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Perspective

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The sex gap in bladder cancer survival — a missing link in bladder cancer care?

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Abstract

The differences in bladder cancer outcomes between the sexes has again been highlighted. Uncommon among cancers, bladder cancer outcomes are notably worse for women than for men. Furthermore, bladder cancer is three to four times more common among men than among women. Factors that might explain these sex differences include understanding the importance of haematuria as a symptom of bladder cancer by both clinicians and patients, the resultant delays in diagnosis and referral of women with haematuria, and health-care access. Notably, these factors seem to have geographical variation and are not consistent across all health-care systems. Likewise, data relating to sex-specific treatment responses for patients with non-muscle-invasive or muscle-invasive bladder cancer are inconsistent. The influence of differences in the microbiome, bladder wall thickness and urine dwell times remain to be elucidated. The interplay of hormone signalling, gene expression, immunology and the tumour microenvironment remains complex but probably underpins the sexual dimorphism in disease incidence and stage and histology at presentation. The contribution of these biological phenomena to sex-specific outcome differences is probable, albeit potentially treatment-specific, and further understanding is required. Notwithstanding these aspects, we identify opportunities to harness biological differences to improve treatment outcomes, as well as areas of fundamental and translational research to pursue. At the level of policy and health-care delivery, improvements can be made across the domains of patient awareness, clinician education, referral pathways and guideline-based care. Together, we aim to highlight opportunities to close the sex gap in bladder cancer outcomes.

Sections

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Introduction

Bladder cancer is the tenth most common cancer worldwide and is responsible for 3% of annual cancer diagnoses and 2.1% of cancer-related deaths[1]. Most patients (75–80%) present with non-muscle-invasive bladder cancer (NMIBC; stages Ta, T1 and Tis); up to 80% of these patients will experience recurrence[2], and up to 44% will progress to muscle-invasive bladder cancer (MIBC; stages T2–T4)[2–4]. Moreover, of the 20–25% of patients initially diagnosed with MIBC, around one-quarter will have incurable, locally advanced or metastatic disease[5]. Thus, muscle invasion is a crucial step in the disease course, having a 5-year survival of only 27–50%, despite radical therapies[3].

The number of incident bladder cancer cases continues to increase, although age-standardized incidence and mortality seem to be decreasing, paralleled by a reduction in smoking-related disease[6]. Smoking is the largest modifiable risk factor for bladder cancer, with exposure to occupational carcinogens also well documented[7]. However, sex is the largest risk factor for bladder cancer, with men three to four times more likely to be diagnosed with bladder cancer than women[8,9]. Furthermore, no clear indication exists of the differential effects of smoking between men and women[10]. Nonetheless, women tend to have more aggressive tumours at diagnosis and experience worse outcomes thereafter than men[11–15].

Bladder cancer that is muscle invasive or metastatic at presentation contributes the most considerable morbidity and mortality, whereas the surveillance of NMIBC means that bladder cancer is one of the most expensive cancers to treat per patient[16]. Thus, identifying and filling the sex-based gaps in our understanding and care for all patients with bladder cancer are required.

In this Perspective, we review the differences in outcomes between men and women with bladder cancer, discuss our current understanding of these differences and propose solutions to pursue (Box 1). These differences are important given the burden of bladder cancer on patients and health-care systems.

Sex differences in outcomes

Data regarding cancer survival in England (cancers diagnosed from 2015 to 2019, monitored to 2020 (ref. 17)) seem to expose the persistent sex gap in survival for patients with bladder cancer. Across all stages of bladder cancer and for 1-year, 2-year, 3-year and 4-year survival, women had worse outcomes than men (Fig. 1). With some 3-year and 4-year stage-specific survival data missing for women only, a knowledge deficit might already be apparent. Notwithstanding this possibility, using an overlapping dataset available for T1–T4 tumours treated from 2013 to 2019, analyses of overall survival for patients with urothelial cancer in England also illustrate a similar situation[18] (Fig. 2). Beyond the UK, such gaps in outcomes continue to be highlighted internationally[19–23] (Box 1).

This phenomenon is neither new nor unexplored[19,22], yet it remains unexplained worldwide. Moreover, these findings in bladder cancer are the inverse of the situation for most cancer sites, in which cancer outcomes are commonly worse for men than for women[24]. Previous European data from 1999 to 2007 also showed reduced bladder survival among women, driven by differences in Northern and Central European countries and the UK[25]. Subsequent data from the Netherlands also mirror the UK data[26]. However, results of other studies have shown no differences in treatment or cancer-specific survival[27]. Results of a 2022 systematic review and meta-analysis showed that that female sex was associated with worse cancer-specific survival and overall survival in patients with MIBC, but no differences were apparent in the relatively lower number of studies with sex-specific outcomes for NMIBC[28]. Concordant with the NHS results, this observation suggests that sex differences in survival are principally driven by patients with non-metastatic MIBC at presentation, or those who progress to develop MIBC.

Possible reasons for outcome differences

The possible explanations for the observed differences in outcomes are complex — the interplay of the signs and symptoms of the disease, the speed of referral into the bladder cancer diagnostic pathway, treatment decisions, treatment responses and biology[29]. Improving understanding of the weight and relevance of each of these factors is important in order to take concrete steps to further investigate and potentially close the apparent gap in overall outcomes (Box 1).

