. Consequently, the disease burden for these countries will become an even larger problem than it already is.

Prevention of bladder cancer

Risk factors

Relevant non-modifiable risk factors *Gender* As mentioned, incidence of BC is three times higher in men than women. In addition, women have higher mortality rates relative to the incidence [2]. While the explanation for a more lethal disease in women has not been definitively proven and is likely multifactorial, it has been demonstrated that women

Table 1 Recommendations for prevention, screening, diagnosis, and evaluation of BC

	LOE	GOR
Recommendations for prevention		
Smoking cessation is recommended, as the risk of developing BC drops almost 40% within 5 years of cessation, although the risk always remains elevated relative to never smokers	3	C
No recommendations for diet, body weight, and physical activity with respect to reducing BC risk can be made based on the current evidence	4	D
Recommendations for screening and early detection		
BC screening, if undertaken, should be confined to high-risk patients	3	C
BC screening cannot be recommended for general population	3	C
Recommendations for endoscopic evaluation of the lower urinary tract		
WLC is the standard approach to diagnosis and management of BC and is the gold standard against which other approaches must be compared	3	B
PDD may be used as an optional adjunct to WLC for the detection of BC and is a valuable adjunct to WLC during the TUR of a suspected BC	1	B
NBI may be used as an optional adjunct to WLC for the detection of BC and is a valuable adjunct to WLC during the TUR of a suspected BC	2	C
Recommendations for TURBT		
A strategy for safe removal of all intravesical components of papillary bladder tumors should be devised before initiating resection	4	C
During resection 3 key principles must be ensured to improve pathologic interpretation of resected bladder tumor:	4	C
Limiting cautery artifact		
Ensuring adequate depth of biopsy according to type of tumor		
Proper handling of tissue for pathologic processing following removal		
Complete tumor resection should be attempted in all patients except for those with diffuse CIS	3	C
A separate specimen from the tumor base should be considered when the tumor appears to be invasive in lamina propria or deeper	3	C
Use of cold-cup biopsy is recommended when possible to minimize cautery artifact especially for small papillary tumors	4	C
For tumors in a diverticulum, aggressive resection should be avoided to reduce risk of perforation	4	C
If ureteral orifice is resected, cutting current should be used and functional study should be performed 3-6 weeks later	4	C
There is insufficient information to support any specific energy modality for TURBT	4	D
Prostatic urethral biopsy/resection should be considered in cases of CIS or visible abnormalities of the prostatic urothelium	3	B
Recommendations for Imaging		
CT urography should be performed in patients suspected to have UTUC	3	B
Imaging for local staging with CT or MRI should be obtained prior to TURBT or 7 days after TURBT to avoid artifacts	4	C
Metastatic workup of patients with MIBC should include CT of the chest, abdomen and pelvis	2	B
Metastatic workup of patients with MICB should include bone scan if bone pain or elevated alkaline phosphatase concentration	4	C
Diffusion-weighted MRI may be used to assess extravesical disease	3	B
There are currently insufficient data regarding the routine use of FDG-PET/CT in MIBC	4	D

LOE level of evidence, *GOR* grade of recommendation

present with higher stage and grade disease [5, 6], larger and more multifocal tumors [7], as well as a higher rate of variant histology [8], all of which correspond to poorer outcomes. However, disparities regarding disease management, with less frequent use of treatments according to guidelines, may also explain poorer outcomes among women [6, 9].

Genetic susceptibility Several genetic alterations have been linked to BC occurrence. Most relevant, *N*-acetyltransferase (*NAT1* and *NAT2*) and *GSTM-1* null genotypes, have shown an increased susceptibility. Interestingly, this occurs when exposed to tobacco [10]. Meanwhile, genome-wide association studies (GWAS) have found several variants associated with occurrence of BC. For example, alterations in the urea transporter encoded by *SLC14A1* are associated with changes in renal urine concentration and can influence the contact of carcinogens with urothelial surfaces [11]. Furthermore, based on an analysis assessing gene–gene interactions in two different GWAS, BC susceptibility has been purportedly associated with decarboxylase protein complexes, which are potential targets for drug therapy [12].

