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Bladder cancer

Lars Dyrskjøt[1,2], **Donna E. Hansel**[3], **Jason A. Efstathiou**[4], **Margaret A. Knowles**[5], **Matthew D. Galsky**[6], **Jeremy Teoh**[7], **Dan Theodorescu**[8,9,10]

[1]Department of Molecular Medicine, Aarhus University Hospital, Aarhus, Denmark.

[2]Department of Clinical Medicine, Aarhus University, Aarhus, Denmark.

[3]Division of Pathology and Laboratory Medicine, University of Texas MD Anderson Cancer Center, Houston, TX, USA.

[4]Department of Radiation Oncology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA.

[5]Division of Molecular Medicine, Leeds Institute of Medical Research at St James's, St James's University Hospital, Leeds, UK.

[6]Division of Hematology and Medical Oncology, Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA.

[7]S.H. Ho Urology Centre, Department of Surgery, The Chinese University of Hong Kong, Hong Kong, China.

[8]Department of Urology, Cedars-Sinai Medical Center, Los Angeles, CA, USA.

[9]Department of Pathology and Laboratory Medicine, Cedars-Sinai Medical Center, Los Angeles, CA, USA.

[10]Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, CA, USA.

Abstract

dan.theodorescu@cshs.org .

Author contributions

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Competing interests

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Additional information

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Bladder cancer is a global health issue with sex differences in incidence and prognosis. Bladder cancer has distinct molecular subtypes with multiple pathogenic pathways depending on whether the disease is non-muscle invasive or muscle invasive. The mutational burden is higher in muscle-invasive than in non-muscle-invasive disease. Commonly mutated genes include *TERT*, *FGFR3*, *TP53*, *PIK3CA*, *STAG2* and genes involved in chromatin modification. Subtyping of both forms of bladder cancer is likely to change considerably with the advent of single-cell analysis methods. Early detection signifies a better disease prognosis; thus, minimally invasive diagnostic options are needed to improve patient outcomes. Urine-based tests are available for disease diagnosis and surveillance, and analysis of blood-based cell-free DNA is a promising tool for the detection of minimal residual disease and metastatic relapse. Transurethral resection is the cornerstone treatment for non-muscle-invasive bladder cancer and intravesical therapy can further improve oncological outcomes. For muscle-invasive bladder cancer, radical cystectomy with neoadjuvant chemotherapy is the standard of care with evidence supporting trimodality therapy. Immune-checkpoint inhibitors have demonstrated benefit in non-muscle-invasive, muscle-invasive and metastatic bladder cancer. Effective management requires a multidisciplinary approach that considers patient characteristics and molecular disease characteristics.

Introduction

In 2020, 573,278 people were newly diagnosed with bladder cancer worldwide[1,2], and this number is expected to double by 2040 based on World Health Organization predictions[3]. If detected early before muscle invasion, this disease is often treatable and can be managed with minimal effects on survival. Muscle-invasive disease can metastasize, predominantly to lymph nodes, bones, lungs and liver[4], and is associated with a median survival of ~15 months[5].

The bladder wall consists of 5–7 epithelial cell layers with surface umbrella cells (urothelium) with underlying layers of fibroconnective tissue and vessels (lamina propria), thick muscular bundles (muscularis propria or detrusor muscle) and perivesical fat (Fig. 1). Urothelial cells are the primary cells of origin of bladder cancer, and urothelial cancer is the most common form of bladder cancer, affecting ~95% of patients[6,7]. Tobacco use is the primary risk factor in ~50% of bladder cancer diagnoses[8,9] as the urothelium is exposed to carcinogenic tobacco metabolites eliminated via the urine[10]. Other urothelial cell-derived bladder cancer types, occurring in <2% of patients, include small cell carcinoma, squamous cell carcinoma and adenocarcinoma[7].

At diagnosis, urothelial cancer is categorized as either non-muscle-invasive bladder cancer (NMIBC; stages Tis, Ta and T1) or muscle-invasive bladder cancer (MIBC; stages T2–T4) when the disease has grown into the muscularis propria. The overall categorization of the disease into NMIBC or MIBC is used frequently as treatment modalities differ substantially between these entities; however, within the NMIBC category, Ta tumours have a much more benign disease course than T1 and Tis tumours, and treatment of these subtypes is also markedly different[7]. The various tumour stages are associated with different genetic features, which can be used as markers for minimally invasive diagnostics and disease aggressiveness[11,12]. The importance of these markers in disease management

will further increase as molecular pathology will become more predominant in diagnosis, treatment selection and follow-up planning. The most informative molecular markers to date are genetic variants of *TP53*, *ERCC1* and *FGFR3* as markers of disease progression, chemotherapy sensitivity and small-molecule therapeutic selection, respectively[11,12].

Of note, bladder cancer incidence and aggressiveness differ considerably between men and women[13]. For instance, bladder cancer is the sixth most common cancer in biological males but only the seventeenth most common cancer in biological females[14]. However, women present clinically with more advanced disease and have a poorer prognosis[15,16] and, perhaps, a lower survival than men (possibly confined to the first 2 years after diagnosis)[17]. In the past few years, efforts have also been made to understand the role of race in bladder cancer biology[18] and further advances in this field are expected in the future.

This Primer focuses on urothelial cancer, the most common form of bladder cancer. We summarize the epidemiology of the disease with a focus on risk factors, discuss mechanisms of pathogenesis, including genetic alterations, and provide an overview of current diagnostic methods. In addition, we review current treatment modalities employed at different disease stages, discuss the quality of life (QoL) of patients with the disease, and discuss outstanding issues and research questions.

Epidemiology

Incidence and mortality—Bladder cancer incidence is highest in higher-income regions of the world, including Europe, North America and western Asia, and is also increased in regions affected by Schistosoma parasites such as Northern Africa[19]. By contrast, South America, eastern Asia, the Caribbean, and middle and southern Africa have much lower rates of bladder cancer. The differences in bladder cancer incidence between these regions have been linked to the prevalence of tobacco use, occupational exposure to aromatic amines in industry, arsenic in drinking water and other causes[2,20]. In 2020, nearly 600,000 people were diagnosed with bladder cancer globally, predominantly affecting individuals >55 years of age and men[1,2] (Figs. 2 and 3). Bladder cancer is the tenth most common cause of cancer globally and the thirteenth most common cause of mortality from cancer[19]. Ongoing efforts to mitigate risk factors, improve timely diagnosis, better understand sex differences and expand therapy seem to have resulted in decreasing global rates of bladder cancer diagnoses and deaths[21].

Risk factors

Cigarette smoking.: Cigarette smoking is the most prominent contributor to bladder cancer development in most countries, with ~50% of all cases linked to this risk factor[8,9]. A global decline in smoking prevalence might have contributed to improving rates of bladder cancer diagnoses and deaths; however, trends vary considerably by country[21]. More than 1 billion people are estimated to smoke tobacco globally but smoking prevalence has decreased since 1990 by ~27% in men and 38% in women[22,23]. The highest reductions seem to have occurred in higher socioeconomic groups, which probably reflects higher health awareness and enhanced access to health care in this population[22,23].

Parasitic infection and chronic inflammation.: Infection with *Schistosoma haematobium*, a parasite in the blood fluke family, is a relatively unique risk factor for bladder cancer in northern Africa[24]. Parasites infect individuals via the skin when swimming in water containing schistosome cercariae and, following maturation in the liver, can deposit eggs within the bladder and mesenteric plexus. Calcification of the eggs and resultant chronic inflammation of the bladder lining leads primarily to the development of squamous cell carcinoma[25]. Efforts to eradicate this parasite have resulted in a decrease in bladder cancer incidence[26]. In addition to parasitic infection, other conditions that can increase chronic inflammation may contribute to the development of bladder cancer, including the presence of diverticula, alterations in the gut or urinary tract microbiome, and dysfunction of the immune system[27].

Sex and age.: Sex and age are two key epidemiological features associated with the development of bladder cancer. Men are more commonly affected by the disease, with the male-to-female ratio remaining relatively steady at approximately 4:1 (ref. 21). This discrepancy is reflected in the finding that bladder cancer is the sixth most common cancer in men worldwide and the fourth most common cancer in men in the USA[1,21]. Several explanations have been proposed, including differences in smoking rates and exposure to specific compounds in work environments, hormonal factors, and the effects of sex chromosomes[13]. Bladder cancer more commonly affects older individuals, with an average age at diagnosis of 73 years and >90% of cases occurring in persons >55 years of age. The discrepancy between sexes exists irrespective of age at diagnosis[1,21].

Occupational exposure.: Occupational exposure to certain chemicals is another risk factor for bladder cancer. Exposure to aromatic amines, such as benzidine and β-naphthylamine in the dye industry, hair dyes, paint products, and other occupational exposures to organic compounds may increase the risk of bladder cancer[28]. Processing of rubber and textiles as well as exposure to diesel fumes may also be associated with an increased risk of bladder cancer[29].

Genetic factors.: Risk factors in the development of bladder cancer include hereditary (germline) DNA alterations. For example, hereditary non-polyposis colon cancer (Lynch syndrome) is indicated in the development of urothelial carcinoma, accounting for ~5% of upper tract urothelial carcinomas and probably also cases of bladder cancer, although studies are ongoing[30,31]. In this hereditary disease, mutations in mismatch repair genes *MLH1*, *MSH2*, *MSH6* and *PMS2* result in microsatellite instability, with mutations in *MSH2* and associated microsatellite instability posing a high risk for the development of urothelial carcinoma[30].

Mechanisms/pathophysiology

Overall, NMIBC (stages Tis, Ta and T1) and MIBC (stages T2–T4) have distinct molecular profiles with considerable molecular heterogeneity within each disease category. T1 tumours often share molecular characteristics with MIBC and these tumours usually differ substantially from low-grade Ta tumours[32–34] (Fig. 4). There is no obligate pathway from NMIBC to MIBC and it seems that these tumour categories have largely non-

overlapping pathogenesis pathways. Histopathological and molecular data indicate that the flat lesion carcinoma in situ (CIS) is the major precursor of MIBC, whereas most papillary NMIBC arise from normal-appearing urothelium. Nevertheless, progression from initially non-invasive to invasive disease occurs in some patients with NMIBC, particularly those with tumours invading the lamina propria.

The normal urothelium—The urothelium is composed of basal, intermediate and superficial cell layers, the latter specialized to form a tight barrier that prevents urine absorption. This barrier function relies on the expression of uroplakins[35] and claudin family members in tight junctions[36]. Keratin 20 is restricted to the umbrella cells[37]. This normally quiescent epithelium can proliferate rapidly in response to damage. Whether a definitive stem cell exists is unclear but evidence suggests that human basal cells have regenerative capacity[38]. In mouse models, both basal and intermediate cells are implicated as tumour cells of origin[39]. PPARγ, a member of the nuclear receptor superfamily, is a regulator of urothelial differentiation whose activation leads to expression of uroplakins, relevant keratins and claudins via transcription factors FOXA1, GATA2 and ELF3. In the absence of PPARγ activation, p63 maintains the undifferentiated (basal) phenotype[40].

