Bladder cancer

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Bladder cancer is a complex disease associated with high morbidity and mortality rates if not treated optimally. Awareness of haematuria as the major presenting symptom is paramount, and early diagnosis with individualised treatment and follow-up is the key to a successful outcome. For non-muscle-invasive bladder cancer, the mainstay of treatment is complete resection of the tumour followed by induction and maintenance immunotherapy with intravesical BCG vaccine or intravesical chemotherapy. For muscle-invasive bladder cancer, multimodal treatment involving radical cystectomy with neoadjuvant chemotherapy offers the best chance for cure. Selected patients with muscle-invasive tumours can be offered bladder-sparing trimodality treatment consisting of transurethral resection with chemoradiation. Advanced disease is best treated with systemic cisplatin-based chemotherapy; immunotherapy is emerging as a viable salvage treatment for patients in whom first-line chemotherapy cannot control the disease. Developments in the past 2 years have shed light on genetic subtypes of bladder cancer that might differ from one another in response to various treatments.

Introduction

Each year, bladder cancer is diagnosed in about 74 000 patients in the USA and in more than 430 000 patients worldwide, making it the fourth most common cancer in men and the 11th most common cancer in women.[1] However, even though bladder cancer is common, it is often mismanaged. A 2012 analysis of Surveillance, Epidemiology, and End Results Program data suggested that of 4790 patients with high-grade non-muscle-invasive disease diagnosed between 1992 and 2002, only one patient received treatment according to formal recommendations.[2] To promote improved adherence to best practices for bladder cancer treatment, we present a state-of-the-art, updated review of diagnosis and management of this disease.

Search strategy and selection criteria

We searched MEDLINE, PubMed, and the Cochrane Library for manuscripts published in English from database inception to Aug 31, 2015. We searched for all articles with the search terms "urothelial carcinoma" or "bladder cancer" in combination with any of the following terms: "epidemiology", "genetics", "pathophysiology", "diagnosis", "urinary markers", "biopsy", "treatment", "surgery", "radiation therapy", "chemotherapy", "medical therapy", "chemoradiation", "trimodality therapy", "bladder-sparing therapy", "bladder preservation", "targeted therapy", "metastatic", "muscle-invasive", "randomized controlled trial", "clinical trial, phase II", or "clinical trial, phase III", "variant", "squamous differentiation", "glandular differentiation", "trophoblastic differentiation", "micropapillary", "plasmacytoid", "nested", "small cell carcinoma", "microcystic", "lymphoepithelioma-like carcinoma", "clear cell", "lipoid", "sarcomatoid", "rhabdoid", "large cell undifferentiated", and "immunohistochemistry". We also searched references cited in selected articles identified by this initial search to identify additional relevant papers. We also searched abstracts from genitourinary oncology meetings sponsored by the American Urological Association (AUA), the Society of Urologic Oncology, the American Society of Clinical Oncology, the American Society for Radiation Oncology, the European Association of Urology (EAU), the European Society for Medical Oncology, and the European Society for Radiotherapy and Oncology. We selected publications from the past 5 years except when an older study had the most robust data about a particular question. We gave more weight to randomised controlled trials and meta-analyses. Additionally, we cross-referenced present AUA, EAU, National Comprehensive Cancer Network, and UK National Institute for Health and Care Excellence practice guidelines for bladder cancer. The articles finally included in this Seminar were selected on the basis of consensus of the Seminar's authors.

Grade and stage of urothelial carcinoma

Overview

Most bladder cancers are urothelial carcinomas. At presentation, roughly 75% of patients have non-muscle-invasive bladder cancer and 25% have muscle-invasive or metastatic disease. About 50% of non-muscle-invasive bladder cancers are low grade, whereas most muscle-invasive or metastatic tumours are high grade.[3] Morphologically, bladder tumours can be divided into papillary, solid, and mixed types. The papillary type is predominant, especially in non-muscle-invasive bladder cancer.

Grading of urothelial carcinoma

In non-muscle-invasive bladder cancer, the most important prognostic factor is grade. In 1973, WHO introduced a numerical grading system for urothelial carcinoma based on cellular anaplasia.[4,5] Since then, the urothelial carcinoma grading system has been modified several times.[6–8] The 2004 WHO grading system[6] categorises urothelial carcinoma as low grade or high grade on the basis of architectural and cytological atypia and includes another category, papillary urothelial neoplasm of low malignant potential (PUNLMP).[9–11] The 1973[4] and 2004[6] WHO grading systems correlate well only at the ends of the grading spectrum (figure 1);[12] about 40% of tumours classified as grade 2 in the 1973 system are classified as high grade in the 2004 system. Nonetheless, several studies[5,13,14] found that the grade determined according to either system was a significant, independent predictor of disease progression and recurrence in multivariate analyses. The 2016 WHO grading system[3] is essentially the same as the 2004 system,[6] but the 2004 version is preferred by most pathologists because it eliminates the ambiguity of diagnostic categories in the 1973 system.

Staging of urothelial carcinoma

In invasive urothelial carcinoma, the most important prognostic factor is stage, which is based on the depth of tumour invasion and metastasis (appendix).[15] Clinical staging, which involves bimanual examination, cystoscopy, and cross-sectional radiographic assessment, is notoriously inaccurate.[16] Pathological staging is the gold standard but can be limited by the quality of the transurethral resection specimens and by cautery and distortion artifacts.[17] On analysis of transurethral resection specimens, pathologists can have difficulty recognising focal, superficial invasion of the lamina propria and differentiating invasion of the muscularis propria from invasion of the muscularis mucosae—ie, stage T1 from T2, which has immense implications for patient care.[18,19]

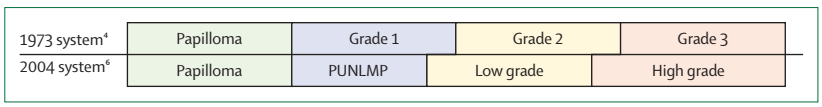

Figure 1: **Overlap between 1973[4] and 2004[6] WHO grading systems for papillary urothelial neoplasms**
PUNLMP=papillary urothelial neoplasm of low malignant potential.