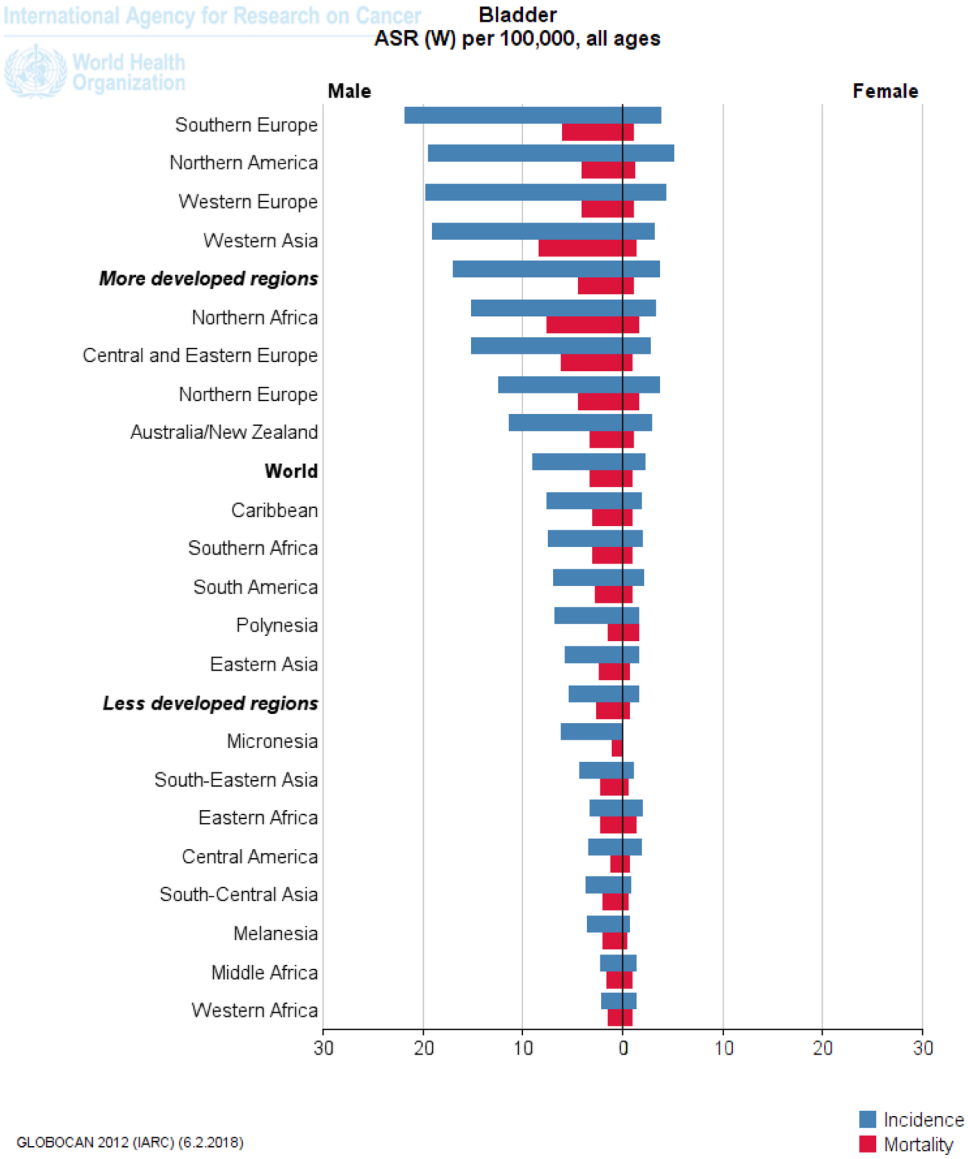

Fig. 1 Age-standardized incidence (blue) and mortality (red) rates of BC in men (left) and women (right) in different world areas in 2012. Source: GLOBOCAN, 2012

Socioeconomic status (SES) There is consensus in the literature that SES is inversely related to BC incidence and outcomes [13]. Populations with a low education level were found to have a 20% higher chance of developing BC, even after adjustment for smoking, which itself is another indicator of low SES [14]. Adults from low-income households are more likely to maintain diets deficient in healthy foods and hold occupations with a higher likelihood of exposure to carcinogens [15].