Field cancerization—Field cancerization, the acquisition of pro-tumorigenic mutations and genomic alterations in normal cell lineages, has been associated with the development of bladder cancer[41]. The origin of transformed cells among normal-appearing urothelial cells is unclear, with original speculation that cancer cells from tumours migrate in the urothelium or are shed from tumours and implanted between normal cells[42]. This is referred to as the ‘tumour-first-field-later’ theory. In the past decade, it has been suggested that field cancerization evolves from transformed stem cells in the urothelium that expand and drive tumour formation (‘field-first-tumour-later’ theory)[43,44]. Both theories may explain frequent recurrences of clonally related bladder tumours that develop years apart[45]. Whole-organ mapping studies demonstrated that genetic alterations can be divided into two categories: low-frequency mutations and high-frequency mutations increasing with disease progression. Based on this, it was estimated that bladder carcinogenesis spans 10–15 years, with a progressive phase of 1–2 years involving high-frequency mutations[46]. In another study, patients with a high level of field cancerization had poor survival, and tumours from these patients harboured a high mutational burden, high neoantigen load and high tumour-associated $CD8^+$ T cell exhaustion[47]. Importantly, non-synonymous mutations in known bladder cancer driver genes, such as chromatin remodelling genes and *TP53, STAG2* and *PIK3CA*, have been identified in non-diseased bladders[48] as well as in histologically tumour-free urothelium from patients with bladder cancer[47].

Common genetic alterations—Mutational signatures are similar regardless of tumour grade and stage despite largely non-overlapping pathogenesis pathways[34,49]. There is a major contribution from the activity of the APOBEC family of cytidine deaminases, accounting for more than 60% of all single-nucleotide mutations[34,50,51] but only few known tobacco use-related signatures despite the association of tobacco use with risk. Compared with NMIBC, the overall mutational burden is much higher in MIBC (>7 mutations per

Mb), surpassed only by lung cancer and melanoma[52], and large structural alterations and aneuploidy are more common[53].

Deletions of chromosome 9 are found in ~50% of both NMIBC and MIBC. These deletions include the *CDKN2A* locus (9p21), encoding p16 and p14ARF, which are regulators of the RB and p53 pathways, respectively. On 9q, loss of *TSC1*, which regulates mTOR signalling, has been found and 9q loss is associated with upregulated expression of mTOR targets[54]. Interestingly, mTOR has been implicated as a regulator of telomerase reverse transcriptase (TERT) gene transcription. In addition to the maintenance of telomere integrity, TERT has non-canonical functions, including upregulation of oncogenic signalling pathways[55], is crucial in maintaining tumour immortality and contributes to tumour progression in bladder cancer[56–59]. Other copy number alterations in NMIBC (8–22%) include gains of 1q, 5p, 18q, 20p, and 20q and losses of 8p, 11p, 17p, and 18q, particularly in stage T1 tumours[32]. These regions are more commonly altered in MIBC, in which amplifications of 3p25 (*PPARG*), 6p22 (*E2F3*), 7p11 (*EGFR*), 17q12 (*ERBB2*) and 19q12 (*CCNE1*) are also found[51]. High-level DNA amplification is uncommon in NMIBC[60].

Commonly mutated genes are shown in Tables 1 and 2. Extremely common in all tumour grades and stages (70–80%) are mutations in the promoter of the telomerase reverse transcriptase *TERT*[57,61,62], which are associated with upregulated expression. Apart from *TERT*, mutated genes and mutation frequencies differ considerably between NMIBC and MIBC. The mutational profile of lamina propria-invasive tumours (stage T1) is more closely related to that of MIBC compared with stage Ta NMIBC. However, the mutational profile of stage T1 tumours does not indicate the presence of some tumours with MIBC-like features and of some with Ta-like features but rather that individual T1 tumours often contain both Ta-like and MIBC-like features[34].

Non-muscle-invasive bladder cancer—NMIBC is characterized by *FGFR3* point mutations (in ~60% of patients), which are associated with low tumour grade and stage[54]. The most common of these mutations (S249C) is predicted to result from APOBEC activity[63]. In cultured normal human urothelial cells, mutant FGFR3 drives cell overgrowth at confluence, suggesting a potential contribution to urothelial hyperplasia in vivo[64]. Mutation of RAS genes and *FGFR3* are mutually exclusive, with mutation of one or the other in 90% of stage Ta tumours[54]. APOBEC target mutations in *PIK3CA* hotspot codons are found in ~30% of patients with NMIBC, often with mutations in *FGFR3* or RAS genes[34], indicating that most NMIBC have activation of both RAS–MAPK and PI3K signalling. Loss of 9q, including *TSC1* in 50% of patients, provides activation of the PI3K pathway downstream of mTOR. In stage T1, gain-of-function mutations in *ERBB2* and *ERBB3* that provide PI3K activation[52] are present in ~15% of tumours and often co-occur[34].

Mutations of *STAG2* and other chromatin regulators (*KDM6A*, *KMT2D*, *KMD2C*, *CREBBP*, *EP300* and *ARID1A*) are common. Inactivation of one or more of these regulators is found in >65% of patients with NMIBC, with *KDM6A* mutations more common in stage Ta than in stage T1 and *ARID1A* mutations more common in stage T1 tumours[34]. The exact roles of these genes in bladder cancer are not well understood and some mutations can be found in normal urothelium of cancer-bearing bladders. Compatible with this is the role of

KDM6A in the regulation of normal urothelial differentiation[65,66] and its antagonistic effect on FGFR3 activation[65]. Mutation of *STAG2*, a subunit of the cohesin complex, is more common in bladder cancer than in other cancers and is implicated in negative regulation of basal cell identity[67]. Inactivating mutations and loss of expression are present in ~30% of low-grade Ta tumours, often with *FGFR3, PIK3CA* and/or *KDM6A* mutations, but in fewer T1 tumours[34,68,69].

MIBC and metastatic disease—MIBC exhibits remarkable intratumour genetic heterogeneity[70]. Despite limited sampling, key players have been clearly identified[51] (Tables 1 and 2). Almost all MIBC have loss of cell cycle checkpoints via *TP53, RB1*, and/or *ATM* mutations and/or alterations affecting their regulators, for example, *E2F3* and *MDM2* amplification, mutation of *FBXW7* (8%), and deletion of *CDKN2A*. Response to DNA damage and DNA repair pathways (for example, through loss of function of *ATM* or *ERCC2* mutation[71]) are also affected; *ERCC2* is also implicated in 24% of T1 tumours[34].

Overall involvement of chromatin modifiers in MIBC is similar to that in NMIBC except that the distribution of mutations differs. Activating point mutations in *FGFR3* and *PIK3CA* are less common than in NMIBC, although upregulated expression of FGFR3 is frequent. Activating translocations involving *FGFR3* are found in some tumours (2–5%)[72]. Upregulated expression and/or isoform switching of FGFR1, with a potential effect on epithelial–mesenchymal transition[73,74], are also found in some tumours. *FGFR3*, *PIK3CA*, *KDM6A* and *STAG2* mutations often co-occur and, in the tumours with this mutation profile and luminal phenotype, loss of 9p (p16 and p14ARF) may contribute to progression[75]. Activation of the RAS–MAPK and PI3K pathways is estimated to occur in ~70% of MIBC[51], commonly via mutation or upregulation of upstream regulators, including gain-of-function mutations of *ERBB2* and *ERBB3*, or amplification of *ERBB2* and *EGFR*[51]. Loss of *PTEN* and *TSC1* also contributes to AKT–mTOR activation[76]. Other pathways implicated in MIBC include upregulated MET signalling[77] and the NOTCH pathway[78].

Tumour microenvironment—The tumour microenvironment (TME) comprises both malignant and non-malignant cells. Cancer-associated fibroblasts (CAFs) are the most common non-malignant cells in bladder cancer, forming distinct regions within the tumour[79], and these CAFs have been associated with tumour aggressiveness, chemoresistance and reduced response to immune-checkpoint inhibitor (ICI) therapy[79–81]. Tumour-associated macrophages are another important non-malignant population in bladder cancer[82]. Tumour-associated macrophages are recruited to sites of inflammation and hypoxia within the TME but, like CAFs, they are co-opted by cancerous cells to promote an immune suppressive environment, drug resistance and metastasis[83–89]. Resistance to inhibition of PD1 or PDL1 in urothelial cancer has also been linked to a pro-inflammatory cellular state of myeloid phagocytic cells detectable in tumour and blood[90]. Tumour-infiltrating lymphocytes (TILs) are immune cells that clear cancerous cells. Mostly composed of $CD8^+$ T cells, TILs develop and expand to recognize foreign antigens present on cancer cells or antigen-presenting cells. Of note, bladder cancer, and MIBC in particular, has a high level of mutational burden[91,92], providing neoantigens for immune cells to recognize. However, the beneficial effect in bladder cancer is lower than expected

because of low numbers of TILs in the tumour and/or the inactivation of TILs that do reach malignant cells. In MIBC, the presence of TILs in or adjacent to the tumour is a predictor of patient response to ICIs and survival[93]. The degree of stromal cell infiltration, most notably CAFs, into tumours also determines patient response to immune therapies. Patients with high numbers of TILs and low stromal gene tumour signatures have improved survival and response to immune therapies[94]. The discoidin domain (DDR1 and DDR2) collagen receptors, which are commonly found on cancer cells and fibroblasts, have been implicated as biomarkers for ICI response in bladder cancer and other cancer types in both the experimental setting[88] and in patients[95]. This important finding supports the link between collagen deposition, fibroblasts and resistance to ICIs. Future clinical trials of targeted therapies, such as DDR1 and/or DDR2 inhibition combined with ICIs, would be expected to enhance the effectiveness of ICIs.

Biological sex differences—Bladder cancer incidence and aggressiveness differ substantially between men and women[13]. Absence of X chromosome gene *KDM6A* leads to an increased incidence of bladder cancer in mouse models[96] but, notably, only in female animals. *KDM6A* is mutated in 24% of patients with bladder cancer and its experimental depletion in human bladder cancer cells enhanced in vitro cell proliferation, migration and in vivo tumour growth; however, the limited number of cell lines investigated prevents a conclusion of whether this effect is dependent on sex[59].

In addition to sex chromosome-mediated effects, androgen receptor (AR) signalling can lead to sexual dimorphism in bladder cancer incidence and therapeutic response. Two studies in 2022 demonstrated that T cell-intrinsic AR promotes $CD8^+$ T cell exhaustion in the TME[97,98]. Furthermore, AR can suppress the expression of CD44 (ref. 99), a well-known driver of tumour progression and metastasis in bladder cancer[100–102] and other cancer types[103]. In mouse studies, AR deletion reduces the incidence of bladder cancer induced by standard orally ingested chemical carcinogens that accumulate in urine and are analogues of those found in cigarette smoke[104]. However, the role of AR in humans is less clear[105,106]. Use of the 5α-reductase inhibitor finasteride was found to reduce bladder cancer incidence in white and Hispanic men but not in Black men[107]. Intriguingly, Black men have higher free testosterone levels than white men[108], yet a lower incidence of bladder cancer[109]. By contrast, reduced AR expression in bladder cancer is associated with more advanced stage[99,110] and aggressive tumour subtypes[111]. Inhibition of AR signalling has shown promise in men with reduced recurrence of NMIBC[112–114].

In a systematic review of 18 studies, the incidence and clinical outcomes of bladder cancer were investigated in patients who received androgen suppression therapy[108]. 5α-Reductase inhibitors or androgen deprivation therapy were not significantly associated with a reduced risk of bladder cancer incidence or cancer-specific, overall or progression-free survival. In a subgroup analysis, only finasteride use was associated with reduced bladder cancer risk, and recurrence-free survival was improved in those receiving androgen suppression therapy compared with those who were not. Hence, finasteride use may represent a strategy for reducing bladder cancer incidence, and overall androgen suppression may reduce recurrence risk in patients with a history of bladder cancer. Only randomized trials with well-characterized study populations can definitively prove these observations.