Histological variants of urothelial carcinoma

Although urothelial carcinoma accounts for most bladder cancers, other histological types can also be found in the bladder, albeit at far lower frequencies.[6,20] Urothelial carcinomas frequently undergo divergent differentiation, resulting in a wide range of histological variants.[6,21,22] These histological variants are generally not limited to the bladder; they can also be present in other sites. Therefore, when a histological variant is encountered in the bladder, metastasis from other organs should always be considered and immunohistochemical analysis used to confirm urothelial origin.[23–26]

Urothelial carcinoma with squamous differentiation is by far the most common variant, reported in up to 60% of cases with this carcinoma (figure 2).[21,27] Urothelial carcinoma with glandular differentiation is another fairly common variant, present in about 6% of cases.[28,29] Squamous or glandular differentiation can be widespread in bladder urothelial carcinoma; however, the terms "squamous cell carcinoma" and "adenocarcinoma" are reserved for carcinomas of pure squamous or glandular differentiation, with no component of urothelial carcinoma.[6,21]

Several uncommon yet distinct histological variants have been found in bladder cancer. The micropapillary variant is characterised by small tumour nests or papillae surrounded by retraction spaces (figure 2). Micropapillary urothelial carcinoma frequently metastasises to local lymph nodes and distant sites.[30,31] The nested variant is characterised by small nests of tumour cells with bland cytology that infiltrate the bladder wall.[32,33] The plasmacytoid variant is composed of tumour cells with eccentric nuclei and abundant eosinophilic cytoplasm (figure 2), resembling plasma cells, and show a strong predisposition for peritoneal spread; cure fraction is low, even after neoadjuvant chemotherapy.[34,35]

As a group, histological variants of bladder urothelial carcinoma are more likely than conventional urothelial carcinoma to be diagnosed at an advanced stage with extravesical disease and metastasis. At present, radical cystectomy is a mainstay in the management of most urothelial carcinoma variants.[20,22] For some variants, surgery is not enough, and systemic treatment should be considered; for example, small-cell carcinoma should be treated with neoadjuvant etoposide-based chemotherapy.[36]

Challenges exist in the diagnosis and reporting of urothelial carcinoma variants, particularly when disease has to be diagnosed on the basis of transurethral resection specimens. Study results showed that analysis of transurethral resection specimens revealed only 39% of cases of histological variants later confirmed at radical cystectomy,[37] and up to 44% of cases of histological variants were not recognised or documented by community pathologists.[38] Collaborative efforts have been made to develop reporting standards and guidelines.[17,39,40] Centralised pathological review might also lead to an improved understanding of such variants.

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See **Online** for appendix

Genetic characteristics of bladder cancer

Papillary and non-papillary disease

Bladder tumours can be categorised as papillary or non-papillary on the basis of distinct genetic alterations, the most notable of which are activating mutations in *FGFR3* in papillary tumours and inactivating mutations involving major tumour suppressors *TP53* and *RB1* in non-papillary tumours.[41] More recently, in 2014, The Cancer Genome Atlas (TCGA)[42] and other groups[43–48] have identified additional mutations that distinguish papillary and non-papillary bladder cancers. Both subtypes have a high frequency of mutations in genes encoding chromatin-modifying enzymes,[45] but mutations histone H3 lysine 4 (H3K4) methyltransterase, *KMT2D*, are more common in non-papillary cancers,[49] whereas mutations in histone H3 lysine 27 (H3K27) demethylase, *KDM6A*, activating telomerase promoter mutations,[43,46,48] and inactivating *STAG2* mutations[44,47] are more common in papillary cancers.

Basal and luminal subtypes

Bladder tumours can be grouped on the basis of gene expression patterns into basal and luminal subtypes, similar to the corresponding subtypes of breast cancer (figure 3).[42,51–56] Basal bladder cancers are enriched with squamous and sarcomatoid histopathological features,[42,51,52,55] express biomarkers characteristic of stemness and epithelial-to-mesenchymal transition,[42,52,53] and are often metastatic at diagnosis.[52] Conversely, luminal bladder cancers are enriched with papillary features[42] and genetic mutations common in non-muscle-invasive bladder cancer, especially *FGFR3* mutations,[42,52,53] suggesting that luminal bladder cancers result from superficial cancers that progressed to

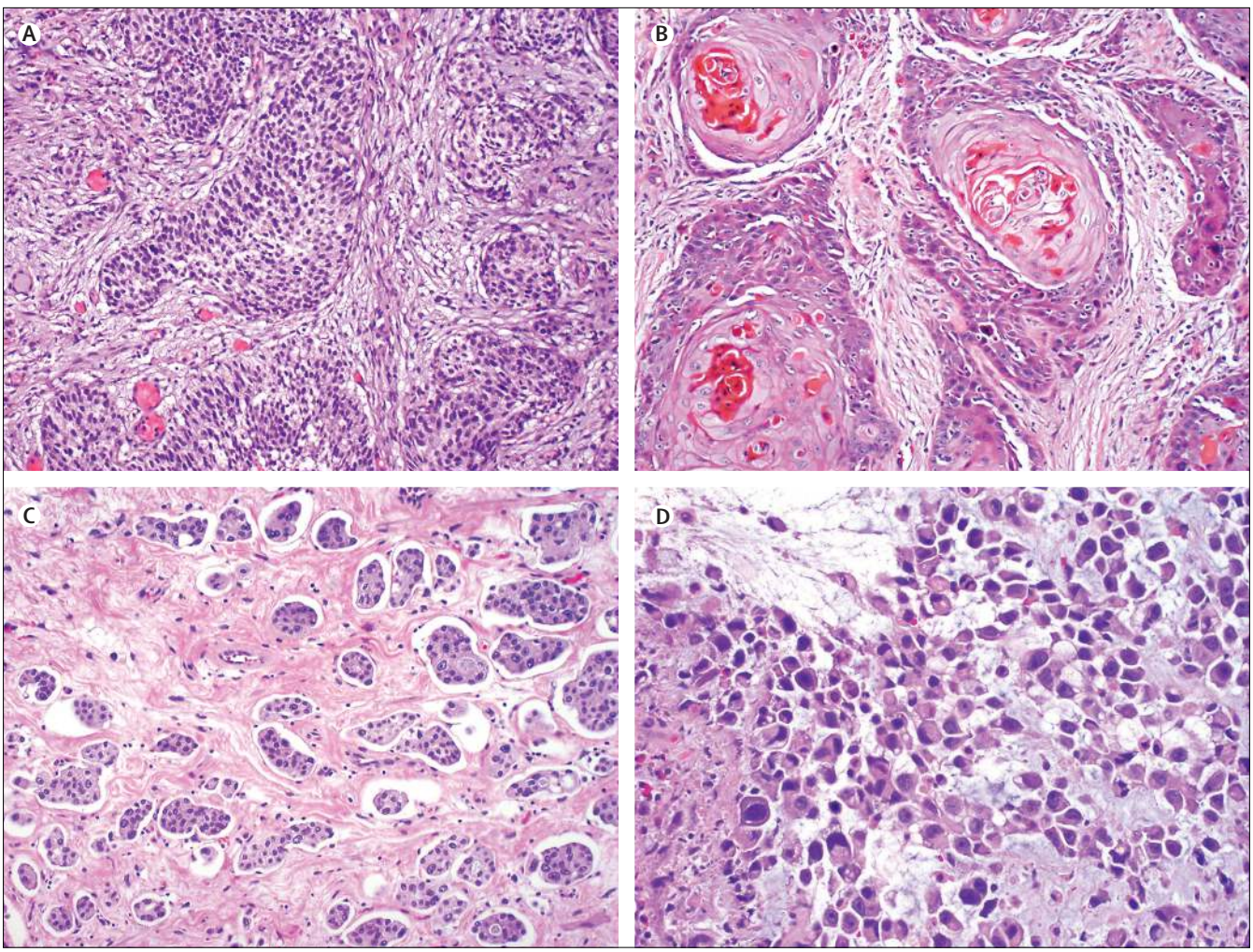

Figure 2: **Urothelial carcinoma histological variants**
(A) Conventional invasive urothelial carcinoma; magnification x100. (B) Urothelial carcinoma with squamous differentiation; magnification x100. (C) Micropapillary variant; magnification x100. (D) Plasmacytoid variant; magnification ×200.

become muscle invasive. Studies[57,58] in preclinical models suggest that luminal and basal bladder cancers arise from different progenitor or stem cells in the normal urothelium.