Medical conditions Certain medical conditions are linked to BC occurrence. Infection with *Schistosoma Haematobium* generates chronic inflammation that results in squamous cell carcinoma [16]. Conventional urinary tract infections and viral infections, specifically Human Papilloma Virus, are also recognized contributors to the risk of developing BC [17]. The causality of radiation exposure upon BC incidence was established from long-term studies of World War II atomic bomb survivors [18]. Patients having undergone radiation therapy for prostate cancer have a latent risk as many as 10 years following treatment [19]. Of common chemotherapeutic agents, only cyclophosphamide has been demonstrated to be associated with BC [20].

Modifiable risk factors *Smoking* The most common risk factor for the development of BC is cigarette smoking. Estimates indicate that tobacco usage is responsible for about 50% of all cases. Interestingly, the impact of cigarette smoking is cumulative, with a lag time of more than 20 years between cigarette exposure and diagnosis [21].

Occupational risk Occupational risk factors are estimated to account for approximately 10% of BC risk. Several meta-analyses have been performed looking at this factor. The most comprehensive systematic review to date by Cumberbatch et al. [22] found the following occupations to have a statistically significant 20% increased risk of BC development: tobacco workers, dye workers, chimney sweeps, nurses, rubber workers, waiters, aluminium workers, hairdressers, printers, seamen, oil and petroleum workers, shoe and leather workers, and plumbers.

Environmental pollution Several reports have demonstrated the effects of environmental pollution on BC risk, particularly in water and food supplies. Arsenic pollution has been correlated with BC risk in Argentina, Chile, and Bangladesh [10].

Primary prevention

Smoking Cessation Smoking cessation prior to the development of BC reduces the overall lifetime risk by almost 40% within 5 years after quitting [23], although even after 20 years of cessation, ex-smokers remain at a 50% increased risk compared with never smokers [24]. Urologists should give advice clearly connecting the patient's potential illness with smoking. A 5-min brief smoking cessation intervention can be easily incorporated into daily clinical practice [25].

Occupational risk avoidance Improvements in working conditions involving exposure to aromatic amines, PAHs, tobacco smoke, heavy metals, and combustion products should be given priority to reduce exposure to these compounds [26].

Environmental pollution Reducing the contribution of environmental pollution on BC depends on public awareness and the election of local/state/national policy makers who should include clean air, drinking water initiatives and green energy sources in their agenda.

Diet, body mass index (BMI), and physical activity In a recent systematic review of all meta-analyses on dietary factors in relation with BC risk, statistically significant associations for several dietary factors were found [26]. Obesity may be associated with a small increase in BC risk, as reported by recent meta-analyses [27, 28]. One meta-analysis showed that high vs. low levels of physical activity were associated with decreased BC risk [29]. However, an authoritative and comprehensive report of the World Cancer Research Fund International/American Institute for Cancer Research (WCRF/AICR) on BC, only based on prospective cohort studies [30, 31], judged the evidence for these dietary and lifestyle factors as limited and inconclusive [32].

Screening and early detection

Prompt detection and treatment of NMIBC offer the potential to prevent invasion and metastasis. While a study from the early 1990s suggested the possibility that screening could detect early BC and possibly improve survival [33], a more contemporary effort produced a low diagnostic yield, raising doubts about the feasibility of this approach [34]. Finally, a report from the US Preventive Services Task Force in 2011 concluded that there was insufficient evidence to balance the benefits and risks of screening for BC in asymptomatic adults [35].