The Y chromosome is essential for male sex determination and spermatogenesis[115]. In ageing men, loss of the Y chromosome (LOY) in haematopoietic cells has been associated with increased risk of several diseases, including cardiac fibrosis[116] and multiple cancer types[116–119]. In bladder cancer, LOY has been found in 10–40% of tumours[120–126]. This is unsurprising as bladder cancer is commonly caused by environmental exposures, such as tobacco and industrial chemicals, that are known to result in DNA damage and LOY[127–129]. Recent studies have shown that LOY and the corresponding loss of Y genes *KDM5D* and *UTY*, which are chromatin modifiers, confer an aggressive phenotype to bladder cancer through acquisition of the ability to evade the adaptive immune system[18]. Fortunately, this also makes LOY tumours more vulnerable to ICIs. This landmark study is the first to show that LOY drives cancer biology and the host immune response to cancer[130].

Diagnosis and screening

Clinical presentation—Around 75% of patients with bladder cancer present with painless, visible (gross) haematuria, which warrants early medical attention[131]. In a prospective observational study, 22.4% of patients presenting with visible haematuria were found to have bladder cancer, with the incidence increasing with age: only 4.7% in those <35 years of age compared with 35% in those >75 years of age[132]. Rates of urological referral of patients with haematuria are generally low[133] and, therefore, the reported rates of bladder cancer can differ in the literature. Patients may also present with microscopic or non-visible haematuria commonly detected upon health checkup, and bladder cancer was found in 3.3–5.2% of that population[132,134]. Presentation with microscopic haematuria seems to correspond to a low disease stage[135]. In a multi-centre cohort study in patients with microscopic haematuria, 68.8% had Ta or Tis disease, 19.6% had T1 disease, and 11.6% had T2 disease, whereas in patients presenting with gross haematuria, 55.9% had Ta or Tis disease, 19.6% had T1 disease, and 17.9% had T2 disease[135].

Bladder cancer is rare in children, with an incidence of only 0.1–0.4%[136,137]. In a systematic review including 243 paediatric patients with bladder cancer[138], gross haematuria was the most common presentation (75.6%), followed by lower urinary tract symptoms (8.6%) and abdominal and/or flank pain (3.4%). Most of the patients presented with Ta (86.4%) and low-grade (93.4%) disease; T2 or above disease was uncommon (4.1%).

Diagnosis—Diagnostic evaluation of patients with haematuria should involve a physical examination including rectal and vaginal bimanual palpation to assess for pelvic masses suggesting a locally advanced tumour[139], although the risk of both clinical under-staging and over-staging is well known[140,141]. Cystoscopy is considered the gold standard for diagnosing bladder cancer. White-light imaging cystoscopy is the conventional method to detect bladder cancer but may miss some lesions such as CIS. CIS usually presents as a velvet-like, reddish area that is difficult to detect and differentiate from inflammation[142], which has led to advanced cystoscopy technologies, such as narrow-band imaging, photodynamic diagnosis and Image 1S, to enhance bladder cancer detection (Supplementary Table 1).

If a lesion is seen on cystoscopy, this is followed by examination under anaesthesia at the time of transurethral resection of bladder tumour (TURBT), although the risk of both clinical under-staging and over-staging with this assessment is well known[141]. Pathological work-up of patients includes the use of urine-based evaluation to detect malignant cells and/or analysis of biopsy or TURBT samples of visibly identifiable lesions.

Urine-based diagnosis of bladder cancer.: Urine cytology is the most cost-effective urine-based method to diagnose high-grade bladder cancer[143]. The sensitivity of this analysis is suboptimal but its specificity is high, especially for high-grade urothelial carcinoma; thus, urine cytology remains the gold standard in the diagnosis of bladder cancer compared with marker-based studies in urine[144,145]. Urine cytology specimens are classified according to the Paris System for Reporting Urinary Cytology published in 2016, which subdivides specimens into non-diagnostic, negative for high-grade urothelial carcinoma, atypical urothelial cells, suspicious for high-grade urothelial carcinoma, high-grade urothelial carcinoma, low-grade urothelial neoplasm, and other malignancies[144]. The risk of cancer with a diagnosis of high-grade urothelial carcinoma is >90% using this classification system[144,145]. Of note, any cytology classification approach to low-grade urothelial carcinomas yields lower sensitivity than those for high-grade carcinomas owing to the more cohesive nature of low-grade lesions and the much closer similarity of low-grade lesions to normal cellular morphology[146].

Over the past few decades, extensive effort has gone into the development of protein-based and molecular-based urine tests to diagnose bladder cancer. These efforts have resulted in numerous FDA-approved tests, including cell-free DNA tests[147–150]. Methodologies of these tests include, for example, analysis of proteins elevated in dividing cells using antibody-based methods to detect chromosome aneuploidy by fluorescence in situ hybridization[148,151]. Although many of these tests show higher sensitivity in detection of bladder cancer than urine cytology, they are often limited by lower specificity, false positive results and better utility in high-grade lesions[147–150]. Efforts to identify new markers, including *TERT* and *FGFR3* alterations, are ongoing, but hurdles remain to determine whether these will outperform existing approaches to urine-based diagnosis[152].

ctDNA analysis.: In addition to tumour markers in urine, cell-free DNA with tumour-specific alterations is released into the blood circulation (circulating tumour DNA; ctDNA) mainly by cell death[153]. ctDNA is cleared through nuclease digestion, renal clearance, and uptake by the liver and spleen[154–157]. The half-life of ctDNA is ~2 hours[158], which makes ctDNA useful for real-time tracking of tumour burden following surgery and during oncological treatment. Analysis of ctDNA in plasma has shown promising results for the detection of minimal residual disease and metastatic relapse in multiple cancer types, including bladder cancer[159]. In one prospective study, ctDNA measurements detected clinical relapse on average 3 months earlier than CT scans and better predicted the outcome following neoadjuvant chemotherapy compared to pathological response[159,160]. Furthermore, ctDNA levels have been shown to correlate to pathological complete response and outcome following neoadjuvant immunotherapy[161]. Of note, another study used ctDNA measurements to document a survival benefit with adjuvant immunotherapy in patients

positive for ctDNA[162,163]. These results are promising overall, especially for the detection of minimal residual disease and for guiding adjuvant treatment, but further replication in large cohorts and development of optimal laboratory procedures for clinical use are needed. Furthermore, additional knowledge of ctDNA assay sensitivity and specificity is needed to address false positive and false negative rates in specific settings. ctDNA-guided clinical intervention trials are currently ongoing to determine the benefit of blood-based tests to guide adjuvant immunotherapy (for example, IMVIGOR011 and TOMBOLA)[164,165]. Importantly, ctDNA analysis can also identify genomic alterations associated with metastatic disease[166,167], potentially serving as actionable therapeutic targets.

Tissue-based diagnosis of bladder cancer.: Analysis of samples from biopsy or TURBT at the time of cystoscopy is the most common method of initial diagnosis. Pathological analysis confirms the presence of cancer, histological type and stage. Bladder carcinoma is subdivided by grade into low-grade and high-grade categories, with low-grade carcinomas showing frequent recurrence but limited progression[168]. High-grade carcinomas can be either NMIBC or MIBC, of which NMIBC commonly shows recurrence and progression to MIBC, requiring more aggressive clinical management and follow-up.

More than 90% of all bladder carcinoma histological subtypes are of urothelial histology, with the remainder comprising squamous cell carcinoma, adenocarcinoma and neuroendocrine carcinoma[168,169] (Fig. 5). These broad categories describe ‘pure’ or non-mixed carcinomas representing a single histological type of carcinoma. Urothelial carcinoma itself can occur as a broad array of variants or subtypes such as micropapillary, plasmacytoid, nested and lymphoepithelioma-like carcinomas. These categories are defined by the WHO Classification of Tumours of the Urinary System and Male Genital Organs[168]. Several subtypes have been associated with unique molecular and/or therapeutic considerations. Micropapillary urothelial carcinoma, which shows clusters of inversely polarized nests of tumour cells within prominent retraction spaces, has a disproportionately higher rate of *ERBB2* amplification than conventional urothelial carcinoma[170–172]. This amplification has been identified in up to 40% of micropapillary urothelial carcinomas, resulting in efforts to selectively target this pathway[170]. Plasmacytoid urothelial carcinoma, which is defined by distinct *CDH1* mutations and a morphology that shows single, plasma cell-like cells that are highly infiltrative, is another research focus[173]. Micropapillary and plasmacytoid urothelial carcinomas are biologically aggressive subtypes and optimizing the approach to these diagnostic categories has resulted in some institutions advocating early cystectomy regardless of stage[168]. Furthermore, micropapillary urothelial carcinoma is often variably mixed with conventional urothelial carcinoma, with higher proportions of micropapillary urothelial carcinoma portending a more aggressive pathological behaviour[174,175]. Despite their urothelial carcinoma origin, these two examples of urothelial carcinoma subtypes highlight the dramatic differences in urothelial carcinoma evolution and differentiation, which complicates a unified approach to understanding and treating bladder cancer.

In addition to histological subtyping, pathological analysis determines the depth of invasion of the carcinoma at biopsy or TURBT and also following cystectomy. Pathological (after cystectomy) staging is defined by the American Joint Committee on Cancer (AJCC),

currently in its eighth edition[176]. NMIBC occurs as either papillary (pTa) or flat urothelial CIS (pTis). Invasion of the lamina propria (pT1), invasion of the muscularis propria (pT2), perivesical fat (pT3) and involvement of adjacent organs (pT4) are associated with a progressive reduction in survival[176]. Determination of pathological stage on cystectomy specimens is straight-forward but diagnosis and staging on TURBT samples are challenging owing to the extent of sampling, interpretation artefact due to cautery or crush phenomenon, and lack of objective markers to conclusively determine if muscularis propria is present.

Use of tissue to predict progression from lamina propria-invasive (T1) disease to muscle-invasive carcinoma has been a subject of interest for some time. A recommendation was made in the AJCC manual to attempt substaging T1 disease based on numerous studies that showed that a larger amount of tumour in the lamina propria correlated with a higher rate of progression[176]. However, various approaches were used in the studies, including different cut-off criteria for substaging, surface orientation in some approaches that was impossible to perform on a considerable subset of specimens and diverse outcome end points. An additional confounder was the challenge of not knowing with certainty whether the lesion was fully resected. Comparison of these various approaches showed that an aggregate tumour measurement of ≥2.3 mm outperformed other histology-based approaches in predicting progression to muscle-invasive disease[177]. Since the endorsement of attempted substaging of T1 disease by the AJCC, numerous studies have evaluated additional approaches to predicting progression to MIBC, including histological, molecular and/or protein biomarkers[178,179]. Ultimately, these are challenging endeavours given the uncertainty regarding the presence of residual tumour, effects of precedent therapies on disease progression, and cellular heterogeneity associated with bladder cancer.

Staging—Diagnostic imaging is critical for both local and distant staging. During a work-up of haematuria, abdominopelvic imaging including imaging of the upper urinary tract (renal pelvis and ureters) should be performed to assess for a bladder mass (ideally prior to TURBT)[180–182]. Imaging informs both location and extent of disease (including potential upper tract involvement, extravesical extension, hydronephrosis, nodal involvement or distant metastatic disease). CT urography with and without an intravenous contrast agent is preferred and has largely replaced intravenous pyelogram[183,184]. In patients with poor renal function or allergy to iodinated contrast agents, MR urogram with a gadolinium-based contrast agent may be considered[185]. Renal ultrasonography or CT without a contrast agent combined with a retrograde ureteropyelography is conducted in patients who cannot receive iodinated or gadolinium-based contrast agents[183,184].

In addition to CT urography, MRI of the pelvis with and without an intravenous contrast agent may be considered for further local staging, especially regarding depth of bladder wall invasion[186]. The best evidence supporting the use of MRI is in MIBC in the pre-TURBT setting to improve staging[187]. Multiparametric MRI has improved soft tissue resolution compared with CT, and the Vesical Imaging Reporting and Data System (VI-RADS) score has been developed to predict the likelihood of muscle invasion[188]. MRI may also have the potential to assess response after treatment, including TURBT, neoadjuvant chemotherapy and/or chemoradiation[189].