Recognizing the importance of haematuria

Women might not recognize the importance of haematuria in a disease for which the preponderance is 3:1 men to women, or might not seek investigation as early[21]. Haematuria is the most common symptom of bladder cancer[2]. However, from a young age, women are much more likely to present with a urinary tract infection (UTI) than men[30] and have associated haematuria in some instances[31]. This occurrence can desensitize both patients and clinicians to this symptom, meaning that they do not recognize the importance of haematuria, particularly in older women at an increased risk of bladder cancer[31].

Referral for investigations

Once haematuria has been identified as a potential symptom of bladder cancer, prompt referral according to guidelines is needed[32]. The preponderance of haematuria related to UTI in women can result in delays in diagnosis, as reported internationally, women presenting with haematuria to their primary care provider are not referred for subsequent investigations as rapidly as men or are investigated less thoroughly[21,29,31,33–36]. Indeed, women were found to experience a significantly higher number of pre-referral consultations than men when presenting with haematuria, with 27% of women requiring three or more consultations compared with only 11% of men requiring the same ($P < 0.001$)[33].

Treatment decisions

In the setting of NMIBC, sex does not seem to influence the use of adjuvant intravesical therapy[37], or the choice of radical treatment for MIBC[38–40], and, in terms of overall treatment paradigms, recommendations do not differ between sexes. The use of continent urinary diversions seems to be lower in women with bladder cancer than men[41,42], but this difference does not alter survival outcomes. This observation might reflect increased rates of tumours of an advanced stage in women and also potential differences in training and practice patterns, with fewer centres worldwide equally comfortable with performing orthotopic continent diversion in women as they are in men, given anatomical and surgical differences pertinent to differences in tumour stage. However, for women undergoing radical cystectomy (which typically involves removal of the uterus, fallopian tubes, ovaries and anterior vaginal wall[3,43]) and bladder substitution, preservation of the uterus and attempted nerve sparing seem to result in better functional outcomes than non-organ-sparing approaches[44]. However, considerable gaps remain in the adoption of female reproductive organ-sparing and nerve-sparing radical cystectomy techniques for patients with organ-confined disease[45]. With emerging data from large series supporting the low rate of female reproductive organ involvement at the

time of radical cystectomy (4.2–5.7%)[46,47], potential sex disparities seem to exist, driven by provider expertise and preference. These disparities might need to be addressed through training and/or the refinement or centralization of specific provider expertise.

Treatment efficacy

Evaluating whether women with bladder cancer derive less benefit from current treatments than men is difficult to dissect and could, in part, be driven by biological and anatomical reasons. Women present with a worse disease stage[9,35,40,48] and more often with non-urothelial tumour histology[9,20,49] than men, therefore, contextualizing subsequent sex-specific treatment responses. In one study including 24,169 patients with bladder cancer in the Netherlands, in the first 2 years after diagnosis, excess mortality for women was higher than for men, but lower thereafter[9]. This observation applied to patients with NMIBC or MIBC, and baseline differences in age, stage, and histology accounted for only part of the excess mortality gap[9]. Similar findings were reported for patients undergoing bladder preservation (trimodality therapy) for T2–T4a N0 M0 MIBC[50]. In 47,229 patients with MIBC in the USA, increased 90-day mortality following radical cystectomy and reduced overall survival was identified in female patients[39]. Worse cancer-specific survival in women than in men following radical cystectomy[38,48], or both worse cancer-specific and overall survival, have also been reported[11,51]. However, other research suggests that increased uptake of neoadjuvant chemotherapy diminishes these sex differences[52]. Such data might indicate that if sex differences in outcomes are attenuated in patients fit enough for chemotherapy, then, simply by selection bias, similar outcomes could also be expected in the generally fitter patients enrolled in clinical trials. In the radiotherapy setting, unpublished data from Manchester, UK, regarding 209 patients with MIBC treated using radiotherapy with concurrent carbogen and nicotinamide (the BCON protocol[53]) show no difference in 5-year cancer-specific survival between men and women (A.C., unpublished data).

In addition to overall survival data, conflicting data show the potential sex differences in response to specific treatments for bladder cancer[54]. Evaluating response to intravesical treatment for NMIBC, results (summarized in a 2018 meta-analysis and systematic review[55]) suggest that women have poorer responses to BCG than men. However, publication bias towards studies reporting a sex-based difference seems to be evident from this meta-analysis and, therefore, doubt exists as to the conclusions suggesting differential responses in NMIBC to BCG between sexes[55]. In line with this suggestion, results from two large contemporary cohorts of patients with NMIBC treated with BCG did not show any sex differences in outcomes of recurrence-free survival or progression-free survival[56,57]. Furthermore, the literature suggests no sex differences in response to intravesical chemotherapy for NMIBC[55].

For advanced bladder cancer, accumulating evidence does not suggest that sex-based differences exist in disease response to immune checkpoint blockade (ICB), including the sex-based analyses presented in KEYNOTE-052 (ref. 58), KEYNOTE-361 (ref. 59) and IMvigor130 (ref. 60). Moreover, the best available data do not suggest sex-specific differences in response to chemotherapy and that women with metastatic urothelial cancer tolerate cisplatin-based chemotherapy in a similar manner to men and experience comparable clinical outcomes[61]. Biological tumour differences and stage differences in presentation confound these studies, which together suggest that, stage-for-stage, treatment responses remain generally similar between men and women. Hence, regional or treatment-specific circumstances might exist in which sex does not seem to be a prognostic factor.