Screening people at increased risk for developing this disease appears to be the solution to the challenges posed in evaluating unselected populations. High-risk populations have been identified and a risk prediction model for BC exists [36]. Screening well-defined groups with occupational exposure to putative carcinogens has resulted in detection of BC with incidences of up to 1.6% [37, 38]. However, contemporary attempts at screening high-risk groups not focused exclusively on occupational exposure yields a much lower rate of detection [39]. There are several factors that may limit the usefulness of BC screening in high-risk populations. First, there is high contamination in the generally targeted population (> 50 years). Many of these individuals will have had urinalyses for other reasons with the potential for detecting asymptomatic hematuria that may lead to the diagnosis of BC [39]. Second, there is no consensus on the best methodology to perform screening. A variety of tests and strategies have been employed, and current non-invasive testing results in many false positives. Third, BC appears to develop along two distinct pathways [40]. Identifying the more common low-risk BC earlier is not likely to result in improvement in survival and identifying high-risk cancers before they become muscle-invasive may not always be possible. We still do not have high LOE to recommend BC screening or early detection. Further studies are needed on this topic and efforts are underway to "screen smarter" [41].

Endoscopic examination of the lower urinary tract

White light cystoscopy (WLC)

White light endoscopic examination of the bladder remains the gold standard for diagnosis of BC. Cystoscopy can be performed utilizing either rigid or flexible endoscopes, depending on the clinical circumstances. Over time, manufacturers have developed improved optics that permit smaller caliber scopes while maintaining high image quality, and the development of a working channel has allowed the use

of flexible instruments [42]. This has permitted a range of office-based procedures.

Photodynamic diagnosis (PDD)

This promising technology takes advantage of the accumulation of protoporphyrin IX (PPIX) in solid tumors. PPIX shows red fluorescence under blue-light excitation [43] leading to the concept of PDD. Several meta-analyses evaluating this methodology are available for 5-aminolevulinic acid (5-ALA)—[44] and for hexylaminolevulinate (HAL)—PDD [45, 46].

On the individual tumor perspective, most meta-analyses consistently have pointed out a strong improvement in detection, notably of CIS, of up to 40% compared to WLC, albeit at the cost of reduced specificity. Indeed, red fluorescence is not tantamount to cancer and false-positive results may impair the surgeon's confidence in PDD. Most false-positive results relate to flat lesions that are among the most demanding situations in uropathology [47].

A distinct meta-analysis of 11 randomized controlled trials addressed specifically the question of the therapeutic outcome after PDD-assisted transurethral resection of bladder tumors (TURBT), confirming the value of 5-ALA and HAL–PDD in the prevention of recurrence [48]. Meanwhile, a recent systematic review and meta-analysis reported a significantly lower rate of progression in patients treated with HAL- vs. WL-based TURBT (median OR 1.64, 95%CI 1.10–2.45; $p = 0.01$) [49].

With respect to cost, simulations have been modeled from the results of the literature. Even taking into account the strong national variations existing in health economics, PDD at the time of TURBT was the dominant option leading to significant savings over time despite the need for investment in a specialized telescope, light source, and camera head [50].

Narrow band imaging (NBI)

For NBI, modified optical filters are used in the light source of a video-endoscope system to narrow the bandwidth of spectral transmittance. This narrow bandwidth of green and blue lights is strongly absorbed by hemoglobin, so NBI enhances visibility of surface capillaries and blood vessels in the submucosa without the use of dyes [51]. By these means, with NBI cystoscopy, the vasculature appears dark green or black against the almost white normal urothelium, whereas with WLC, tumors appear red in a background of normal pink urothelium. By permitting better visualization of the margins of papillary and flat bladder lesions, NBI cystoscopy may facilitate more thorough excision of tumor. In fact, NBI has been shown to be a potentially useful adjunct to WLC in the detection of BC. It is practical to use in combination with modern digital endoscopes and appears to have a reasonably short learning curve [52, 53].

Studies focusing on clinical outcomes have consistently shown an improved sensitivity for NBI compared to WLC, though this likely comes at the cost of lower specificity and positive predictive value. Three recent meta-analyses have reached the same fundamental conclusion [54–56]. In addition, NBI may improve recurrence-free survival in the short term, particularly in those at the lowest risk of recurrence according to a recent multicentric study [57]. However, the final long-term results of several ongoing clinical trials will be needed to truly confirm this.

Transurethral resection of bladder tumors

The foundation for decision making for the patient with BC is the removal of all obvious papillary and sessile tumor(s), when technically possible, as well as a biopsy of suspicious areas. The challenge of removal of the entire tumor by TURBT is evidenced by the relatively high residual tumor rate on restaging resection for T1 tumors. To improve surgical quality in performing TURBT, a standardized procedural checklist has been developed and subsequently employed [58].