For patients with NMIBC, chest and other metastatic imaging is not necessary, whereas for patients with MIBC, chest CT is recommended[140]. Bone scans and brain MRI have limited value and are typically reserved for symptomatic patients or those at very high risk (stage, tumour size, adverse pathology)[190]. ^{18}F-fluorodeoxy glucose-PET (FDG PET)-CT is not as commonly used and does not have a clearly established role in patients with localized disease, although it may have more value in locally advanced disease and when metastatic disease is suspected[191–194].

Prognostic and predictive biomarkers—In NMIBC, several prognostic biomarkers have been described; however, none have yet been implemented in clinical decision-making. For example, in one study, patients with NMIBC at high risk for progression were subdivided into groups with good, moderate and poor risk of progression based on mutations in *FGFR3* and methylation of *GATA2* (ref. 195). In addition, studies using measurements of genome-wide copy number alterations through array-based comparative genomic hybridization[54] or SNP array analysis[32] separated patients with Ta tumours or NMIBC, respectively, into different groups and found an association between a high level of copy number alterations and poor outcomes. Furthermore, tumour mutational burden (TMB) and APOBEC-associated mutations have been associated with increased NMIBC aggressiveness[32]. However, when analysing T1 tumours only, a high TMB was associated with better survival[196]. Earlier studies of gene expression subtypes in NMIBC identified two major molecular subtypes associated with disease aggressiveness[197,198]. Five subtypes of bladder cancer were identified when considering the whole spectrum of bladder cancer stages. The subtypes urothelial-like, genomically unstable, and a group of infiltrated cases were specifically associated with NMIBC[199]. Three expression-based subtypes were reported by the UROMOL consortium, which showed different clinical outcomes and molecular characteristics[33]. The work from the UROMOL consortium was later expanded and four subtypes were identified: the UROMOL2021 classification system showed overlap with previously reported subtypes but with increased granularity[32]. In another multi-omics approach, further molecular heterogeneity within disease stage categories was discovered, enabling further subclassification of Ta and T1 tumours[34].

In MIBC, several classification systems based on gene expression subtypes have been reported, ranging from two major subtypes (luminal and basal)[200] to six subtypes[201]. A consensus classification of six subtypes using previous classification systems has been reported[202]. The subtypes harbour different molecular alterations and immune cell characteristics and, overall, have been reported to be prognostic. In patients with MIBC, high TMB and neoantigen loads have been associated with particularly good survival and a high mutational contribution from APOBEC mutational processes was also associated with improved survival[51], similar to observations in T1 tumours[196].

Several studies sought to develop predictive biomarkers in both NMIBC and MIBC. In relation to Bacillus Calmette–Guérin (BCG) treatment in NMIBC, high PDL1 expression has been associated with BCG unresponsiveness, linking immune inhibitory pathways to BCG failure[203]. In another study, T cell exhaustion in the tumour was associated with outcome following BCG instillations[204]. In one study, molecular profiling of high-risk BCG-naive NMIBC and recurrent tumours after BCG treatment found three distinct BCG

response subtypes (BRS1–3)[205]. Patients with BRS3 tumours had reduced recurrence-free and progression-free survival than patients with BRS1 and BRS2. BRS3 tumours expressed high epithelial–mesenchymal transition and basal markers and had an immunosuppressive profile. Tumours that recurred after BCG were enriched for BRS3. In a second cohort of BCG-naive patients with high-risk NMIBC, BRS molecular subtypes outperformed guideline-recommended risk stratification based on clinicopathological variables.

In MIBC, expression of and mutations in genes involved in DNA damage response are associated with a particularly good outcome following chemotherapy and chemoradiation[206–210]. Some of these genomic alterations have been tested in a clinical trial evaluating bladder-sparing approaches; however, the study did not reach the primary end point and further study refinements are needed[211]. In addition, a $CD8^+$ T effector cell phenotype, high TMB and high neoantigen load have been demonstrated to be predictors of immunotherapy response in MIBC, whereas lack of response was associated with a signature of transforming growth factor-β (TGFβ) signalling in fibroblasts[212]. Other studies demonstrated that MIBC tumours of the luminal subtypes show an improved response to chemotherapy[213,214] but contradicting results have also been reported[215]. Further gene expression profiling studies have shown that increased immune cell infiltration in MIBC is associated with improved outcomes after chemoradiation, whereas increased stromal infiltration is associated with worse outcomes after neoadjuvant chemotherapy and cystectomy[216]. Several seminal studies have shown substantial intratumour heterogeneity using single-cell and spatial transcriptomic analysis, which is likely complicating the utility of current subtype classifications for clinical outcome prediction[79,217].

Management

The management of bladder cancer requires careful consideration of disease stage and tumour characteristics as well as patient demographics, comorbidities and preferences. Optimal treatment involves a multidisciplinary approach that may include surgery, chemotherapy, radiation therapy, immunotherapy and targeted therapy.

TURBT and en bloc resection of bladder tumour—TURBT is a diagnostic, staging and, for NMIBC, therapeutic tool, making it a cornerstone in management. The procedure starts with a comprehensive inspection of the bladder, followed by resection of the exophytic part of the tumour, and separate resection of the underlying bladder wall and edges of the resection area[142]. TURBT has two main goals: complete (possibly curative) resection in the case of NMIBC, and proper local staging and expediting subsequent definite treatment in the case of MIBC. To ensure complete tumour eradication in NMIBC, the quality of resection is extremely important, but the procedure is highly dependent on operator skills and experience[218]. Although TURBT aims to completely resect NMIBC, this is not always possible due to its technical difficulty and fear of bladder perforation. A second TURBT, 2–6 weeks later, is indicated if the tumour was not completely resected in the first TURBT, if the patient has T1 disease, or if detrusor muscle is absent in the first TURBT specimen with the exception of Ta low-grade tumours and primary CIS[142]. Second TURBT may be associated with improved progression-free survival in patients with T1 NMIBC[219]. A meta-analysis of 81 studies found that the pooled rates of any residual tumours and upstaging

on second TURBT were 31.4% and 2.8%, respectively[220], highlighting the limitations of the conventional TURBT procedure. In the case of MIBC, maximal TURBT is also important to optimize subsequent treatment such as radical cystectomy and trimodality therapy (TMT)[221,222]. Maximal resection of all visible bladder tumours down to the detrusor muscle layer should be pursued even when MIBC is suspected endoscopically[221,222].

En bloc resection of bladder tumour (ERBT), that is, removal of the bladder tumour in one piece, has been proposed as a potentially more favourable surgical approach than conventional TURBT[223,224]. Results from three randomized trials comparing ERBT and TURBT have been reported[225–227]. In one trial[225], the rate of detrusor muscle presence for ERBT was non-inferior to TURBT (94% versus 95%), and T1 substaging was more feasible in the ERBT group (100% versus 80%; $P = 0.02$). In a second trial[226], the ERBT group had a higher rate of detrusor muscle presence (80.7% versus 71.1%; $P = 0.01$) and a lower rate of bladder perforation (5.6% versus 12%, difference –6.4%, 95% CI –12.2 to −0.6%) than the TURBT group. In a third trial[227], ERBT resulted in a reduction in the 1-year recurrence rate from 38.1% to 28.5% ($P = 0.007$), and 30-day complications were similar between the two groups.

A single dose of intravesical chemotherapy (commonly mitomycin C or epirubicin) immediately after TURBT is associated with a decreased risk of recurrence[228]. A systematic review and individual patient data meta-analysis of a total of 2,278 patients found that a single dose of intravesical chemotherapy reduced the risk of recurrence by 35% ($P < 0.001$)[228]. However, this benefit was not observed in patients with a prior recurrence rate of >1 per year, or in patients with a European Organization for Research and Treatment of Cancer (EORTC) recurrence score of ≥5 (ref. 228). Single-dose intravesical chemotherapy should not be given when there is a concern for bladder perforation as chemotherapy extravasation can result in severe consequences[229].

Although TURBT with or without single-dose intravesical chemotherapy is the standard of care for the treatment of NMIBC, it is a major surgery requiring formal anaesthesia, which could be a burden for patients with recurring diseases. As the risk of disease progression for recurrent Ta low-grade bladder tumours is low, fulguration or laser vaporization of small papillary recurrences on an outpatient basis has been proposed to reduce the therapeutic burden[142,230,231]. In particular for patients at advanced age, watchful waiting with urine cytology and regular cystoscopy without resection can also be considered[232].

Intravesical therapy for NMIBC—Intravesical therapy with BCG vaccine was first proposed in 1976 as an immunotherapy to treat bladder cancer[233] and became a standard of care for NMIBC. A randomized study to investigate the optimal BCG schedule for intermediate-risk and high-risk NMIBC with a primary outcome of disease-free interval, concluded that 1 year and 3 years of full-dose BCG should be given to patients with intermediate-risk and high-risk NMIBC, respectively[234]. Adverse effects of BCG include inflammation and/or infection of the bladder, prostate, epididymis, and testis as well as general malaise, fever and BCG sepsis[142]. Since 2013, an intermittent BCG shortage has been a global problem and alternative treatment options are urgently needed[235,236]. Intravesical maintenance chemotherapy can be an alternative in intermediate-risk NMIBC,

but its efficacy in high-risk NMIBC is limited[142]. New intravesical therapies, such as intravesical gene therapy with nadofaragene firadenovec[237] and systemic ICI therapy with pembrolizumab[238] have been approved by the FDA for BCG-unresponsive NMIBC with CIS, with or without papillary tumours.

Intravesical maintenance chemotherapy, given repeatedly on a weekly or monthly basis[239,240], has been investigated as an alternative to intravesical BCG therapy. A meta-analysis compared TURBT plus intravesical maintenance chemotherapy with TURBT only and found that the use of intravesical maintenance chemotherapy was associated with a 44% reduction in 1-year recurrence ($P < 0.001$)[241]. In an individual patient data meta-analysis comparing intravesical maintenance chemotherapy and intravesical BCG, the use of BCG was associated with a 32% reduction in the risk of recurrence ($P < 0.001$)[240]. In patients with intermediate-risk NMIBC who cannot tolerate intravesical BCG, intravesical maintenance chemotherapy can be considered noting its inferiority in oncological efficacy.

Radical cystectomy—Radical cystectomy is a standard of care in localized MIBC[182] and in patients with BCG-unresponsive NMIBC[182]. The surgery itself includes three major components: cystectomy, pelvic lymph node dissection (LND) and urinary diversion. In men, standard radical cystectomy includes removal of the bladder, prostate, seminal vesicles and distal ureters[182]. In women, standard radical cystectomy includes removal of the bladder, the entire urethra, anterior vaginal wall, uterus and distal ureters[182]. Standard LND includes removal of bilateral obturator, internal and external iliac lymph nodes. Two randomized trials investigated the role of extended LND (including the common iliac, presacral and up to, at least, the aortic bifurcation) and found that extended LND was associated with more grade ≥3 complications[242,243] but no benefit in recurrence-free survival[242], cancer-specific survival[242], disease-free survival[243] and overall survival[242,243]. For urinary diversion, ileal conduit and orthotopic neobladder are commonly performed. The choice of urinary diversion depends on patient factors (for example, age, renal function, ability to perform self-catheterization and patient preference) and disease factors (for example, urethral involvement, locally advanced disease and need for adjuvant therapy)[244]. Patients should be carefully counselled about the advantages and disadvantages of each option so that a shared decision can be made in the best interest of the patient. Radical cystectomy can be performed in an open, laparoscopic or robot-assisted approach. In a meta-analysis comparing robot-assisted radical cystectomy (RARC) with open radical cystectomy (ORC), no difference in terms of recurrence-free survival (HR 0.99, 95% CI 0.75–1.31) and overall survival (HR 0.98, 95% CI 0.73–1.30) was found[245]. RARC had a lower transfusion rate (OR 0.42, 95% CI 0.30–0.59) but a longer operative time (mean difference 78.54 min, 95% CI 45.87–111.21 min) than ORC[245]. Overall complications, major complications, positive margin rates and length of hospital stay did not differ[245]. High-quality data comparing RARC with intracorporeal versus extracorporeal urinary diversion are lacking, although non-randomized studies favoured the intracorporeal approach showing benefits in blood loss and hospital stay[246,247]. High-quality data on laparoscopic radical cystectomy is limited[245].