Implications for targeted treatment

Several research groups have identified DNA mutations associated with sensitivity of bladder cancer to cisplatin;[59–61] by contrast, the luminal subtype of bladder cancer corresponding to TCGA "cluster II",[42] termed "p53-like"[52] or "infiltrated",[51,55] seems to be resistant to neoadjuvant cisplatin-based chemotherapy.[52] Chemosensitive basal bladder cancers seem to be enriched with an immune signature,[52] and although some data suggest that basal tumours might be sensitive to immune checkpoint blockade,[49,62] other data suggest that although basal tumours have the highest level of programmed death ligand 1 (PD-L1)-enriched T cells, their rate of response to anti-PD-L1 therapies is lower than that of luminal cluster-II tumours.[63] Basal bladder cancers are also enriched with epidermal growth factor receptor (EGFR)[42,52,54] and hypoxia-inducible factor 1.[52] Preclinical data confirmed that basal tumours are sensitive to EGFR inhibitors,[54] and patients with basal tumours responded better than patients with luminal tumours to combination treatment with dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) plus bevacizumab,[64] which inhibits the hypoxia-inducible factor 1 target vascular endothelial growth factor (VEGF). Luminal bladder cancers, in addition to being enriched with activating *FGFR3* mutations, are enriched with activating *ERBB2* and *ERBB3* mutations,[49,65] which support the clinical assessment of *FGFR*-targeting and *ERBB*-targeting drugs in patients with luminal tumours.

Clinical presentation, screening, and diagnostic assessment

Clinical presentation

Most patients with bladder cancer are diagnosed during diagnostic testing prompted by haematuria.

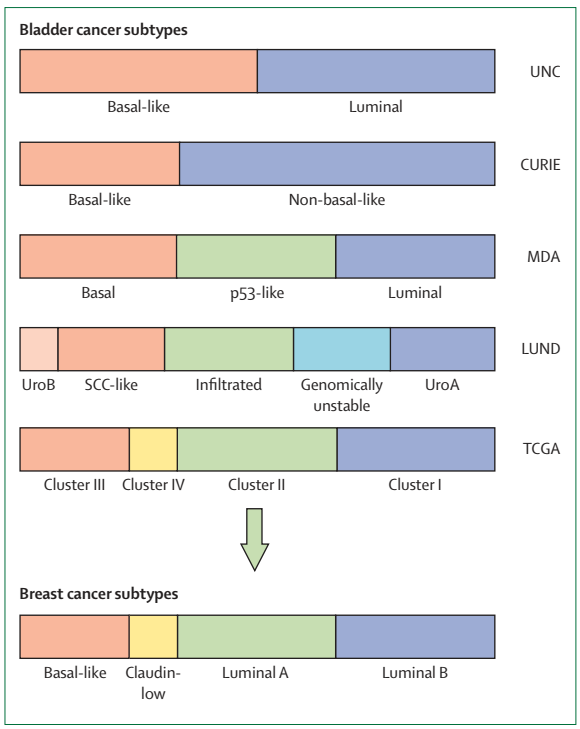

Figure 3: **Molecular subtype classification of bladder cancer and breast cancer**
Subtype grouping in each dataset were made independently and associations between subtype calls were assigned on the basis of The University of Texas MD Anderson Cancer Center (MDA) classifiers,[3] except for the Curie dataset. The Curie subtype was matched to the other subtypes on the basis of the basal-like markers that the authors used in their study.[50] The colour bars indicate the subtype classification made by each institution. Expression of molecular markers in each subtype are shown in the appendix. TCGA=The Cancer Genome Atlas. UNC=University of North California. CURIE=Institut Curie. SCC=squamous cell carcinoma. LUND=Lund University. UroB=Orobasal B

Visible haematuria is one of the symptoms most strongly correlated with bladder cancer diagnosis; 3 year positive predictive values are 7·4% (95% CI 6·8–8·1) in men and 3·4% (2·9–4·0) in women.[66] Patients without haematuria typically have a longer time from onset of symptoms (eg, urgency or recurrent infections) to diagnosis.[67] At presentation, most patients present with a solitary lesion smaller than 15 mm.[68]

Screening

In the general adult population, non-visible haematuria is found in 2–7% of men and 3–15% of women.[69] Non-visible haematuria is often intermittent and varies in intensity over time; as such, the diagnostic yield of screening with dipstick urine testing is too small to make screening cost-effective,[70] even in selected high-risk groups, such as heavy smokers and individuals with environmental exposure to bladder carcinogens.[71,72] A Cochrane analysis[73] published in 2015 concluded that the quality of the screening studies was too low to support any recommendation.

Diagnostic assessment

In patients in whom urothelial cancer is suspected, CT urography is used to assess the upper urinary tract, and cystoscopy is used to assess the lower urinary tract. In the detection of bladder tumours, CT urography and cystoscopy have sensitivities of 0·87 versus 0·87, specificities of 0·99 versus 1·0, positive-predictive values of 0·91 versus 0·98, and negative predictive values of 0·98 versus 0·98.[74]

Two new technologies have been introduced to improve the detection of malignant lesions in the bladder, especially flat lesions: blue-light cystoscopy (or photodynamic diagnosis) and narrow-band imaging (appendix). Blue-light cystoscopy is done with hexaminolevulinate hydrochloride (Hexvix [known as Cysview in the USA], Photocure ASA, Oslo, Norway) and is approved by the US Food and Drug Administration as an adjunct to white-light cystoscopy. A meta-analysis[75] of data from prospective studies showed that blue-light cystoscopy significantly improved the rate of detection of Ta (non-invasive papillary) tumours (odds ratio [OR] 4·90, 95% CI 1·94–12·39) and carcinoma in situ lesions (OR 12·37, 6·34–24·13) and was associated with lower recurrence rates for up to 12 months in patients with T1 (superficial cancer) or carcinoma in-situ lesions (relative risk [RR] 0·70, 95% CI 0·48–1·00; p=0·05) and Ta tumours (RR 0·80, 0·65–0·99; p=0·040). A consensus document[76] about blue-light cystoscopy outlines some details of this procedure.