Options for type of anesthesia include endotracheal intubation, spinal anesthesia and a laryngeal mass airway (LMA). Complete paralysis is recommended to decrease patient movement during the procedure and to lessen the possibility of obturator reflex which could result in bladder perforation and premature termination of the procedure.

The location and configuration of all tumors should be documented, and a plan established for the sequence of resection: tumors most likely to cause an obturator reflex or bladder perforation should be removed last. Extent of resection should be tailored to the type of tumor. Thus, if a patient has one or more tumors that are papillary and appear to be low grade Ta, and particularly if the patient has a history of similar tumors, the urologist can minimize trauma by removing the tumor(s) by cold-cup resection and subsequent fulguration.

If the urologist feels the tumor might invade the lamina propria (i.e., T1 or higher stage), he/she should attempt to resect the entire tumor and include muscularis propria in the resected tissue. This is important to allow the pathologist to properly stage the tumor. The urologist should minimize the cautery effect on the tissue for the same reason.

There are two basic approaches to performing TURBT: staged resection and *en bloc* resection. A staged TURBT is performed in several phases. First, the exophytic portion of the tumor is resected. Then, the next layers of tissue are resected in a similar fashion until the base of the tumor is reached. Finally, the base of the tumor is resected. *En bloc* resection may be used for small tumors, generally

those < 3 cm in the greatest dimension. The advantages of an *en bloc* resection include more accurate pathologic assessment because of decreased cautery artifact, avoidance of tumor fragmentation, and preservation of the spatial orientation of the tumor relative to the bladder wall. However, there are no comparative studies of staged vs. *en bloc resection*.

Several comparisons between monopolar and bipolar TURBTs, including one meta-analysis of six randomized controlled trials, reported shorter operative time, less blood loss, and shorter hospital stay along with fewer complications from obturator nerve reflex and bladder perforation for the latter [59]. It is, however, important to note that overall complication rate for a TURBT is low and the difference between monopolar and bipolar TURBT is relatively small.

Imaging in BC

Imaging in diagnosis of BC

Most patients with BC present with hematuria and hence would have undergone imaging workup to exclude other common causes prior to presenting for definitive diagnosis of BC. Use of imaging for specific detection of BC is not common due to certain limitations of imaging modalities and the costs involved. Ultrasound of the pelvis using a high-frequency probe may have a role in non-invasive screening for BC in high-risk individuals. However, there is no good evidence to support its use in routine clinical practice [60]. Cystoscopy and biopsy remain the gold standard in diagnosing BC.

Imaging in staging of BC

Imaging has a significant role in staging of MIBC. The primary purpose of imaging is to assess the degree of local invasion and to detect nodal and distant visceral metastasis.

Upper tract imaging Patients with BC are at an increased risk of developing synchronous and metachronous tumors in the upper tracts. However, the incidence of upper tract urothelial cancer (UTUC) in this setting is low, even in patients with MIBC [61]. Hence, a risk stratified approach for upper tract surveillance should be considered.

Local staging (cT) *Computed tomography (CT)* In addition to its important role in upper tract assessment, CT may also be helpful in identifying extravesical invasion. It is indeed the most widely used imaging study to stage BC. However, difficulty in reliably defining anatomical planes, poor contrast resolution in the pelvis, and the inability to distinguish between inflammatory perivesical stranding from tumor infiltration remain major limitations for accurate staging with this modality, leading to both over- and understaging [62].

Magnetic resonance imaging (MRI) MRI offers significant improved soft-tissue resolution compared to CT with striking contrast between the low signal bladder wall and the high signal of surrounding fat in both T1- and T2-weighted sequences, thereby giving MRI an advantage over CT in detecting adjacent organ involvement [63]. The addition of diffusion-weighted imaging (DWI) has resulted in further improvement of the staging accuracy [63–65]. Tumors are found to have restricted diffusion relative to non-neoplastic tissues including inflammatory and fibrotic changes related to treatment. In addition to improved local staging, DWI studies can also be helpful in assessing therapeutic response by differentiating tumoral disease from inflammatory and fibrotic changes in patients receiving chemoradiation [66]. However, DWI suffers from low signal to noise ratio and is also susceptible to several artifacts.