Some patients with pT3/T4 pN0–2 bladder cancer (N0, no regional lymph node metastasis; N1, metastasis in a single regional lymph node; N2, metastasis in multiple regional lymph

nodes) may be candidates for postoperative adjuvant pelvic radiotherapy to the pelvic lymph nodes with or without the cystectomy bed following radical cystectomy[248,249]. Addition of adjuvant radiotherapy to chemotherapy alone was associated with improved local relapse-free survival[250].

Partial cystectomy may be considered in highly selected patients, including those with solitary tumours at favourable locations, such as the bladder dome, without concomitant CIS[251]. Special caution must be taken to avoid urine and tumour spillage during the procedure. To date, there are no randomized trials comparing partial with radical cystectomy, but previous retrospective studies showed comparable results[251]. Patient selection is key should partial cystectomy be contemplated.

Trimodality therapy—TMT is a bladder-preserving treatment of MIBC that includes a maximal, ideally visibly complete, TURBT followed by concurrent radiosensitizing chemotherapy and radiotherapy (chemoradiotherapy). TMT is an accepted alternative to radical cystectomy for selected patients with MIBC who have a desire to retain their native bladder or who are medically unfit for radical cystectomy[181,182,252] and may be most effective in patients with specific characteristics (Box 1). Randomized controlled trials comparing TMT to radical cystectomy closed due to lack of accrual[253], but best available data from prospective TMT trials (including from NRG/RTOG in the USA and from UK-based trials), meta-analyses and multi-institutional cohorts demonstrate comparable survival[254–258]. Chemoradiotherapy is considered standard in patients who can tolerate combined therapy, following a phase III randomized BC2001 trial that showed that concurrent chemoradiotherapy with 5-fluorouracil and mitomycin leads to improved locoregional disease control compared with external beam radiotherapy alone[257]. Other options for concurrent chemotherapy include cisplatin-based regimens or single-agent gemcitabine[259]. Ongoing randomized trials are investigating the addition of immunotherapy (for example, atezolizumab or pembrolizumab) to TMT[260,261].

Lifelong post-treatment bladder surveillance is essential for the detection of in-bladder recurrences (10-year rates: NMIBC 20–26%, MIBC 13–18%) or second primary tumours, and 10–15% of patients may require a salvage cystectomy, which is associated with a higher risk of overall and major late complications than primary cystectomy and most often requires an incontinent urinary diversion[262]. Patients with MIBC and who are appropriate candidates should be offered the choice between radical cystectomy and TMT approaches. MIBC treatment, and in particular TMT, requires close multidisciplinary collaboration and environments that enable shared and informed decision-making[263]. A multi-institutional study in 722 patients (440 radical cystectomy, 282 TMT) used propensity score matching and logistic regression to show similar oncological outcomes between these two treatment modalities[258]. Although there are no conclusive randomized trials supporting the equivalence of TMT to radical cystectomy for selected patients in bladder cancer, the current evidence from other studies as summarized above supports that TMT, in the setting of multidisciplinary shared decision-making, should be offered to all suitable candidates with MIBC and not only to patients with considerable comorbidities for whom surgery is not an option[258].

Bladder-preserving TMT has also been evaluated in a small phase II single-arm study in patients with recurrent high-grade NMIBC following intravesical therapy for whom the next step would be cystectomy, with chemoradiotherapy leading to favourable (88%) cystectomy-free survival results at 3 years[264].

Radiotherapy of the primary tumour and possible sites of metastases may also have a role in oligometastatic bladder cancer. Studies suggest a possible survival benefit when adding local therapy to the bladder (including radiotherapy over chemotherapy alone) in metastatic disease[265,266] and when using metastasis-directed therapy[267,268]. However, data are limited in the adjuvant, recurrent NMIBC and oligometastatic settings, and further prospective research is needed.

Perioperative systemic therapy—For patients with MIBC, the risk of metastatic recurrence despite curative-intent local therapy (that is, radical cystectomy or TMT) is high and systemic therapy has been explored to further improve outcomes. The BA06 30894 trial compared neoadjuvant cisplatin, methotrexate plus vinblastine followed by definitive local therapy versus definitive local therapy alone in patients with clinical stage T2–T4aN0M0 and is the largest neoadjuvant study reported to date[269]. This trial revealed that neoadjuvant cisplatin, methotrexate plus vinblastine improved survival (HR 0.84, 95% CI 0.72–0.99). The Southwest Oncology Group 8710 trial randomized patients with clinical stage T2–T4aN0M0 to neoadjuvant methotrexate, vinblastine, doxorubicin plus cisplatin (MVAC) followed by cystectomy versus cystectomy alone[270]. This trial reported an improvement in overall survival with neoadjuvant MVAC (HR 0.75, 95% CI 0.57–1.00). Importantly, these trials of neoadjuvant cisplatin-based chemotherapy have revealed an increased likelihood of achieving a pathological complete response at cystectomy with neoadjuvant chemotherapy followed by cystectomy versus cystectomy alone[270]. Meta-analyses of the neoadjuvant chemotherapy trials in MIBC have confirmed the survival benefit leading to this approach becoming standard care[271]. The optimal form of neoadjuvant chemo therapy, gemcitabine plus cisplatin or dose-dense MVAC remains controversial[272–274].

Deferring decisions regarding the use of systemic therapy for MIBC to the postoperative setting is attractive given the ability to base treatment decisions on more precise pathological staging rather than clinical staging. Notwithstanding, clinical trials exploring adjuvant chemotherapy in patients with pT3–4 and/or pN+ urothelial cancer of the bladder have provided less robust evidence[275] despite observational analyses and meta-analyses suggesting a benefit[275,276].

There has historically been no standard perioperative systemic therapy to decrease the risk of recurrence after curative-intent surgery in cisplatin-ineligible patients with high-risk pathological features at cystectomy (pT3 and/or pN+) or patients who received prior neoadjuvant therapy with high-risk pathological features at cystectomy (pT3 and/or pN+). Two phase III trials with a similar design sought to define the role of adjuvant PD1 or PDL1 blockade in this population by randomly allocating patients to 1 year of adjuvant PD1 or PDL1 blockade versus observation or placebo. Checkmate 274 demonstrated a significant improvement in disease-free survival in the overall population (HR 0.70, 95% CI 0.55–0.90) and in the subset of patients with tumours with increased PDL1 expression (HR 0.55, 95%

CI 0.35–0.85)[277], leading to regulatory approval of adjuvant nivolumab for bladder cancer in several parts of the world. IMvigor 010 did not demonstrate an improvement in the primary end point of disease-free survival[278]. However, an exploratory analysis suggested a disease-free and overall survival benefit with adjuvant atezolizumab versus placebo in patients with detectable baseline ctDNA[162], paving the way for ctDNA-based studies of adjuvant therapy in bladder cancer.

Systemic therapy for metastatic bladder cancer—Cisplatin-based combination chemotherapy became a standard treatment for metastatic bladder cancer in the early 1990s after a randomized clinical trial demonstrated a survival benefit with MVAC versus cisplatin alone[279]. A series of subsequent randomized trials found that administration of MVAC in a dose-dense fashion and/or with granulocyte colony-stimulating factor support was associated with less toxicity and possibly enhanced efficacy[280,281] and that the combination of gemcitabine plus cisplatin yielded similar efficacy but less toxicity than MVAC[282]. Although cisplatin-based chemotherapy became a standard of care for patients with metastatic urothelial cancer, many patients with bladder cancer are of advanced age and many are ineligible for cisplatin[283]. For these patients, gemcitabine plus carboplatin is generally substituted[284].

By 2015, PD1 and PDL1 ICIs had demonstrated durable responses in 20–25% of patients with metastatic urothelial cancer and received regulatory approval initially in patients progressing despite first-line platinum-based chemotherapy and, subsequently, as first-line treatment for cisplatin-ineligible patients[285–289]. Only the approval of pembrolizumab in patients with platinum-resistant metastatic urothelial cancer was based on a randomized phase III trial[287] with the remainder based on single-arm phase II studies. Potential adverse events with PD1 and PDL1 ICIs include but are not limited to immune-related adverse events such as colitis, pneumonitis, dermatitis, hepatitis and endocrinopathies. Although requiring thorough validation in larger series, if the early data showing that LOY tumours are more vulnerable to ICIs holds, this would be a potentially valuable marker to stratify patients to this approach[130].

Several phase III trials were launched to optimize the use of these therapies. IMvigor 130 (ref. 290) and Keynote 361 (ref. 291) compared platinum-based chemotherapy versus PD1 or PDL1 blockade versus platinum-based chemotherapy plus PD1 or PDL1 blockade as first-line treatment for metastatic urothelial cancer. These trials failed to demonstrate a benefit of concurrent platinum-based chemotherapy plus PD1 or PDL1 blockade versus platinum-based chemotherapy alone. A randomized phase II and III trial compared switch maintenance PD1 or PDL1 blockade (pembrolizumab and atezolizumab, respectively) versus placebo or observation in patients with at least stable disease after initial platinum-based chemotherapy[292,293]. These trials met their primary endpoints, with the phase III JAVELIN-Bladder 100 study demonstrating an overall survival benefit, resulting in switch maintenance ICI being adopted into standard treatment paradigms. After decades of investigation, platinum-based chemotherapy remains the standard-of-care first-line treatment for most patients with metastatic urothelial cancer with switch maintenance ICI employed for patients, with stable disease after ~4–6 cycles of chemotherapy. However, in some regions, the combination of an antibody–drug conjugate (enfortumab

vedotin) plus pembrolizumab has received regulatory approval as first-line treatment for cisplatin-ineligible patients based on relatively high response rates and promising response durations[294]. Several new therapies with distinct mechanisms of action have subsequently been integrated into standard therapeutic strategies for metastatic bladder cancer (Table 3).

Quality of life

A cross-sectional survey investigated the health-related QoL (HRQoL) of 1,796 patients with bladder cancer, of whom 868 (48%) had NMIBC, 893 (50%) received radical cystectomy or radiotherapy, and 35 (1.9%) had unknown treatment[295]. Most patients (69%) reported at least one problem in any EQ-5D dimension[295]. HRQoL outcomes adjusted for age and sex were similar across all stages and treatment groups. Sexual problems were common in male patients and increased with younger age and radical treatment[295]. A prospective study of 133 patients using the Short-Form 36-item survey (SF-36) found that physical functioning, social functioning and role-emotional of patients worsened with first, second and third TURBT, and finally improved when TURBT was performed ≥4 times[296]. Patient mental health was also impaired at first TURBT but gradually returned to normal with repeated TURBT.

A study investigated the QoL of 103 patients with NMIBC who received intravesical BCG or mitomycin C using the EORTC QLQ-C30 and QLQ-BLS24 questionnaires[297]. QoL seemed to drop after the induction course and returned to baseline at 3 months. QoL was more affected in patients aged >70 years, especially in those who received intravesical BCG therapy. In another study, QoL of 106 patients with NMIBC who underwent intravesical chemotherapy was evaluated using the EORTC QLQ-C30 and the Core Lower Urinary Tract Symptom Score questionnaire, finding that global health status and social functioning decreased and that Core Lower Urinary Tract Symptom Score also worsened significantly[298].