Narrow-band imaging improves the visibility of blood vessels and other structures on the bladder mucosa. In one study,[77] the diagnostic OR on a per-person basis was 185·32 (95% CI 45·71–751·26) for narrow-band imaging and 42·93 (8·09–227·88) for white-light cystoscopy. The area under the curve for detection of carcinoma in situ with narrow-band imaging was 0·94 (SE 0·03).[77] A meta-analysis[78] showed that patients undergoing narrow-band imaging had a lower recurrence rate than patients undergoing white-light cystoscopy (OR 0·48, 95% CI 0·28–0·80), but found no difference in recurrence rates between narrow-band imaging and blue-light cystoscopy. New imaging technologies such as virtual cystoscopy, optical coherence tomography, confocal laser endomicroscopy, and Raman spectroscopy could in the future be added to the diagnostic armamentarium for bladder cancer.

Urinary markers

At present, cytological or molecular analysis of urine has a restricted role in the initial diagnostic tests for a suspected urothelial tumour. Several urine-based tumour markers have been developed that are based on differential expression of tumour-related proteins, DNA, RNA, or cellular markers.[79–81] A review[80] designed to compare the diagnostic performance of cytological and molecular analysis of urine showed that cytology had low sensitivity (34–55%), especially in the detection of

low-grade tumours, but high specificity (>90%); cytology also has poor interobserver and intraobserver reproducibility.[81] In the review,[80] new molecular biomarkers generally had a better diagnostic performance than cytology but were still deemed suboptimum. The pooled sensitivity of most molecular markers has ranged from 50% to 80%, higher than for urine cytology, and the specificity of most molecular markers has ranged from 70% to 90%, lower than for urine cytology.[79,80,82] Additionally, no present molecular marker has a validated sensitivity high enough to replace cystoscopy.

Some molecular assays, such as the Urovysion fluorescence in-situ hybridisation assay, might have a role in patients with atypical findings on cytology or cystoscopy,[83] as a predictive marker for patients being given intravesical immunotherapy,[84] or to stratify patients for enrolment in clinical trials,[85] but whether these assays are effective for both these needs to be further elucidated. Whether markers can be used in lieu of cystoscopy or at intervals between cystoscopy has not been adequately studied. Newer marker panels based on RNA and methylation techniques could improve on present technologies, but this possibility awaits assessment in large cohorts.

Management of non-muscle-invasive bladder cancer

Risk stratification

Reported 5 year rates of non-muscle-invasive bladder cancer recurrence range from 50% to 70%, and reported 5 year rates of progression range from 10% to 30%. Factors associated with recurrence and progression include high stage, high grade, large tumour size, multifocality, high number of previous recurrences, and presence of concomitant carcinoma in situ.[86–89] Other negative prognostic factors include the presence of lymphovascular invasion, histological variants (eg, micropapillary features), and greater depth of invasion (eg, so-called deep T1 tumour).[88,90] Non-muscle-invasive bladder cancer can be classified as low risk, intermediate risk, or high risk according to risk of recurrence and progression, and risk categories have been used to guide management (table 1).[91]

Transurethral resection

The initial step in the management of non-muscle-invasive bladder cancer is transurethral resection to remove all visible tumours with adequate surgical margins and depth to include the muscularis propria. To more accurately assess stage and improve response to adjuvant intravesical treatments, many authorities advocate a repeat (or restaging) transurethral resection within 4–6 weeks of the initial transurethral resection.[93–95] Repeat transurethral resection for high-grade T1 tumours results in upstaging and a change in management in 24–49% of patients.[96]

Intravesical chemotherapy and intravesical immunotherapy

For patients with low-risk non-muscle-invasive bladder cancer, a single immediate instillation of intravesical chemotherapy (eg, mitomycin, epirubicin, or gemcitabine) after transurethral resection is recommended. A meta-analysis[97] of randomised trials reported benefit in patients with low-risk and intermediate-risk disease (hazard ratio [HR] 0·65, 95% CI 0·58–0·74) but not in patients with high-risk disease or more than one previous recurrence per year. The optimum timing is within 6 h after transurethral resection; efficacy decreases if chemotherapy is delivered more than 24 h after transurethral resection.[98]

For patients with intermediate-risk non-muscle-invasive bladder cancer, a meta-analysis[99] of randomised trials showed benefit from the addition of 1 year of maintenance intravesical chemotherapy after transurethral resection (1 year recurrence HR 0·56); however, no studies have shown that chemotherapy decreases progression rates.

Patients with high-risk non-muscle-invasive bladder cancer are best treated with intravesical immunotherapy.[100] Several randomised studies[101] have compared BCG immunotherapy with various intravesical

	Recommended treatment[92]
Low-risk non-muscle-invasive bladder cancer (low-grade Ta tumour)	Single immediate postoperative instillation of intravesical chemotherapeutic drug
Intermediate-risk non-muscle-invasive bladder cancer (multifocal or multirecurrent low-grade Ta tumours)[91]	
None of the following factors: multiple tumours, tumour ≥3 cm, >1 recurrence per year, recurrence within 1 year after transurethral resection	Same as treatment for low-risk non-muscle-invasive bladder cancer
One or two of the following factors: multiple tumours, tumour ≥3 cm, >1 recurrence per year after transurethral resection	Single immediate postoperative instillation of intravesical chemotherapeutic drug; induction plus maintenance treatment (1 year) with either an intravesical chemotherapeutic drug or BCG
Three or more of the following factors: multiple tumours, tumour ≥3 cm, >1 recurrence per year, recurrence within 1 year after transurethral resection	Same as treatment for high-risk non-muscle-invasive bladder cancer
High-risk non-muscle-invasive bladder cancer (T1 [invasive into lamina propria], carcinoma in situ, or any high-grade tumour)	Restaging transurethral resection in 4–6 weeks; induction plus maintenance treatment (3 years) with BCG; consider early cystectomy if high-grade T1 tumour with any of the following: multiple tumours or large tumour, micropapillary histological variant, concomitant carcinoma in situ in bladder or prostatic urethra, or presence of lymphovascular invasion

Table 1: **Risk stratification and treatment for patients with non-muscle-invasive bladder cancer**

chemotherapies. In these studies,[102] not only was BCG vaccination superior in terms of reducing recurrences but also the BCG vaccine was the only intravesical treatment that delayed disease progression. A meta-analysis[103] of randomised trials showed a significantly lower rate of relapse in patients given the BCG vaccine than in patients given transurethral resection alone or transurethral resection plus intravesical chemotherapy (OR 0·41, p<0·0001). In a subset analysis,[103] this difference was significant only when maintenance BCG was used (OR 0·57, p=0·04). More recently, a 2014 randomised trial[104] showed that in high-risk disease, recurrence-free survival was best when maintenance BCG was delivered at full dose for 3 years; however, for intermediate-risk non-muscle-invasive bladder cancer, 1 year of maintenance treatment was sufficient. A randomised trial[105] comparing BCG followed by electromotive mitomycin with BCG alone reported that the combination was associated with lower rates of disease progression (9·3% *vs* 21·9%; p=0·004) and mortality (21·5% *vs* 32·4%; p=0·045). A 2016 trial[106] compared BCG with hyperthermic administration of mitomycin and reported a higher 24 month relapse-free survival rate with mitomycin (78·1% *vs* 64·8%; p=0·08) but no difference in progression.[106] These findings warrant validation.