MRI has limitations in assessing upper tracts compared to CT. This is due to several factors including poorer spatial resolution and long acquisition times. Hence, although MRI offers superior local staging, CT urography offers a potential for comprehensive evaluation including assessment of upper tracts. Choice of modality should be made after factoring individual patient risks, availability of resources, and local expertise.

The role of MRI in staging of BC is yet to be determined, also considering its low availability in several regions worldwide. Similar to prostate, the VI-RADS score, a standardized approach to imaging and reporting, has been recently proposed according to risks of muscle invasion. MRI may be, therefore, most useful in expediting radical surgery in NMIBC cases or for determining response to bladder-sparing approaches [67].

Nodal staging (cN) MRI is slightly superior to CT in detecting pelvic lymph nodes [68]. However, there are no well-established criteria to distinguish between malignant and benign lymph nodes apart from size on both modalities. Lymphotropic nanoparticle-enhanced MRI has shown promise in detecting micrometastasis in normal sized lymph nodes with a sensitivity of up to 96% [69]. Meanwhile, use of fluorine-18-2-fluoro-2-deoxy-D-glucose (FDG)-PET/CT does not appear to improve characterization of lymph node metastasis compared to CT [70].

Distant metastasis (cM) Increasing tumoral stage and grade show a linear association with incidence of metastases. In patients with MIBC, preoperative imaging may improve overall survival by improving selection of patients for cystectomy [71]. CT scans of the chest, abdo-

men, and pelvis in addition to a bone scan if clinically indicated are recommended in these patients.

FDG–PET/CT has shown to detect occult metastasis in patients with negative conventional imaging (CT and bone scans) in small prospective trials [72]. However, there are currently insufficient data supporting routine use of PET/CT in staging of BC.

Conclusions

Management of BC patients includes a thorough understanding of its risk factors, with special attention to those potentially modifiable (e.g., smoking). The importance of primary prevention needs to be stressed, and urologists should be an active part of these strategies. Meanwhile, new diagnostic and staging tools raise the hope of improving initial assessment of the disease, holding the promise in providing a better risk-adopted approach and thereby improving clinical outcomes.

Author contributions MIF: data collection, data analysis, manuscript writing, and editing. LAK: data collection, data analysis, manuscript writing, and editing. MSC: data collection, data analysis, manuscript writing, and editing. AV: data collection, data analysis, manuscript writing, and editing. HBG: data collection, data analysis, manuscript writing, and editing. MK: data collection, data analysis, manuscript writing, and editing. PEC: data collection, data analysis, manuscript writing, and editing. BM: data collection, data analysis, manuscript writing, and editing. RS-S: data collection, data analysis, manuscript writing, and editing. MSS: data collection, data analysis, manuscript writing, and editing. RS-S: data collection, data analysis, manuscript writing, and editing. RV: data collection, data analysis, manuscript writing, and editing. MB: project development, data collection, data analysis, manuscript writing, and editing. AMK: project development, data collection, data analysis, manuscript writing, and editing.

Compliance with ethical standards

Conflict of interest MCookson has received personal fees from Jansenn Biotech, MDxHealth, Astellas Pharma, Bayer, Genomic Health, Carden Jennings, Abbott, and Altor. HB Grossman has received personal fees from Abbott Molecular, Cepheid, and Nucleix. A Kamat is a consultant to the following companies; TMC Innovation, Merck, BMS, Arquer, MDxHealth, Photocure, Theralase, Cepheid, Medac, Asieris, Pfizer, and Astra Zeneca and has received research funding from FKD, Merck, Telesta, and Adolor. In addition, A Kamat has a patent CyPRIT—Cytokine Panel for Response to Intravesical Immunotherapy pending. The rest of the authors declare that they have no conflict of interest.

Research involving human participants and/or animals This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent Informed consent was not required, since this article does not contain any studies with human participants.

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