Box 1

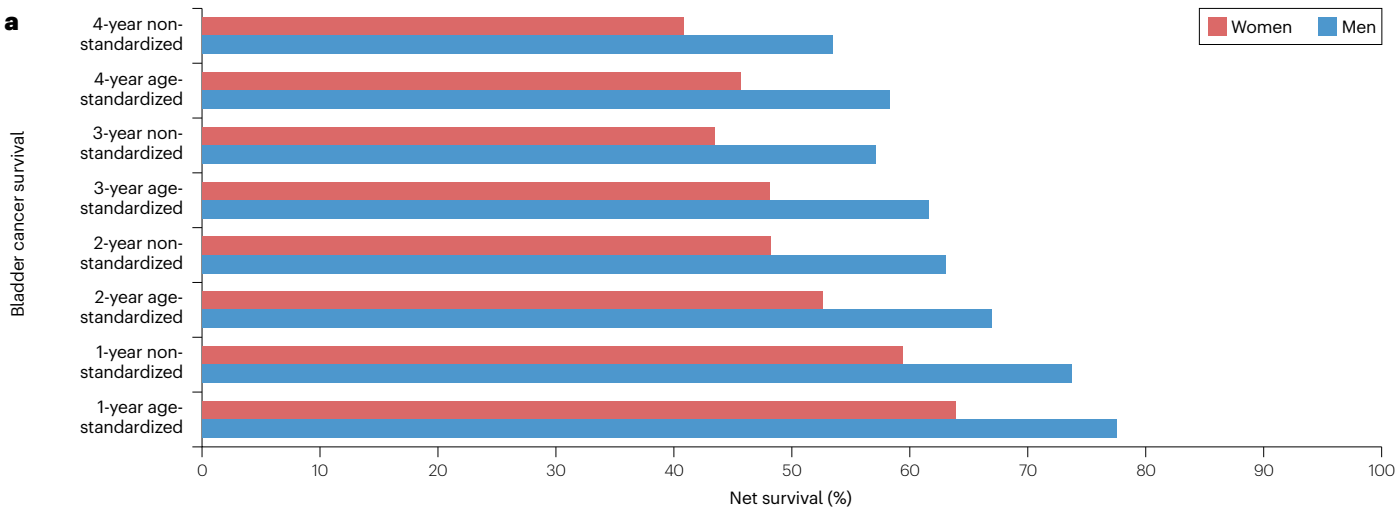
Key aspects of the sex gap in bladder cancer

- Bladder cancer is a common malignancy with a 3–4:1 preponderance in men, suggesting relative 'resistance' to the development of the disease in women compared with men. Environmental exposures, hormone signalling, gene expression, immunology and the tumour microenvironment probably coalesce to underpin this sexual dimorphism.
- Bladder cancer outcomes are considered to be notably worse for women than for men, but this finding is not consistent across territories and treatment modalities, suggesting the considerable influence of health-care system factors on outcomes. Such factors might include diagnostic delays and discrepancies in the appropriate and timely use of guideline-based care.
- Addressing health-care system factors by the implementation of best practices for referral, diagnosis and treatment could provide rapid improvements in outcomes for which deficiencies exist.
- The biological phenomena driving the sexual dimorphism in disease incidence are likely to also influence treatment responses, and improved understanding of these mechanisms through carefully designed fundamental research, and preclinical and clinical studies, might reveal sex-specific biomarkers or treatment approaches to benefit all patients with bladder cancer.

Biological and anatomical phenomena

Thorough assessment of the fundamental sex differences in urothelial transformation and subsequent cancer biology has been undertaken in few studies — the interplay of sex hormones, environmental exposures, microenvironment, microbiome, immunology and genomics are important and highly complex[19,22]. The laboratory studies available to date provide some insights into potential drivers of biological differences in bladder tumours that might also drive differences in outcomes between men and women (Box 1).

Sex hormones. Knockout studies in mice suggest that the androgen receptor (AR) in the urothelium is important for urothelial carcinogenesis[62,63]. Furthermore, oestrogen receptor-α (ERα)-knockout and oestrogen receptor-β (ERβ)-knockout mice experiments suggest that ERα has a protective role against bladder cancer initiation and progression, whereas ERβ could promote bladder cancer[64–66]. These results from mice are consistent with immunohistochemical studies demonstrating downregulated ERα expression in high-grade and high-stage bladder tumours[67] and upregulated ERβ and aromatase protein expression in high-grade and aggressive bladder tumours[67–70]. Using the 'four cores genotypes' mouse model, which decouples chromosomal and gonadal sex, researchers found that gonadal sex (that is, hormonal exposure) had the single largest influence on chemically induced bladder tumour development[71];


a
Bladder cancer survival
4-year non-standardized
4-year age-standardized
3-year non-standardized
3-year age-standardized
2-year non-standardized
2-year age-standardized
1-year non-standardized
1-year age-standardized
Women
Men
0
10
20
30
40
50
60
70
80
90
100
Net survival (%)