Upfront cystectomy for very high risk non-muscle-invasive bladder cancer

Patients with very high risk non-muscle-invasive bladder cancer include those with multiple or large high-grade T1 tumours, or both; micropapillary histological variants; concomitant carcinoma in situ in bladder or prostatic urethra; or presence of lymphovascular invasion.[87,88,90,107] For these patients, upfront radical cystectomy is appropriate to improve survival.

Treatment of disease unresponsive to or relapsing after BCG vaccination

Instances of so-called BCG failure can be stratified into the following three categories, in order from worst to best prognosis: no response to BCG (BCG-refractory disease), relapse after BCG, and BCG intolerance (panel).[92,108] To assist patient selection for clinical trial enrolment, a category called "BCG unresponsive" has recently been adopted by the US Food and Drug Administration, the International Bladder Cancer Group, and the American Society of Clinical Oncology GU Cancers Group.[92,109,110] This category includes BCG-refractory disease and a subset of the patients with relapsing BCG who have recurrence within 6 months of last exposure to BCG (eg, in patients on maintenance treatment). Patients with BCG-unresponsive disease are at highest risk of recurrence and progression, do not benefit from continued BCG, and are strongly recommended to undergo radical cystectomy. Patients with late BCG relapse (more than 1–2 years after last BCG exposure) who are reluctant to undergo radical surgery can undergo a trial of salvage intravesical treatment with repeat induction BCG, BCG with interferon α2a, gemcitabine, or valrubicin. Among BCG failures, BCG relapse is the one with the most advances in terms of clinical trials, underscoring the absence of effective treatments.

***Panel*: Classification of BCG failures**

BCG refractory

Persistent high-grade disease at 6 months after adequate* BCG induction and maintenance treatment or any progression in stage at 3 month assessment (ie, after induction BCG cycle).

BCG relapsing

Recurrence of high-grade disease after a disease-free interval of ≥6 months after adequate* BCG induction and maintenance treatment.

Early relapse: <12 months; intermediate relapse: 12–24 months; late relapse: >24 months.

BCG unresponsive

This category (developed for clinical trial design) includes patients with BCG-refractory and BCG-relapsing disease as already defined. The patients with BCG-relapsing disease should have recurrence within 6 months of last BCG exposure (eg, for patients on maintenance treatment).

Patients in the BCG unresponsive subgroup are at highest risk of recurrence and progression.

BCG intolerant

Disease persistence because the patient cannot receive adequate* BCG owing to BCG toxicity.

Adapted from Kamat and colleagues.[92] *Adequate BCG treatment is defined as the patient receiving at least five of six planned instillations of induction treatment and at least two of three planned instillations of maintenance treatment over 6 months.

Management for muscle-invasive and metastatic bladder cancer

Radical cystectomy and pelvic lymphadenectomy

Radical cystectomy and bilateral pelvic lymphadenectomy, often preceded by neoadjuvant cisplatin-based chemotherapy, is the gold-standard definitive surgical treatment for bladder cancer.[111,112] Although nerve-sparing radical cystectomy is appropriate in men and women, except when sparing nerves would compromise tumour control (eg, in patients with T3–T4 [advanced] tumours),[113] the long-term safety of prostate or seminal vesicle sparing (proposed to optimise sexual function and continence), or both, remains in question as whole-mount step sectioning of the prostate shows urothelial cancer in 40% of patients[114,115] and prostate adenocarcinoma in 40% of patients.[114,116]

To determine the safety of constructing an orthotopic neobladder, analyses of intraoperative frozen sections of the urethra, preoperative transurethral resection biopsy samples of the prostatic urethra, or bladder neck biopsy samples are necessary to rule out cancer at the apical urethral margin.[117,118] The use of intraoperative frozen section analysis to ensure a negative proximal ureteral margin is controversial because long-term follow-up suggests that a positive margin (other than frankly invasive disease) has no negative effect on outcomes.[119,120]

Tumour metastasis to the contralateral side is common; for this reason, a bilateral pelvic lymphadenectomy is

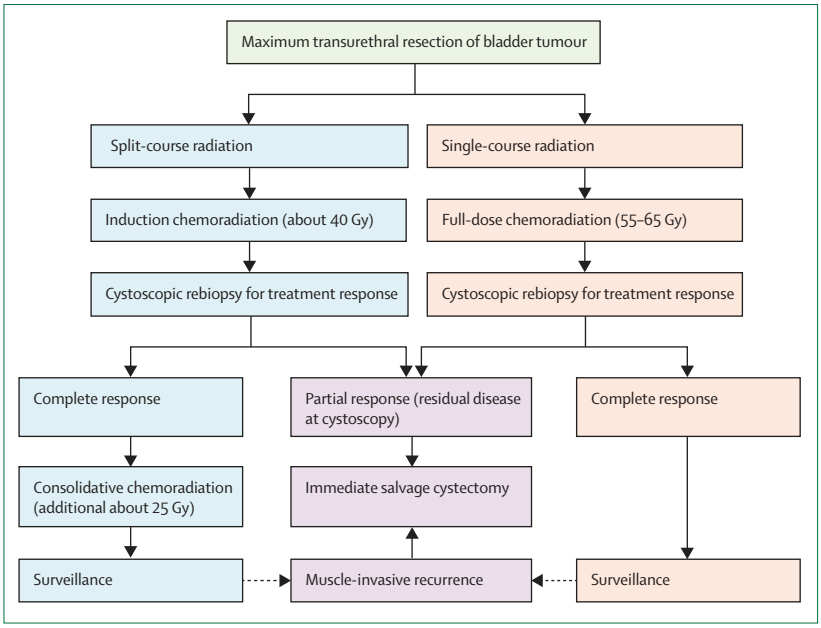

Figure 4: **Trimodality treatment scheme**

necessary. A complete pelvic lymphadenectomy[121] should be done as it results in better regional control than the more restricted dissection and less than complete lymphadenectomy.[122] Two trials, AB 25/02—LEA (Germany)[123] and SWOG S1011 (NCT01224665; Canada and the USA),[124] are testing whether extended pelvic lymphadenectomy results in better survival or locoregional control than standard bilateral pelvic lymphadenectomy. However, at present, no level 1 evidence is available supporting improved outcomes with extended pelvic lymphadenectomy.