A meta-analysis investigated the HRQoL following radical cystectomy and urinary diversion[299]. All included studies reported an initial deterioration in overall HRQoL but general health, functional and emotional domains at 12 months after surgery were similar to or better than baseline. Overall, there was no significant difference in HRQoL between continent and incontinent urinary diversion. Subgroup analysis showed greater improvement in physical health for patients undergoing incontinent urinary diversion but mental health and social health did not differ between diversion types[299]. Qualitative analysis showed that patients with neobladder had better emotional function and body image than those with cutaneous diversion[299].

A meta-analysis comparing RARC and ORC showed no significant difference in QoL (standard mean difference –0.02, 95% CI –0.17 to 0.13; $P = 0.78$)[300]. In the RAZOR study comparing RARC plus extracorporeal urinary diversion and ORC, no significant difference in the Functional Assessment of Cancer (FACT)-Vanderbilt Cystectomy Index was found between the two groups at any time point. In the iROC study comparing RARC plus intracorporeal urinary diversion and ORC, patients undergoing ORC had worse QoL at 5 weeks and greater disability at 5 weeks and 12 weeks, but their QoL improved with time and QoL did not differ between RARC and ORC after 12 weeks[301].

TMT experiences have shown favourable toxicity profiles and good long-term QoL. Late pelvic (genitourinary or gastrointestinal) grade ≥3 toxicity rates from the NRG/RTOG and BC2001 trials are acceptable and low (1–6%)[257,302]. Analysis of long-term survivors from four NRG/RTOG trials showed that TMT was associated with 5.7% genitourinary and 1.9% gastrointestinal late grade 3 toxic effects (that rarely persist) and no late grade 4 toxic effects or treatment-related deaths[302]. In TMT series, <1% of patients required cystectomy due to treatment-related toxicity[222,258]. Other studies from prospective trials and retrospective cohorts and using validated instruments as well as urodynamic studies in long-term survivors of TMT for MIBC made three QoL-related findings. First, the BC2001 trial showed short-term declines in HRQoL during treatment and immediately following chemoradiation, as would be expected, but these improved to baseline levels after 6 months with no impairment from the addition of chemotherapy[303]. Second, most patients have normally functioning bladders following therapy[304]. Third, TMT resulted in QoL gains compared with radical cystectomy, including modestly better general HRQoL, markedly better sexual function and QoL, better-informed decision-making, less concerns about appearance, and less life interference from cancer or cancer treatment[305].

A Swedish bladder cancer data base investigated the natural history of patients unable or unwilling to receive therapy with curative intent[306]. Among patients with T2–3 M0 disease, a median of 2.4 hospitalizations per patient occurred during the first 12 months of diagnosis and half of these hospitalizations were due to cancer or genitourinary symptoms[306]. These patients experienced substantial disease-specific morbidity, which might have been avoided if they underwent treatment with curative intent[306].

Several large phase III trials have evaluated QoL of patients with bladder cancer receiving systemic therapy. There are limited available instruments that have been designed and validated to assess both general and bladder cancer-specific QoL domains in these patients. The FACT-Bladder (FACT-BI) is a 39-item questionnaire that integrates questions regarding general QoL domains (FACT-General) as well as a cancer site-specific bladder subscale and has been assessed for validity in a cohort of patients with metastatic bladder cancer receiving ICIs[307]. This tool and the National Comprehensive Cancer Network/Functional Assessment of Cancer Therapy Bladder Symptom Index-18 (FBlSI-18), EORTC QLQ-C30 and EuroQol-4D (EQ-5D) have been most commonly employed in bladder cancer trials.

The effects of neoadjuvant cisplatin-based chemotherapy on QoL are not well studied. In a randomized trial comparing two cycles of neoadjuvant MVAC followed by cystectomy versus cystectomy alone in 99 patients, QoL was assessed using the FACT-Bl instrument[308]. QoL after completion of chemotherapy was lower than baseline scores in domains including physical and functional well-being as well as for total FACT-Bl scores; however, there was no difference in these domains between study arms on follow-up after radical cystectomy. In the Checkmate 274 trial comparing adjuvant nivolumab versus placebo in 709 patients, QoL was assessed using the EORTC QLQ-C30 and the EQ-5D-3L[309]: adjuvant nivolumab was non-inferior to placebo on changes from baseline across all major domains. In the JAVELIN-Bladder 100 trial of switch maintenance avelumab versus observation in 700 patients with at least stable disease after first-line platinum-based chemotherapy, the FBlSI-18 and EQ-5D-5L instruments were explored[310]. Switch maintenance avelumab was demonstrated

to have minimal effects on QoL. QoL with ICIs was also assessed in the Keynote-045 trial comparing pembrolizumab versus chemotherapy in 519 patients with platinum-resistant metastatic bladder cancer[311]. Pembrolizumab prolonged the time to deterioration in global QoL compared with chemotherapy (median 3.5 months versus 2.3 months, hazard ratio 0.72; nominal one-sided $P = .004$). QoL with systemic therapy in patients with bladder cancer is complex to measure and interpret given the variability of instruments, time points and heterogeneity in clinical disease states with differential effects of disease-related and treatment-related burden.

Because of its unique biology, such as high recurrence rates, procedural requirements related to surveillance and expensive treatments, bladder cancer management contributes considerably to medical costs. In the USA, the overall annual costs of cancer were US$183 billion in 2015 and are projected to increase to US$246 billion by 2030 (ref. 312). Bladder cancer contributed US$7.93 billion in 2015, with an anticipated increase of US$11.6 billion by 2030. Similarly, among European Union members, cancer costs totalled € 152.8 billion in 2012, of which bladder cancer contributed € 5.24 billion (adjusted to 2019 values)[313]. Multiple cost-effectiveness analyses and reviews have been published and provide perspectives on the cost, efficacy and effects on QoL of interventions in patients with bladder cancer[314–316].

Outlook

Bladder cancer is a considerable and growing global health issue and its prevalence is expected to increase by 2040. However, with advances in molecular biology and therapy culminating progress over the past 100 years (Fig. 6), there is hope for the development of more effective diagnostic and treatment options that can improve patient outcomes.

One promising area of research is the development of minimally invasive diagnostic tools, such as urine-based or blood-based tests, that can detect disease recurrences and minimal residual disease. These tests could provide a less invasive and more convenient alternative to current diagnostic methods. Furthermore, the tests could ultimately lead to new ways of guiding oncological decisions and follow-up programmes. Further research in this area should focus on validation of clinical applicability of the tests in clinical trials to demonstrate clinical utility. Furthermore, development of robust multi-cancer early detection tests may ultimately lead to better screening for bladder cancer and in this way detect the disease at earlier stages.

The development of precision medicine approaches is also critical for improving bladder cancer management. The distinct molecular profiles of NMIBC and MIBC suggest that personalized treatment approaches based on the specific genetic mutations of a tumour could lead to more effective outcomes. Similarly, understanding the sex and race differences in bladder cancer incidence and prognosis can help tailor treatment approaches to individual patients and improve outcomes. In addition, there is an urgent need to delineate tumour heterogeneity using single-cell and spatial transcriptomic analysis, which is likely compromising the utility of current subtype classifications for clinical outcome prediction[79,217]. These approaches will likely provide much-needed clues to clinically tractable approaches that can be used to determine the primary driver populations in each

specific tumour and use that driver as a prognosticator, predictor or therapeutic target. Finally, it is essential to continue to prioritize research into the causes and risk factors for bladder cancer. With a better understanding of the underlying biology of the disease, more effective prevention strategies can be developed to identify patients who are at increased risk for developing bladder cancer. This could include lifestyle interventions, such as smoking cessation and dietary changes as well as targeted screening for populations at high risk.

Machine learning, a subdiscipline of artificial intelligence that focuses on data analytics, has played a prominent role in cancer research and care because of the complexity of the disease and the availability of big data from technologies such as genomics and imaging. Applications include predicting regulatory elements in DNA sequences, predicting disease risk in populations, and diagnosing cancer from pathology and radiology images as well as modelling and predicting physiological and biological behaviours or systems biology[317,318].

In conclusion, the outlook for bladder cancer is promising, with multiple advances in the understanding of the biological context of bladder cancer, development of novel non-invasive test methods to potentially guide treatment and, finally, the development of multiple novel oncological treatments. A multidisciplinary approach that considers sex and race differences as well as the genetic and molecular characteristics of the disease, will be critical for improving patient outcomes and reducing the global burden of bladder cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Box 1

Optimal patient characteristics for trimodality bladder-sparing treatment for muscle-invasive bladder cancer

- Predominant urothelial cancer histology
- Unifocal tumour <7 cm in size
- Visibly complete transurethral resection of bladder tumour
- Clinical stage T2–T3a
- Lack of extensive carcinoma in situ
- Absence of hydronephrosis
- Good bladder function

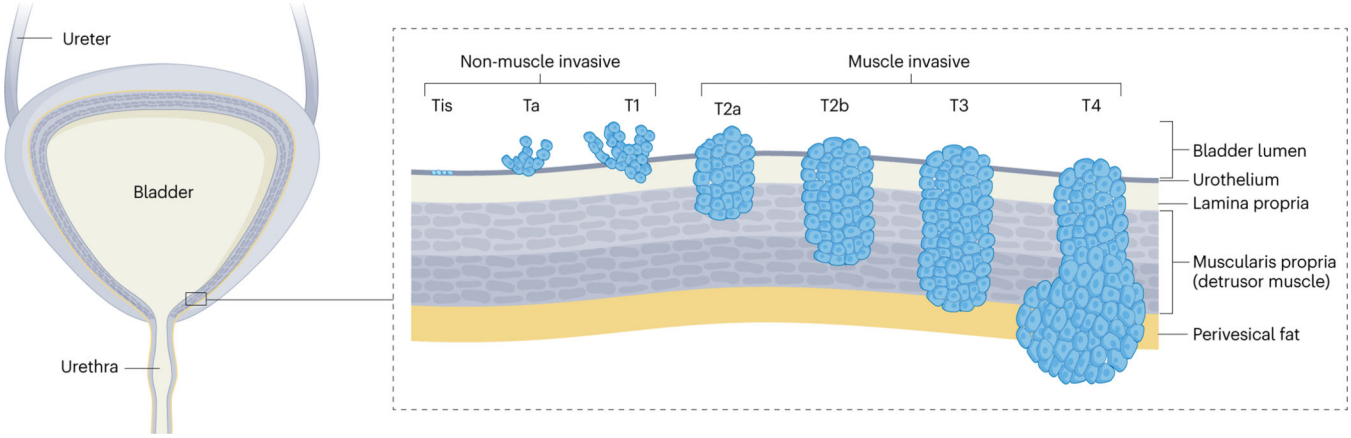

Fig. 1 |. Bladder cancer categories.

Bladder cancer can be categorized into grades, which is the cytological appearance of the urothelium, and stages, which are determined by the spread and depth of bladder wall invasion of the tumour. Non-invasive papillary carcinomas are classified as Ta disease, whereas urothelial carcinoma in situ is classified as Tis disease. All invasive urothelial cancers arise from either high-grade papillary carcinoma or urothelial carcinoma situ. Adapted from ref. 319, Springer Nature Limited.