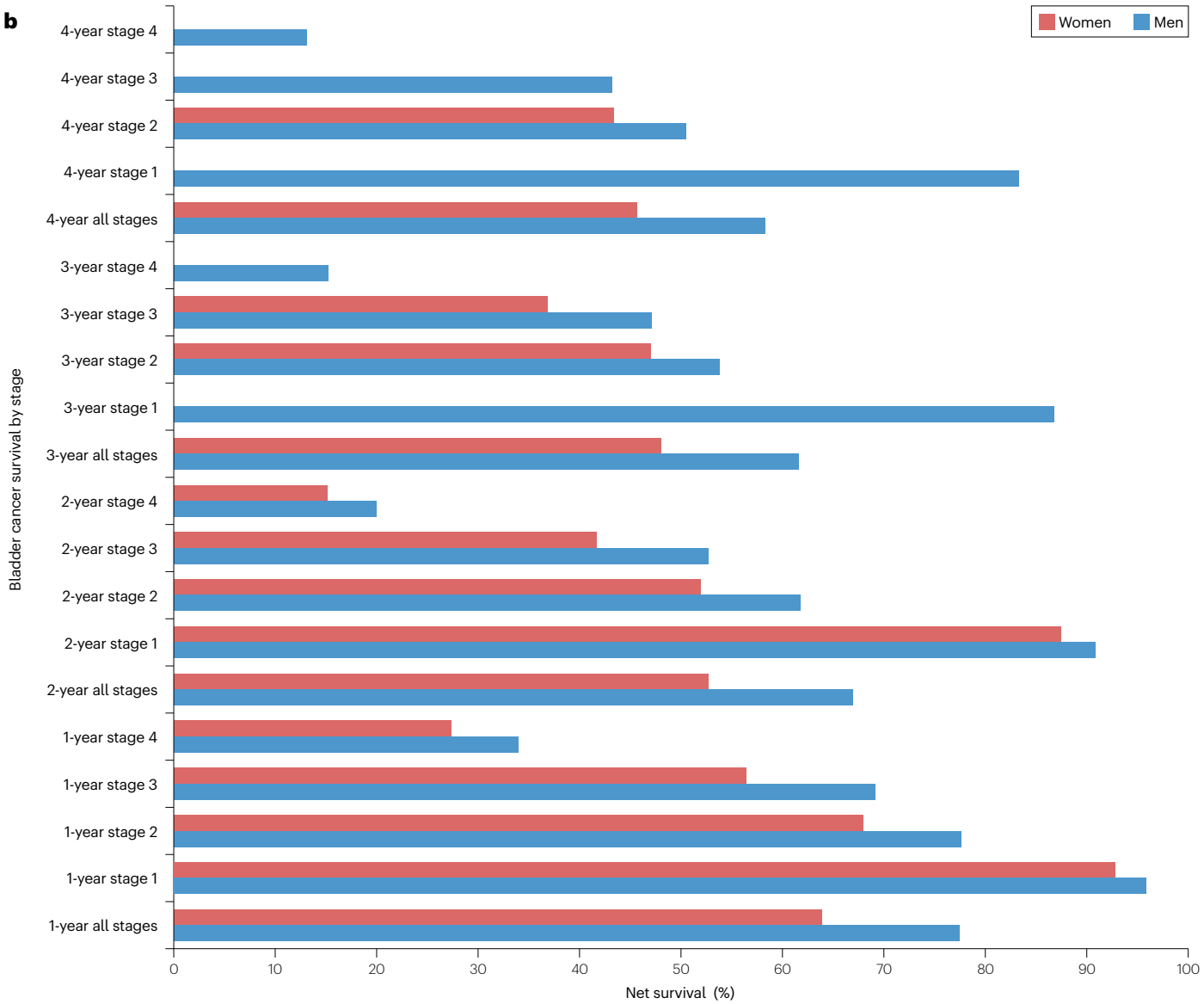

b
Bladder cancer survival by stage
4-year stage 4
4-year stage 3
4-year stage 2
4-year stage 1
4-year all stages
3-year stage 4
3-year stage 3
3-year stage 2
3-year stage 1
3-year all stages
2-year stage 4
2-year stage 3
2-year stage 2
2-year stage 1
2-year all stages
1-year stage 4
1-year stage 3
1-year stage 2
1-year stage 1
1-year all stages
Women
Men
0
10
20
30
40
50
60
70
80
90
100
Net survival (%)

Fig. 1 | 1-year, 2-year, 3-year and 4-year bladder cancer survival (%) for adults (aged between 15 and 99 years) diagnosed in England from 2015 to 2019, followed until to 2020 (ref. 17). a, Age-standardized and non-age-standardized net survival (%) by sex. **b**, Age-standardized net survival (%) by stage and sex. 3-year stage 1, 3-year stage 4, 4-year stage 1, 4-year stage 3 and 4-year stage 4 data are all missing for women. Age-standardization represents a weighted average of mortality for each sex based on the International Classification of Survival Standard.

however, chromosomal sex also independently influenced tumour development[71].

Sex steroids have direct effects on the activity and function of various subsets of innate and adaptive immune cells and are known to contribute to immunological differences between sexes[72]. The role of systemic hormones in the incidence and progression of bladder tumours remains incompletely defined, particularly in women. Epidemiological studies of bladder cancer among women suggest an increased age at menopause, parity (versus nulliparity) and use of hormone-replacement therapy could be associated with decreased bladder cancer incidence[73–77]. However, results of a meta-analysis of 12 studies including 3,719 patients with bladder cancer suggested that the age of menarche does not affect the risk of bladder cancer in women[78], and so a need for clarification remains owing to inconclusive evidence.