Radical cystectomy is associated with reported 90 day mortality rates as high as 9%;[125,126] enhanced recovery after surgery protocols aim to reduce perioperative morbidity.[127–129] A randomised trial[130] of robotic-assisted laparoscopic versus open radical cystectomy showed no difference in morbidity or length of hospital stay but longer operative time and increased cost in the robotic group, similar to results from the CORAL study[131] from the UK. Two other clinical trials[132,133] comparing open and robotic radical cystectomy are in progress, but final results have not been reported.

Radiotherapy

Bladder-sparing trimodality treatment

Patients who want to preserve their native bladder could be candidates for bladder-sparing trimodality treatment, which consists of visibly complete transurethral resection followed by conformal radiotherapy and concurrent radiosensitising chemotherapy (figure 4).[134] This approach is supported by completed prospective trials and international consensus guidelines.[111,135–137]

Trimodality treatment for non-muscle-invasive bladder cancer

For Ta or Tis (flat in situ) tumours, trimodality treatment is generally not supported by available evidence. In T1 bladder cancer, early studies[138,139] showed encouraging response rates with radiotherapy alone for unifocal tumours. A single institution study[140] evaluated chemoradiation after transurethral resection and showed a complete response rate of 88% and disease-specific survival rates of 82% at 5 years and 73% at 10 years. Notably, a large UK study[141] of radiotherapy in T1 disease showed no significant differences in recurrence-free interval (HR 0·77, 95% CI 0·54–1·17, p=0·137), progression-free survival (1·35, 0·92–1·98, p=0·133), or overall survival (1·32, 0·86–2·04, p=0·193) between radiotherapy and intravesical BCG or mitomycin C alone; however, radiotherapy was not compared with surgery. An ongoing prospective trial (Radiation Therapy Oncology Group [RTOG] 0926)[142] is assessing chemoradiation for high-risk recurrent T1 bladder cancer after BCG failure.

Trimodality treatment for muscle-invasive bladder cancer

Evidence supporting the appropriateness of trimodality treatment is most robust for muscle-invasive bladder cancer. Ideal patient selection criteria include conventional urothelial histology, minimally invasive of superficial T2 disease, complete tumour resection at transurethral resection, and absence of tumour-associated hydronephrosis.[143] Concurrent chemoradiation is superior to radiotherapy alone (HR for 2 year locoregional disease-free survival 0·68 [95% CI 0·48–0·96]; p=0·03).[144] Although cisplatin-based chemotherapy has been the RTOG standard,[145] 5-fluorouracil plus mitomycin C[144] and single-drug low-dose gemcitabine[146] are alternatives.

Long-term data from trials in the past 5 years suggest that more than 70% of patients given trimodality treatment will achieve a complete response to induction chemoradiation and retain their native bladder.[147–149] 5 year disease-specific survival rates range from 65% to 70%.[147–149] Notably, results for trimodality treatment are favourable in elderly people (>75 years), an otherwise undertreated population who often are not offered curative treatment.

Follow-up and outcomes of patients given trimodality treatment

In patients given trimodality treatment, careful lifelong post-treatment cystoscopic surveillance is essential.[150] Expedient salvage cystectomy is associated with acceptable surgical outcomes and morbidity.[151] Studies of quality of life after trimodality treatment, although small, have shown good function of the native bladder and mild long-term toxic effects of chemoradiation on pelvic organs.[152–154] Biomarkers of radiation response, such as MRE11, could help identify patients most likely to benefit from trimodality treatment.[155]

Adjuvant radiotherapy

In patients with locally advanced bladder cancer, whose 5 year rate of pelvic recurrence after radical cystectomy can be as high as 20–45%, adjuvant radiotherapy can improve locoregional control.[156,157] However, at present, adjuvant radiotherapy remains investigational. NRG Oncology recently launched a randomised phase 2 trial (NRG-GU001)[158] of postcystectomy intensity-modulated radiotherapy for patients with pT3 or pT4 urothelial bladder cancer.

Systemic treatment

Muscle-invasive bladder cancer standards of care

The key systemic treatment regimens for muscle-invasive bladder cancer are summarised in table 2.[144,145,159–172] At present, the data supporting a benefit for chemotherapy are strongest for neoadjuvant chemotherapy before radical surgery or radiotherapy; data for adjuvant chemotherapy are less robust. In the neoadjuvant setting, cisplatin-based regimens, including MVAC and CMV (cisplatin, methotrexate, and vinblastine), have shown overall survival benefits in individual phase 3 trials and in meta-analyses,[159,160,164] and the widely used regimen of cisplatin plus gemcitabine has produced similar clinical outcomes.[163] In phase 2 trials, neoadjuvant treatment with dose-dense MVAC showed safety and promising pathological complete response rates (26–38%).[161,162]

In the adjuvant setting, the largest phase 3 trial of platinum-based chemotherapy (n=284) reported a significant improvement in 5 year progression-free survival (48% *vs* 32%; p<0·0001) and a non-significant improvement in 5 year overall survival (57% *vs* 47%; p=0·13) with immediate versus deferred chemotherapy.[165] Although meta-analyses of adjuvant treatment trials have shown a 22–25% reduction in risk of death with combination cisplatin-based adjuvant treatment,[166,167] most experts believe that these analyses are underpowered to permit definite conclusions.

Metastatic bladder cancer standards of care

For patients with metastatic disease eligible for cisplatin-based treatment, a phase 3 trial[169] showed similar overall survival with cisplatin plus gemcitabine (13·8 months) and MVAC (14·8 months; p=0·75) but substantially less mucositis (1% *vs* 22%; p=0·001) and neutropenic sepsis (1% *vs* 12%; p<0·001) with cisplatin plus gemcitabine. In a different phase 3 trial,[170] dose-dense MVAC produced better complete response rates (21% *vs* 9%; p=0·009) and median progression-free survival (9·1 *vs* 8·2 months; p=0·037) than MVAC, and resulted in similar overall survival (15·5 months for dose-dense MVAC *vs* 14·1 months for MVAC; p=0·121).