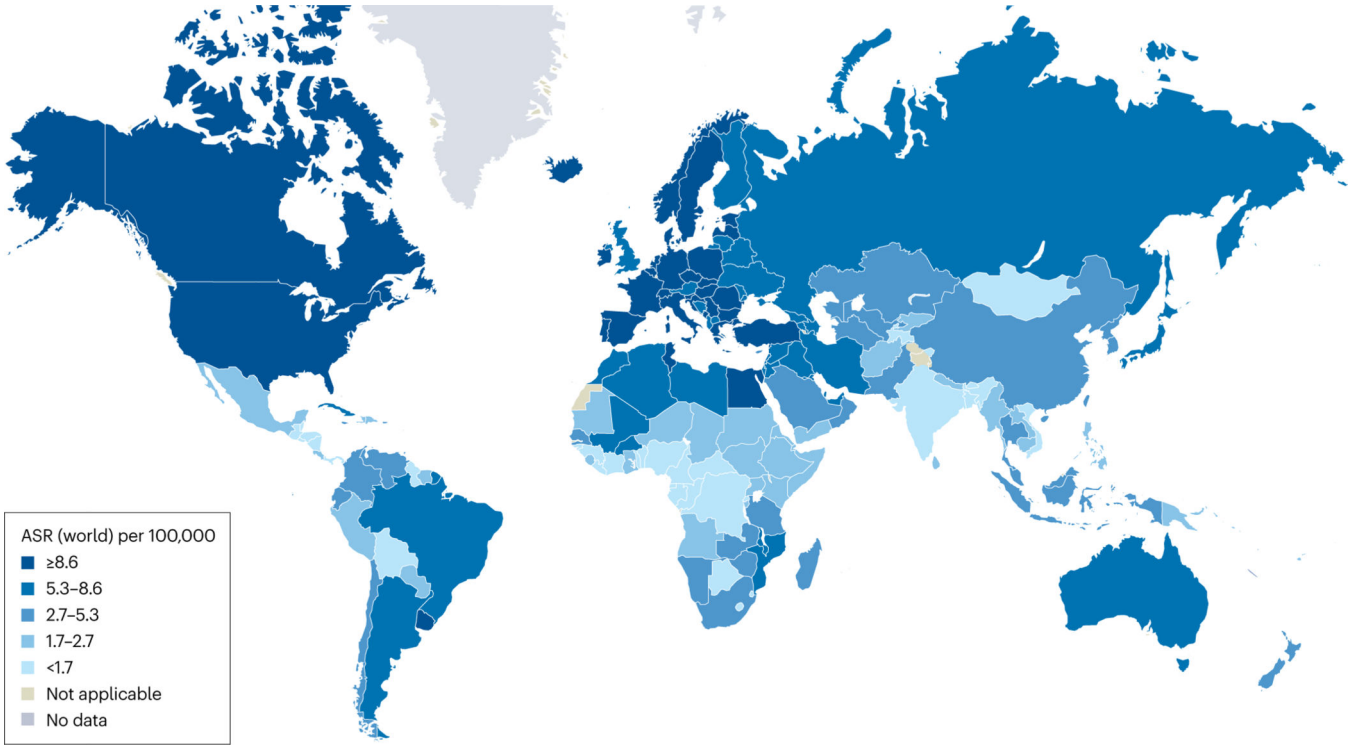

Fig. 2 |. Global incidence of bladder cancer.

Global estimated incidence of bladder cancer in 2020 in men and women of all ages. Data are expressed as age-standardized rates (ASRs; adjusted to World Standard Population) to account for differing age profiles among regions. Data were obtained from GLOBOCAN 2020. Map was produced by the World Health Organization/International Agency for Research on Cancer (https://gco.iarc.fr/today).

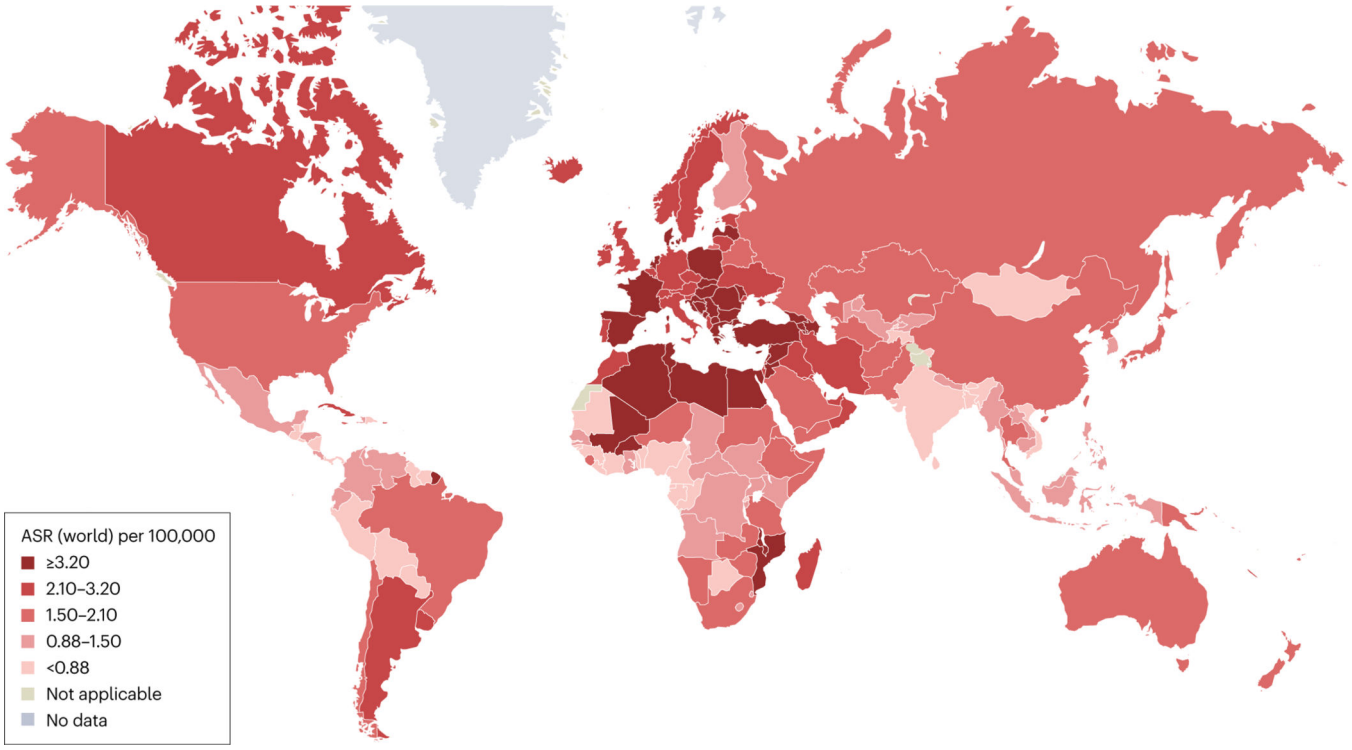

Fig. 3 |. Global mortality of bladder cancer.

Global estimated mortality due to bladder cancer in 2020 in men and women of all ages. Data are expressed as age-standardized rates (ASRs; adjusted to World Standard Population) to account for differing age profiles among regions. Data were obtained from GLOBOCAN 2020. Map was produced by the World Health Organization/International Agency for Research on Cancer (https://gco.iarc.fr/today).

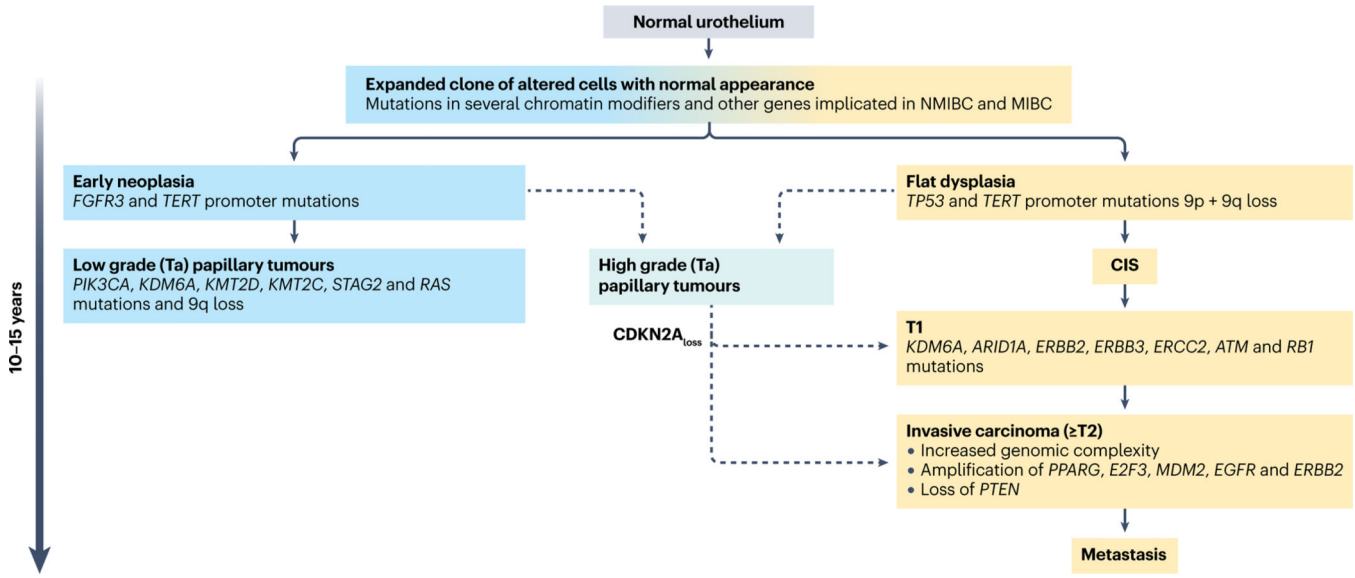

Fig. 4 |. Pathogenesis pathways.

Potential pathogenesis pathways to papillary non-muscle-invasive bladder cancer (NMIBC) and solid muscle-invasive bladder cancer (MIBC), including key genomic events, are shown (Tables 1 and 2). Solid arrows indicate pathways for which there is histopathological and/or molecular evidence. Dashed arrows indicate pathways for which there is uncertainty. Estimated time for tumour development is shown on the left. CIS, carcinoma in situ.