Genomics. The genomic and molecular understanding of bladder cancer has advanced in the past few years[79–83]. MIBCs are heterogeneous[84] and characterized by many single-nucleotide variants and copy number variants[79,85,86]; loss of multiple tumour suppressors and alteration of multiple pathways are common[81,82]. Currently, six consensus gene expression-based subtypes of MIBC are recognized and share some characteristics[81], but remain heterogeneous with respect to genomic aberrations and behaviour; temporal and spatial plasticity in subtype has also been reported[87] (Table 1). NMIBC is arguably more complex than MIBC[82,83], comprising multiple grades of disease[88].

Within this landscape, bladder cancers (alongside other cancers) demonstrate extensive sex-biased molecular signatures, with sex-biased expressed genes enriched in the sex chromosomes and evidence of sex-biased DNA methylation patterns (such as *TOP2B*)[89]. Sex-biased pathways include those related to immune responses, apoptosis and the cell cycle, metabolism, DNA repair and p53 pathways[89]. Furthermore, *KDM6A* alterations are common in bladder cancer (24–33%[79,83]) with the gene functioning as an epigenetic regulator of downstream gene expression; importantly, *KDM6A* escapes X chromosome inactivation[19]. Loss of *Kdm6a* increases bladder cancer risk in female mice, and mutation or reduced expression of human *KDM6A* is associated with poor prognosis in women with bladder cancer[71]. Other research has suggested a higher rate of *KDM6A* mutations in NMIBCs from women than in those from men[90].

Histopathology and molecular pathology. In bladder cancer pathology, several notable differences exist between the sexes. Results of a review of >27,000 patients in the National Cancer Database in the USA showed that women have more non-urothelial carcinomas than men (15.1% versus 9.9%), with squamous carcinoma the predominant histology[49]. Similarly, UK national data from >100,000 patients with T1–T4 bladder cancer demonstrated that women had more non-urothelial cancer than men (27% versus 16%)[91]. For MIBC, women seem to have an increased proportion of tumours with a basal molecular subtype, whereas men have an increased proportion of luminal papillary and neuro-endocrine-like subtypes[92]. However, an analysis of NMIBC did not show differences in molecular subtypes according to sex[93].

Tumour immunology and microenvironment. The wide repertoire of immunomodulatory agents used across stages for the treatment of bladder cancer, including in clinical trials, means that the contribution of sex-specific immunological and microenvironmental factors is likely to be clinically important. Such factors can include genetic, epigenetic and transcriptional effects[89], which could relate to XX and XY chromosomal differences[94], as well as hormonal effects[95]. Several preclinical and clinical studies highlight these factors and provide some explanation for the divergent observations of an increased incidence of bladder cancer in men yet inferior survival outcomes in women.

Studies of bladder tumour AR expression do not show sex-based differences[96]. However, a fascinating androgen-driven mechanism of T cell exhaustion has been described in bladder cancer[95]. These insights provide some explanation for why spontaneous rejection of early immunogenic bladder tumours is less common in men than in women, and hence the male predisposition for the development of bladder cancer. In this study, three different bladder tumour models were evaluated, MB49 (transplantable syngeneic tumours), BBN (carcinogen-induced tumours) and BKL171, in which BBN-induced tumours develop in a testis-bearing mouse with an XX chromosome to eliminate any immune response to male-specific minor antigens. More aggressive tumour growth in male mice than in female mice was demonstrated with these three models[95]. This effect was eliminated using *Tcrb*/*Tcrd*-knockout or *Rag2*-knockout mice, which specifically lack T cells, and reinstated with adoptive transfer of $CD8^+$ T cells. A twofold higher frequency of polyfunctional $CD8^+$ T cells able to produce interferon-γ (IFNγ), tumour necrosis factor (TNF) and granzyme B (Gzmb) was seen in MB49 tumours of female than of male mice at day 9 of tumour growth. Collectively, these results demonstrate more effective immune-mediated tumour control in female than in male mice.

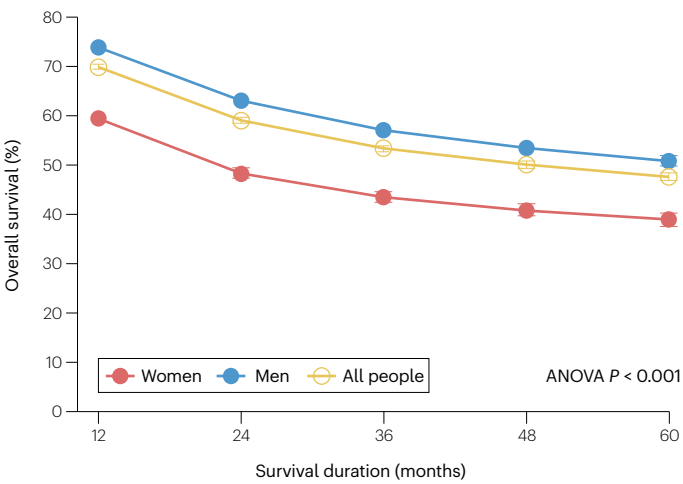


Fig. 2 | Overall survival for patients with T1–T4 bladder cancers treated in England from 2013 to 2019, plotted using the Kaplan–Meier method with respect to sex. Reprinted from ref. 18, CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/).