In patients ineligible to receive cisplatin, carboplatin-based regimens are most commonly used,[171] although the regimens have shown restricted efficacy. In patients already treated with platinum-containing regimens, no regimen has shown an overall survival advantage compared with best supportive care.[150] The key systemic treatment regimens for metastatic bladder cancer are summarised in tables 2[144,145,159–172] and 3.[63,173–176]

Details of study and regimen	
Muscle-invasive bladder cancer	
Neoadjuvant	
Grossman et al (2003)[159]	MVAC followed by cystectomy *vs* cystectomy alone; improvement in pathological complete response rates and overall survival with MVAC
Advanced Bladder Cancer Meta-analysis Collaboration (2005)[160]	Landmark meta-analysis of neoadjuvant muscle-invasive bladder cancer trials showed a 5% absolute overall survival advantage with cisplatin-based combination neoadjuvant chemotherapy
Plimack et al (2014)[161] and Choueiri et al (2014)[162]	Phase 2 trials that established the efficacy and safety of neoadjuvant ddMVAC
Dash et al (2008)[163]	Retrospective study showed that neoadjuvant GC produced pathological complete response rates similar to those with MVAC; no randomised trial with GC has been done so far
Griffiths et al (2011)[164]	Neoadjuvant CMV followed by cystectomy *vs* radiotherapy *vs* radiotherapy plus cystectomy; improvement in overall survival with CMV
Adjuvant therapy	
Sternberg et al (2015)[165]	Phase 3 trial showed improved 5 year progression-free survival (48% *vs* 32%) with cisplatin-based adjuvant chemotherapy (MVAC, ddMVAC, or GC) compared with deferred treatment at progression with trend toward improved 5 year overall survival (57% *vs* 47%)
Advanced Bladder Cancer Meta-analysis Collaboration (2005)[166]	Landmark meta-analysis of adjuvant muscle-invasive bladder cancer trials showed a 9% absolute 3 year overall survival advantage with cisplatin-based combination adjuvant chemotherapy
Leow et al (2014)[167]	Updated meta-analysis of clinical trials of adjuvant treatment showed a 22% reduction in risk of death with cisplatin-based regimens compared with surgery alone
Bladder-sparing chemoradiotherapy	
James et al (2012)[144]	BC2001: 5-fluorouracil plus mitomycin-C plus EBRT *vs* EBRT alone; improved locoregional control with combined chemoradiation
Gogna et al (2006)[168]	Weekly cisplatin plus EBRT produced 70% complete response rate; safety demonstrated
Mitin et al (2013)[145]	RTOG0233 randomised phase 2 trial showing efficacy of cisplatin plus 5-fluorouracil (or paclitaxel) plus EBRT
Metastatic bladder cancer	
Chemonaive, cisplatin-eligible	
Von der Maase et al (2000)[169]	Phase 3 trial of GC *vs* MVAC. Did not show superiority of GC over MVAC; rates of grade 3–4 toxic effects similar in the two groups, but far less mucositis and neutropenic sepsis with GC
Sternberg et al (2001)[170]	EORTC 30924: ddMVAC *vs* MVAC; improved complete response rate (21% *vs* 9%) and median progression-free survival (9·1 *vs* 8·2 months) with ddMVAC; less neutropenic fever with ddMVAC; similar overall survival in the two groups
Chemonaive, cisplatin-ineligible	
De Santis et al (2012)[171]	Phase 3 trial of CaG *vs* MCaV; no difference in response rate, progression-free survival, or overall survival outcomes between groups; established the CaG efficacy benchmarks for future study comparisons
Post-platinum second-line	
Bellmunt et al (2009)[172]	Vinflunine *vs* best supportive care; negative study in the intention-to-treat analysis; established efficacy benchmarks (response rate, progression-free survival, overall survival) for future study comparisons; vinflunine approved in Europe but not in the USA

MVAC=methotrexate, vinblastine, doxorubicin, and cisplatin. ddMVAC=dose-dense MVAC. GC=emcitabine carboplatinum. CMV=cisplatin, methotrexate, and vinblastine. BC2001=bladder cancer 2001. EBRT=external-beam radiotherapy. RTOG= Radiation Therapy Oncology Group. EORTC=European Organisation for Research and Treatment of Cancer. CaG=carboplatin and gemcitabine. MCaV=methotrexate, carboplatin, and vinblastine.

Table 2: **Details of studies establishing standard systemic treatment regimens for muscle-invasive and metastatic urothelial carcinoma of the bladder**

	Target	Population	Response rate (n/N [%])	Median progression-free survival (months)	Median overall survival (months)
Atezolizumab[63]	PD-L1	Post-platinum therapy metastatic urothelial carcinoma	45/310 (15%); 26/100 (26%)*	2·1	7·9
Avelumab[173]	PD-L1	Post-platinum therapy metastatic urothelial carcinoma	7/44 (16%); 4/10 (40%)*	..	..
Pembrolizumab[174]	PD-1	Post-platinum therapy metastatic urothelial carcinoma	8/29 (28%); 6/18 (33%)*	2·0	12·7
Ipilimumab[175]	CTLA-4	Muscle-invasive bladder cancer	..	..	..
Gemcitabine plus cisplatin and ipilimumab[176]	CTLA-4	Metastatic urothelial carcinoma	23/36 (64%)	..	14·6

PD-L1=programmed death-ligand 1. PD-1=programmed cell death protein 1. CTLA-4=cytotoxic T-lymphocyte-associated protein 4. *Response rates in patients with high immune or tumour cell PD-L1 expression by immunohistochemistry.

Table 3: **Results of clinical trials of checkpoint-inhibitor treatments in urothelial carcinoma published after 2010**

Emerging bladder cancer treatments

Bladder cancer has seen a substantial increase in drug development activity in the past 5 years. Spurring this increase is the improved understanding of the molecular targets of invasive bladder cancer that has emerged from the TCGA project. Drugs targeting fibroblast growth factor receptor 3, EGFR, VEGF, mechanistic target of rapamycin, signal transducer and activator of transcription 3, androgen receptor, and CD24 have all shown preclinical activity,[177] and many of these targets are under investigation in human clinical trials.

Additionally, increased expression of cytotoxic T-lymphocyte-associated protein 4, PD-1, PD-L1, or a combination of these molecules on tumours or their surrounding immune cells has been implicated as a method by which urothelial carcinoma can escape from the cell-killing effects of traditional treatments.[178] In 2015–2016, data have been presented for atezolizumab (PD-L1 inhibitor), avelumab (PD-L1 inhibitor), and pembrolizumab (PD-1 inhibitor) in the treatment of urothelial carcinoma.[63,173,174] Although some subtle differences exist, all three drugs show response rates superior to those historically seen with cytotoxic chemotherapy in patients with metastatic urothelial carcinoma treated in the postplatinum era (after the introduction of platinum-based therapy). Furthermore, response rates are near 30% in patients with tumours with increased expression of PD-L1, as measured by immunohistochemistry. Additionally, all three drugs are better tolerated than chemotherapy: rates of grade 3 or 4 toxic effects are less than 15%. Finally, a phase 2 trial[176] completed in 2016 of ipilimumab (cytotoxic T-lymphocyte-associated protein 4 inhibitor) in combination with cisplatin plus gemcitabine in patients with chemonaive metastatic urothelial carcinoma reported no significant inhibition of the immunostimulatory effect of ipilimumab, opening the door to further combinations.[176]

Follow-up after treatment of urothelial carcinoma

Surveillance for bladder cancer is important because of the high rate of recurrence of both non-muscle-invasive and muscle-invasive disease and the short time to progression and death in patients with metastatic disease. Surveillance strategies are driven by the stage and grade of the tumour and are designed to minimise overtesting while optimising early detection of recurrences.