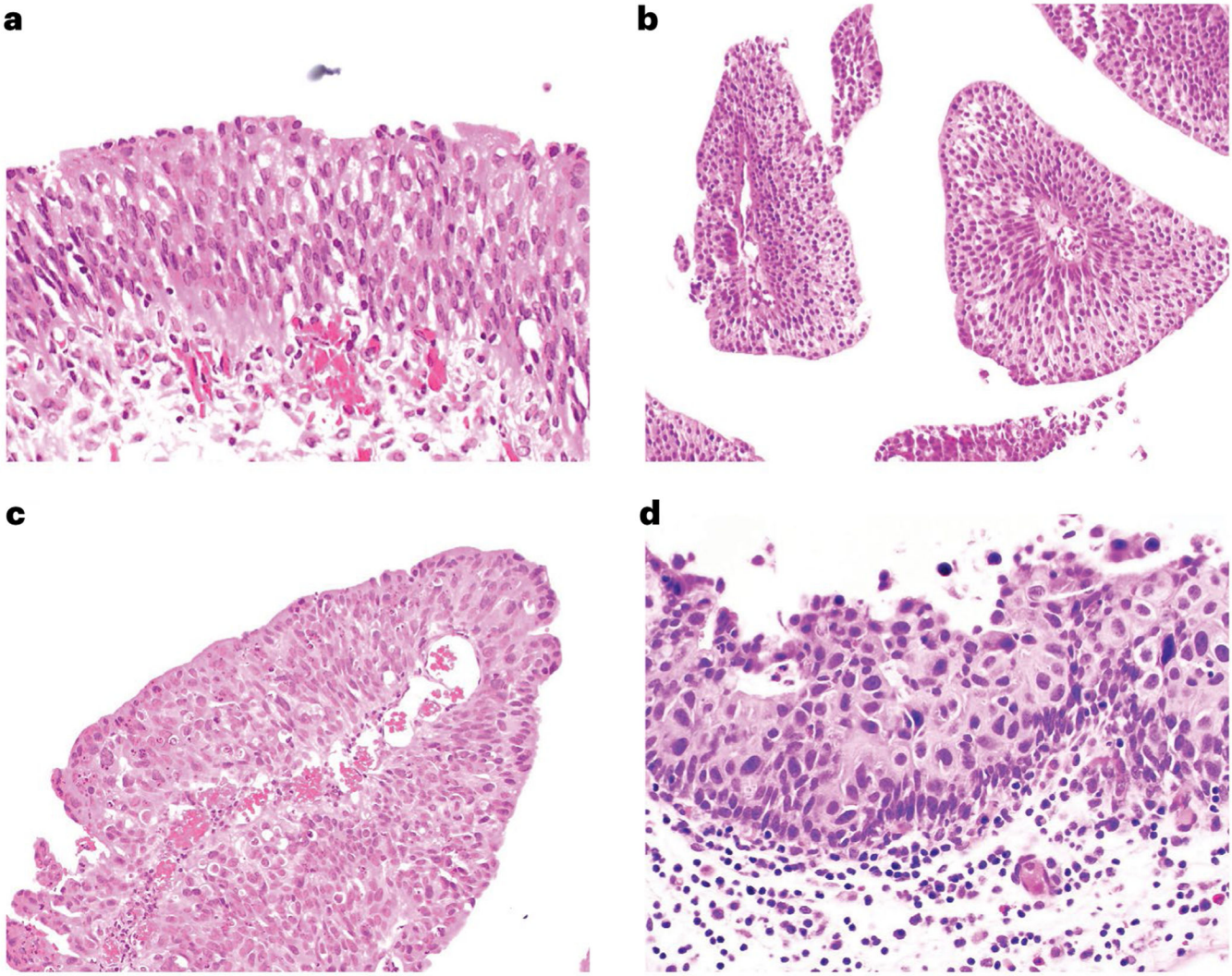

Fig. 5 |. Histopathology of bladder cancer.

Normal urothelium (part **a**) is defined by cellular polarization towards the luminal surface with individual cells relatively monotonous in appearance and containing open chromatin. Low-grade papillary urothelial carcinoma (part **b**) shows papillary cores, in this image cut in cross-section, lined by urothelium that remains relatively monotonous and polarized but with hyperchromasia of some nuclei. Non-invasive high-grade neoplasia in the bladder may be papillary (part **c**) or flat (part **d**) and demonstrates disorganization, nuclear enlargement, nuclear pleomorphism, and hyperchromasia. High-grade lesions have the potential to invade beyond the basement membrane and into the underlying bladder wall.

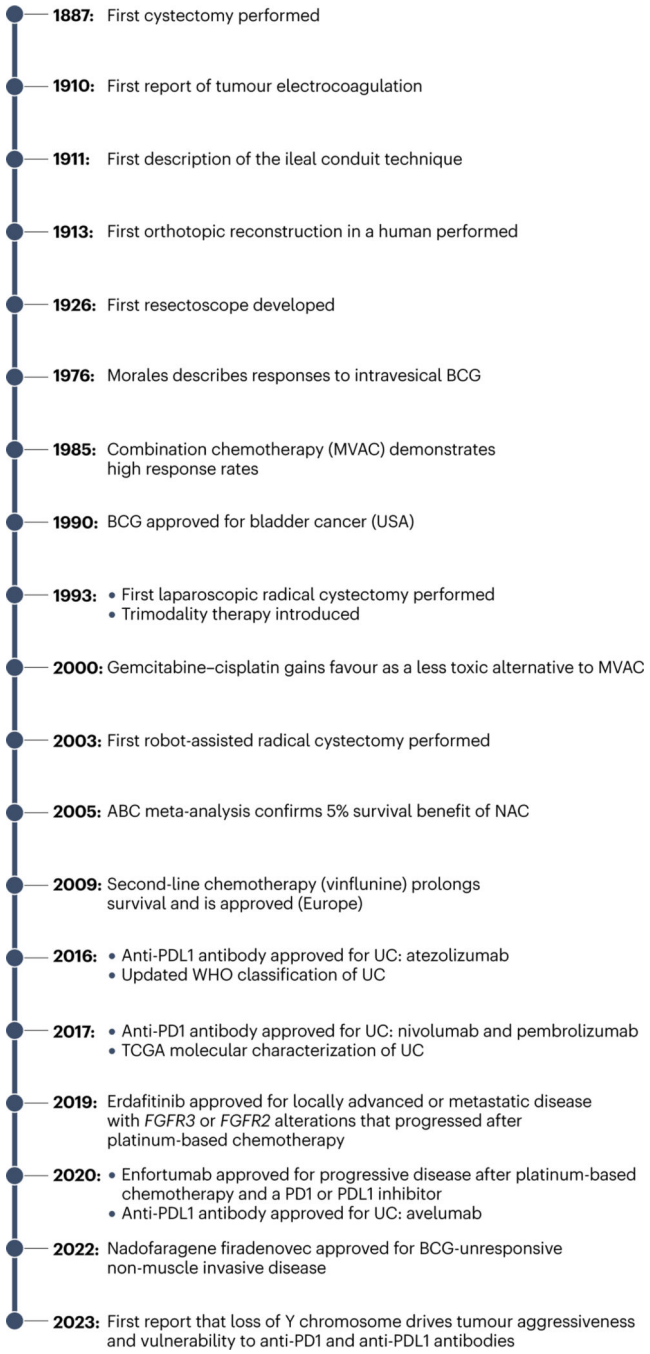

Fig. 6 |. Landmarks in understanding, diagnosis and treatment of bladder cancer.
This timeline shows seminal developments in bladder cancer, highlighting clinical, scientific and technical advances that have changed or will change clinical practice or scientific thinking in the field[51,130,233,271,277,285,287,289,293,324–332]. BCG, Bacillus Calmette–Guérin; MVAC, methotrexate, vinblastine, doxorubicin plus cisplatin; NAC, neoadjuvant chemotherapy; TCGA, The Cancer Genome Atlas; UC, urothelial carcinoma.

Table 1 |

Oncogenes activated in bladder cancer

Gene	Chromosome	Frequency (%)			Alteration	Functions affected
		Ta	T1	T2+		
TERT	5p15	70–80	70–80	70–80	Point mutation	Senescence and other functions
FGFR3	4p16	80	30	10–15	Point mutation	RAS–MAPK signalling
		70–80	50–60	40	Upregulated expression	
PIK3CA	3q26	40	20	20	Point mutation	PI3K signalling
HRAS and *KRAS*	11p15 and 12p12	10–15	10–15	10–15	Point mutation	RAS–MAPK and PI3K signalling
ERBB2	17q12	≤2	10–15	10–15	Mutation or amplification	RAS–MAPK and PI3K signalling
ERBB3	12q13	≤2	10–15	10–15	Mutation	RAS–MAPK and PI3K signalling
EGFR	7p12	≤2	≥2	11	Amplification	RAS–MAPK and PI3K signalling
PPARG	3p25	≤2	10	15	Amplification	PPARG signalling
		≤2	9	3	Mutation	
RXRA	9q34	2	5	6	Mutation	PPARG signalling
E2F3	6p22	≤2	5–10	10–15	Amplification	Cell cycle regulation
MDM2	12q15	0	5–15	5–15	Amplification	Cell cycle regulation
CCND1	11q13	≤2	10	10	Amplification	Cell cycle regulation
CCNE1	19q12	≤2	≤2	10	Amplification	Cell cycle regulation

Genes with activating mutations or high-level DNA amplification in >10% of at least one bladder cancer stage are shown. If very low frequencies have been found in stage Ta tumours but samples were too few for accurate estimation, ≤2% is shown. Adapted from ref. 319, Springer Nature Limited.

Table 2 |

Genes commonly inactivated by mutation in bladder cancer

Gene	Chromosome	Frequency (%)			Alteration	Functions affected
		Ta	T1	T2+		
CDKN2A	9p21	30	60	60	Loss of heterozygosity, deletion	Cell cycle
		≤2	12	22	Homozygous deletion	
		1	7	7	Mutation	
RB1	13q14	0	14	17	Inactivating mutation	Cell cycle
ATM	11q22	12	16	14	Inactivating mutation	Cell cycle
CDKN1A	6p21	11	11	9	Inactivating mutation	Cell cycle
TP53	17p13	4	24	48	Inactivating mutation	Transcription
ELF3	1q32	8	22	12	Inactivating mutation	Transcription
ZFP36L1	14q24	12	11	6	Inactivating mutation	Transcription
KDM6A	Xp11	40	40	26	Inactivating mutation	Chromatin regulation
KMT2D	12q13	35	27	28	Inactivating mutation	Chromatin regulation
CREBBP	16p13	23	20	12	Inactivating mutation	Chromatin regulation
KMT2C	7q36	23	14	18	Inactivating mutation	Chromatin regulation
STAG2	Xq25	30	9	14	Inactivating mutation	Chromatin regulation
ARID1A	1p36	11	27	25	Inactivating mutation	Chromatin regulation
KMT2A	11q23	11	15	11	Inactivating mutation	Chromatin regulation
EP300	22q13	15	11	15	Inactivating mutation	Chromatin regulation
ASH1L	1q22	10	12	7	Inactivating mutation	Chromatin regulation
ARID2	12q12	7	11	8	Inactivating mutation	Chromatin regulation
ERCC2	19q13	4	24	18	Inactivating mutation	DNA repair
BRCA2	13q13	10	10	9	Inactivating mutation	DNA repair
PTEN	10q23	7–12	20–30	50	Loss of heterozygosity, deletion, mutation	Regulator of AKT signalling
TSC1	9q34	12	15	8	Inactivating mutation	Regulator of mTOR signalling
RBM10	Xp11	7	13	5	Inactivating mutation	RNA splicing

Genes affected in >10% of at least one bladder cancer stage are shown. Large genes not formally identified as significantly mutated or with unknown function are not listed.

Table 3 |

New systemic therapies for metastatic bladder cancer

Drug	Mechanism of action	Evidence	Select adverse events
Erdafitinib	Small-molecule inhibitor of fibroblast growth factor receptor 3	In a phase II study of patients with *FGFR3*-mutated metastatic urothelial cancer progressing despite prior platinum-based chemotherapy, erdafitinib demonstrated an objective response rate of 42%[320]	Hyperphosphataemia, stomatitis, hand–foot syndrome as well as ocular disorders such as central serous retinopathy
Enfortumab vedotin	Antibody–drug conjugate comprised of a monoclonal antibody directed against nectin 4 linked to a monomethyl auristatin E payload	The phase III EV-301 trial[321] randomized patients with metastatic urothelial cancer progressing despite prior platinum-based chemotherapy and PD1 or PDL1 blockade to treatment with enfortumab vedotin versus standard chemotherapy (docetaxel, paclitaxel or vinflunine); the trial demonstrated an improvement in overall survival with enfortumab vedotin versus chemotherapy (HR 0.70, 95% CI 0.56–0.89; $P = 0.001$); the combination of enfortumab vedotin plus pembrolizumab has been explored as first-line treatment in cisplatin-ineligible patients with metastatic urothelial cancer[322], yielding a 73% response rate	Peripheral neuropathy, hyperglycaemia, rash
Sacituzumab govitecan	Antibody–drug conjugate comprising a monoclonal antibody directed against TROP2 linked to the topoisomerase I inhibitor SN-38 payload	A large phase II trial demonstrated an objective response rate of 27% with sacituzumab govitecan in patients with metastatic urothelial cancer progressing despite prior platinum-based chemotherapy and PD1 or PDL1 immune-checkpoint inhibition[323]	Diarrhoea, neutropenia

New systemic therapies that have received regulatory approval in at least one region of the world are shown.