Table 1 | Summary of the main characteristics of the consensus classes of muscle-invasive bladder cancer

Class name	Percentage of MIBC	Oncogenic mechanisms	Mutations	Clinical characteristics	Median overall survival (years)
Luminal papillary	24%	*FGFR3*+ *PPARG*+ *CDKN2A*–	*FGFR3* (40%) *KDM6A* (38%)	T2 stage+	4.0
Luminal non-specified	8%	*PPARG*+	*ELF3* (35%)	Older patients+(80+ years)	1.8
Luminal unstable	15%	*PPARG*+ *E2F3*+ *ERBB2*+ Genomic instability Cell cycle+	*TP53* (76%) *ERCC2* (22%) TMB+ APOBEC+	NR	2.9
Stroma-rich	15%	NR	NR	NR	3.8
Basal/squamous	35%	*EGFR*+	*TP53* (61%) *RB1* (25%)	Women+T3 or T4 stage+	1.2
Neuroendocrine-like	3%	*TP53*– *RB1*– Cell cycle+	*TP53* (94%) *RB1* (39%)	NR	1.0

MIBC, muscle-invasive bladder cancer; NR, not reported; TMB, tumour mutational burden. Adapted with permission from ref. 81, Elsevier.

In support of these observations, use of single-cell RNA sequencing enabled identification of increased effector-like CD8$^+$ T cells in the female versus male mouse tumour microenvironment (TME). By contrast, the male TME was enriched for progenitor exhausted CD8$^+$ tumour-infiltrating lymphocytes, as defined by their stem-like genetic profile (such as TCF1/*Tcf7*$^+$). These tumour-infiltrating lymphocytes showed accelerated progression to terminally differentiated TCF1$^-$ TIM3$^+$ exhausted T cells incapable of restimulation. In keeping with these results, male mice with loss of AR exclusively in CD8$^+$ T cells were equally protected against cancer as female mice. Finally, a negative correlation was observed between type I interferon signalling and AR activity in T cells; the authors suggested that this balance could underlie sexual dimorphism in cancer immunity, whereby AR-specific T cell reprogramming may tilt CD8$^+$ T cells towards progenitor exhausted states and away from the effector CD8$^+$ T cell states typically associated with interferon signalling. Insights from this study are corroborated by observations that androgen deprivation therapy can promote responses to ICB[96,97]. Furthermore, results of one study has highlighted the frequency of loss of the Y chromosome in male patients with bladder cancer, with a resultant and striking dysfunction or exhaustion of CD8$^+$ T cells in the TME accompanied by an increased response to anti-PD1 ICB therapy[98]. These results show that cancer cells with loss of the Y chromosome mutations alter T cell function, promoting T cell exhaustion, and sensitizing them to PD1-targeted immunotherapy[98]. However, other important T cell populations, including CD4$^+$ T cells, are also known to be important in bladder cancer immunology[99], and so other sex-specific mechanistic insights into T cell biology, beyond the CD8$^+$ T cell-specific biology, are likely to be uncovered in the future.

Studies to explore a biological basis for different responses to bladder cancer therapy have yielded interesting results. An analysis of the whole transcriptomes of 460 tumours from the UROMOL cohort, together with multiplex immunofluorescence of tumours from the Kingston Health Services Centre cohort (n = 332, 22% female)[100] showed increased expression of the immune checkpoint genes *CTLA4*, *PDCD1*, *LAG3* and *ICOS* in high-grade tumours from women compared with high-grade tumours from men or low-grade tumours from either sex. In addition, increased expression of CXC ligand 13 (*CXCL13*, an important B cell-recruiting chemokine) and the B cell surface-associated molecule *CD40* were seen more frequently in high-grade tumours from women than in those from men. Increased infiltration of CD163$^+$ M2-like tumour-associated macrophages (TAMs) was also observed in both low-grade and high-grade NMIBC tumours from women compared with those from men[100]. As CD163$^+$ TAMs are typically tumour promoting, this observation might provide a mechanistic basis for inferior therapy responses in NMIBC arising in women versus men. Of further clinical relevance, increased density of CD163$^+$ M2-like TAMs and CD79a$^+$ B cells was independently associated with reduced recurrence-free survival across all high-grade tumours in the Kingston Health Services Centre cohort, supporting a functional relevance of this sexually dimorphic observation. Together, these findings suggest that the TME of NMIBC from women tends towards increased immune exhaustion in which immune dysfunction is accentuated by reciprocal communication between increased immunosuppressive macrophage and B cell populations.

Research findings also indicate that oestrogen inhibits IL-6 and, therefore, decreases the expression of receptor complexes required for BCG adherence to urothelial cells, such as integrin α5β1 (refs. 101,102). A therapeutic strategy combining the anti-oestrogen therapy ICI 182780 with BCG was shown to improve treatment efficacy in in vitro and in vivo preclinical systems, in part via enhancing TNF signalling[103]. Furthermore, the immune checkpoint inducible T cell costimulator (ICOS) shows greater upregulation in whole blood following stimulation of healthy women than of healthy men treated with BCG[104]. However, these findings require careful interpretation in view of the considerable immunological differences between post-menopausal women and younger healthy volunteers. Overall, a current key research gap is to understand the sex-specific longitudinal innate and adaptive immune changes that occur both intra-tumourally and systemically over the months to years following BCG treatment, including how these relate to a differential therapeutic response.