For non-muscle-invasive bladder cancer, the risk of recurrence after 5 years ranges from 50% to 90%, with higher rates seen in high-grade disease and carcinoma in situ; the risk of progression after 5 years ranges from 10% to 30% and is mainly limited to high-grade disease and carcinoma in situ.[89] All guidelines recommend cystoscopy at 3 months after initial resection to assess for recurrent or residual disease.[179–181] Subsequent to this, for high-grade disease, the guidelines recommend cystoscopy at 3 month intervals for 2 years, then at 6 month intervals until year 5; for low-grade disease, some guidelines recommend cystoscopy at 3 months, at 9 months, and then yearly in patients with no recurrences.[179–181] For high-grade disease, all guidelines recommend consideration of upper tract imaging yearly or every other year and indicate that use of urinary tumour markers is optional. For low-grade non-invasive disease, upper tract imaging has restricted value because the risk of a tumour in the ureter or kidney is only 1–2% and the associated cost, inconvenience, and radiation exposure outweigh the yield in this particular group.[179]

Surveillance after cystectomy, after multimodal treatment, or in patients with metastatic disease mainly focuses on identifying distant disease. Most guidelines recommend imaging of the chest, abdomen, and pelvis every 3–6 months for 2 years and then at longer intervals.[112,180] Stage-adapted follow-up schemes have been developed in an attempt to maximise detection of recurrence, progression, or distant disease and minimise patients' exposure to radiation; for example, in patients with pT0 (no evidence of primary tumour) at cystectomy, consideration can be given to relaxed imaging schedules.

Controversies and uncertainties and outstanding research questions

Bladder cancer is a complex disease, and its biology has only begun to be understood. Further research into urinary markers for diagnosis is needed. However, for maximum positive effect on patient care, research should focus on response prediction and monitoring patients during treatment rather than diagnostic evaluation of haematuria. An example of a tool for response prediction is the CyPRIT (Cytokine Panel for Response to Intravesical Therapy), which could potentially allow for real-time monitoring of

patients' immune response during intravesical immunotherapy.[182] Challenges exist in recognising and reporting urothelial carcinoma histological variants in small transurethral resection specimens, particularly among community pathologists. Collaborative efforts and centralised pathological review will lead to an improved understanding of urothelial carcinoma variants.

There is widespread agreement that the optimum treatment for patients with intermediate-risk or high-risk non-muscle-invasive bladder cancer is induction BCG after transurethral resection and maintenance treatment three times a week for up to 3 years, with optimised intravesical chemotherapy as an option. However, several questions remain regarding the management of non-muscle-invasive bladder cancer. Is there a benefit from the addition of electromotive or hyperthermic mitomycin administration to BCG treatment? Is there a role for trimodality treatment or immunomodulation with PD-1/PD-L1 in patients with BCG failure? What is the effect of the BCG strain on therapeutic efficacy?

For surgical management of bladder cancer, the roles of radical transurethral resection and partial cystectomy remain unclear. Radical cystectomy is well accepted as the gold standard, and debate centres around ways to enhance patient recovery without affecting patients' cancer-related survival. Of the completed trials comparing open radical cystectomy to robotic radical cystectomy, some suggest no benefit from the robotic approach; larger studies are ongoing. Additionally, the long-term oncological efficacy of robotic-assisted radical cystectomy compared with open radical cystectomy has not been determined.

Bladder preservation with chemoradiation is no longer regarded as controversial. However, further study is needed with regard to which patients should initially be offered bladder-sparing chemoradiation approaches rather than surgery and the benefit of the addition of targeted and immunotherapeutic concurrent treatments to radiotherapy.

In the area of advanced disease, rapid developments based on data from the TCGA project are close. For now, although most patients with muscle-invasive disease should receive neoadjuvant cisplatin-based treatment before cystectomy, well selected patients might be able to safely avoid neoadjuvant chemotherapy, and molecular subtyping could help to select these patients.[183] Research groups are investigating whether tumour genetic profiling allows reliable identification of patients who are likely to respond to molecularly targeted drugs or traditional chemotherapy. Examples of such trials include the SWOG trial of the co-expression extrapolation (COXEN) score, which aims to direct the choice of neoadjuvant chemotherapy for patients.

Because bladder tumours have a very high mutagenic load, immunotherapy has emerged as a key treatment for advanced-stage disease, building on the success of BCG in non-muscle-invasive bladder cancer. Further developments will answer questions regarding PD-1 and PD-L1 immune checkpoint inhibitor treatment; for example, whether these treatments should be restricted to patients with high PD-L1 expression by tumour or immune cell infiltrate. Data from the IMVigor 210 trial[63] (atezolizumab for metastatic urothelial cancer after failure of platinum-based treatment) provide tantalising clues as to the response of tumours based on their intrinsic subtypes; in this study, luminal type 2 tumours had the best response even though basal tumours had predominant immune infiltrate.These are exciting times for all involved in the care of patients with bladder cancer because after almost four decades of slow progress, momentum is building to meaningfully improve patient outcomes.

Contributors

AMK initiated the Seminar and circulated an outline for co-authors to comment on. The co-authors jointly did electronic searches, and contributed towards the initial first draft and the subsequent and final drafts.

Declaration of interests

AMK reports consulting fees from Theralase, Sanofi, Taris, Spectrum Pharmaceuticals, and MDxHealth; reports research support from Heat Biologics, Photocure, Telesta Therapeutics, Merck, Abbott Molecular, FKD, and Pacific Edge; and has a patent pending for cytokine assay for response to intravesical therapy (CYPRIT) for the University of Texas. NMH reports consulting for Merck, Oncogenex, and Bristol-Myers Squibb, and research funding to institution from Novartis, Genentech, Merck, Oncogenex, Mirati Therapeutics, and Acerta Pharma, outside the submitted work. JAE reports consulting for Medivation and Astellas. SPL reports consulting fees from BioCancell, Vaxxion, UroGen, Telesta, Sitka, Neucleixx, Taris, Bladder Cancer Journal, and Ferring and grants from ENDO Pharmaceuticals, FKD, Viventia, Roche/Genentech, and Genome DX, during the conduct of the study. P-UM reports speaker fees from Medac GmbH and scientific advisory from Photocure ASA, and APIM Therapeutics AS, outside the submitted work. WC has a patent pending for methods of characterising and treating molecular subset of muscle-invasive bladder cancer. YL reports grants from Abbott, Cepheid, and MDxHealth and grants and personal fees from Pacific Edge, during the conduct of the study; and grants from genomedx and grants and personal fees from photocure, outside the submitted work. CCG and WK declare no competing interests.

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