Immunological ageing or immunosenescence is known to have sex-specific biological characteristics[105]. In a study in which bulk RNA sequencing was used, enrichment of B cell function-associated pathways was shown in bladders from aged healthy female mice versus those from their aged male counterparts[106]. Multiplex immunofluorescence showed an increased number of organized tertiary lymphoid structures

in the healthy bladders of female mice. Somewhat surprisingly, no difference in tertiary lymphoid structures was seen between male and female mice bladders treated with several weeks of the carcinogen BBN. Instead, an increase in plasma cells was seen in the lamina propria of female aged mice, and female mice had a more immune-infiltrated and oedematous lamina propria across ages than male mice. In combination, these studies point to sex-specific immune parameters in aged healthy bladders and bladder tumours — further research is needed to define how these differences associate with tumour control and disease-specific survival.

A difference in the response to ICB according to sex has not been clearly established in bladder cancer. However, we know that immune cell PDL1 is associated with inferior survival outcomes across sexes, and that androgen signalling in T cells represses IFNγ to limit ICB responses[97]. Furthermore, oestrogen plus a number of X-linked microRNAs, including miR-221, miR-222 and miR-106b, can regulate PDL1 expression[94,107]. Our incomplete understanding of the sex-specific immunogenomic changes underlying differential responses to ICB urgently warrants further research to optimize novel combination strategies across disease stages (Fig. 3).

Microbiome. Current research is being conducted to define whether differences in the urinary, tumoural or gut microbiome between men and women could contribute to differential outcomes[108]. Differences in the urinary microbiome might be associated with the risk of recurrent UTIs contributing to carcinogenesis, but the causal implication of potential microbiome differences in tumour progression or treatment response remains to be defined[22].

Anatomy. Anatomically, men have more outlet obstruction than women, which is related to prostatic enlargement and subsequent detrusor hypertrophy[109]. By contrast, women have thinner bladder walls than men[109], which could help to explain the higher incidence of non-organ-confined disease at diagnosis in women[48]. Differential urinary dwell times in men and women might contribute to differences in bladder cancer development, with men more commonly having

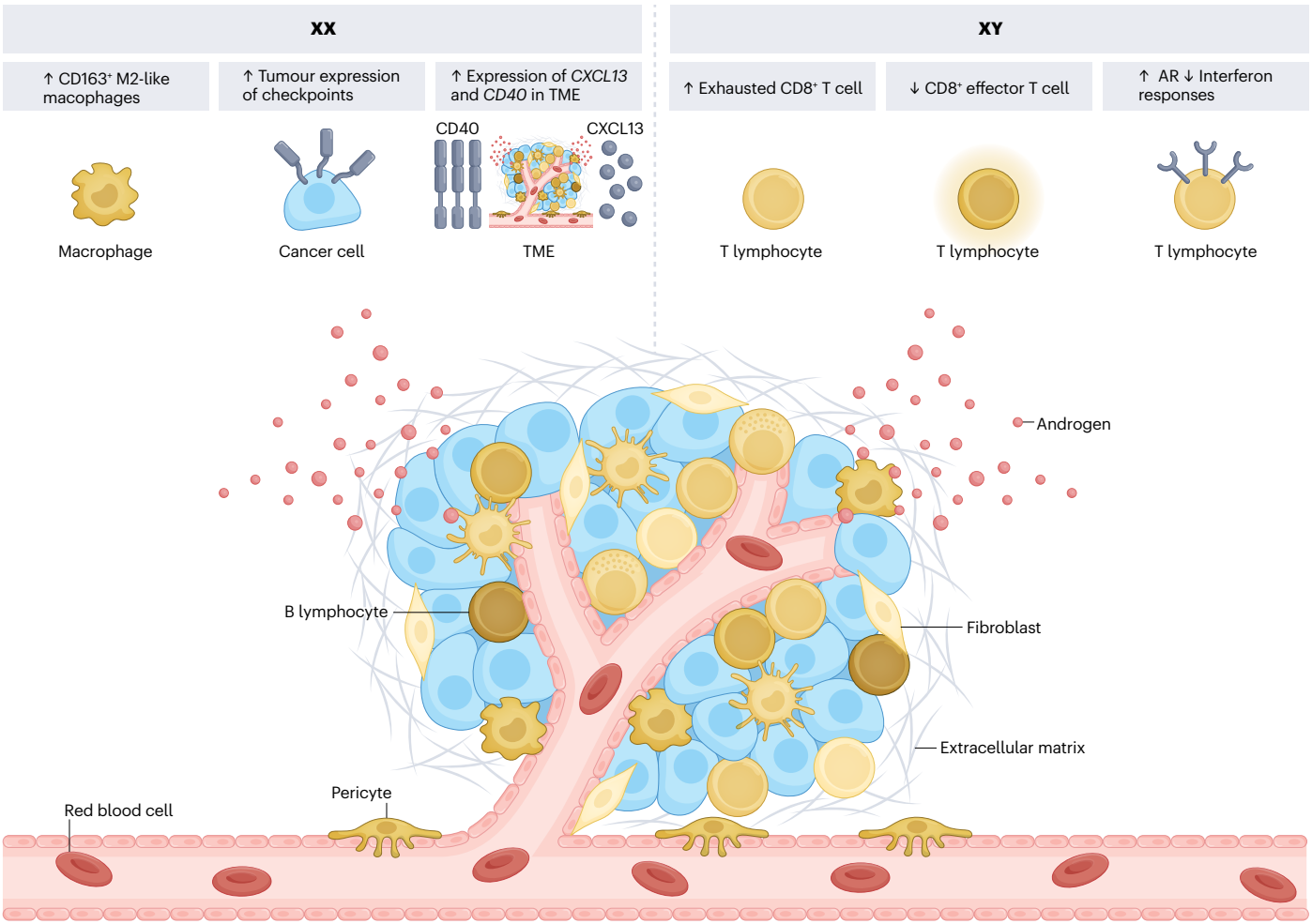


Fig. 3 | A summary of immunological sex differences in bladder cancer. The female tumour microenvironment (TME) is characterized by increased infiltration of immunosuppressive CD163⁺ M2-like macrophages and increased tumour expression of immune checkpoints. In addition, an increase in the expression of genes related to B cell recruitment (*CXCL13*) and function (*CD40*) has been shown in the female TME. By contrast, the male TME is characterized by increased exhausted CD8⁺ T cells (both of progenitor and terminally differentiated subtypes), which is driven by androgen receptor (AR) signalling specifically in CD8⁺ T cells.

Table 2 | Bladder cancer-associated phenomena that demonstrate confirmed differences between the sexes

Phenomenon	Men	Women
Incidence[1] (age-standardized rate per 100,000 persons per year)	9.6	2.4
Referral[21,29,31,33–36]	Prompt referral commonplace	Delayed referral frequent
Treatment	No differing recommendations between sexes. Differential responses potentially treatment-specific and territory-specific	
Sex hormones[62,63,67–70,73–78]	Androgens might promote carcinogenesis via the androgen receptor	Differential roles of oestrogen receptor-α and oestrogen receptor-β, equivocal role of oestrogens
Genomics[71,89,90]	Maintained *KDM6A* expression might be protective (most relevant in women). Methylation differences predominate	
Histopathology and molecular subtypes[49,91,92]	For muscle-invasive bladder cancer, urothelial cancer predominates, with increased proportion of luminal papillary and neuro-endocrine-like subtypes	For muscle-invasive bladder cancer, increased frequency of basal subtype and squamous carcinoma
Immunology and microenvironment[95,98,100]	Evidence of androgen receptor-driven T cell exhaustion. Loss of Y chromosome promoting T cell exhaustion	In non-muscle-invasive bladder cancer, immune exhaustion might result from increased immunosuppressive macrophage and B cell populations

higher post-void residuals with increased age. These differences are conceptually sound, but experimental validation remains lacking and difficult to undertake.

Possible strategies to mitigate the sex gap

Despite little difference in treatment patterns or quality measures, female sex is associated with worse overall survival among individuals with MIBC[19]. However, although the UK data[17,18] highlight a sex gap in outcomes that is most apparent for stages 2 and above (≥pT2), such differences are not uniformly reported internationally. Differences in health-care system access, cancer registry reporting, and treatment availability might explain the disparity between regions; publication bias in the available literature could also contribute to some discrepancies[110]. Given the differences in immunobiology, the reported sex differences in outcomes across patients with NMIBC or MIBC remain inconsistent and ambiguous, in contrast to the unequivocal dichotomy in incidence (Table 2). Future initiatives should focus on root causes of sex-specific differences in pathological staging and features at diagnosis[49], as well as prospectively collecting relevant data[18] — the avoidance of stage migration subsequent to symptom ignorance or delayed referral to secondary care is fundamental[111].

Increased adoption of guideline-recommended treatments (such as neoadjuvant chemotherapy, trimodality therapy and so on) could be attenuating such outcome differences between sexes. However, much work needs to be done to improve understanding of the differences in disease incidence between men and women, and the seemingly worse outcomes for women with MIBC[19,28] (Fig. 4).

Awareness of diagnostic differences between the sexes

To avoid diagnostic and referral delays, clinicians need to be aware of the differential presentations of bladder cancer between sexes. Similar situations are present in other diseases: for example, symptoms experienced during acute coronary syndrome differ between the sexes, with an increased proportion of women who present without typical chest pain[112]. This occurrence leads to improved detection in men and worse comparative survival in women presenting with acute coronary syndrome; specific awareness drives have been undertaken internationally to reduce this difference, the outcomes of which are awaited[113]. For bladder cancer, raising awareness of haematuria as a sign of bladder cancer is important. Previous work on symptom awareness (such as haematuria[114]) has suggested that mass-media campaigns combined with targeted high-intensity community-based programmes for high-risk populations (for example, those with low socio-economic status, old age, and specific racial groups) can effect change[115]. Campaigns specifically aimed at women might be required.

Overall, the importance of haematuria in both sexes should be underlined in primary care, in which most patients initially present. Primary care physician education drives, through presentations at conferences, decision support tools (DSTs) and practice-specific presentations, have been shown to improve referral rates for dementia[116] and their use for early diagnosis of bladder cancer should be investigated.

Addressing clinical and health-care system factors

Addressing health system, access and referral issues leading to stage migration and sex differences in outcomes remains important. Compared with biological differences, problems such as delay in diagnosis and suboptimal treatment are readily modifiable factors that can improve outcomes. However, understanding the severity of these problems might vary by jurisdiction. For example, in an American National Cancer Database study, women with MIBC had poorer overall survival than men, but this difference did not seem to be related to measures of treatment quality, with data suggesting lower rates of treatment delay in women[49]. However, the bladder cancer diagnostic and treatment pathway is prolonged for all patients and strategies to reduce delays are urgently needed for all patients[117,118]. Accurate diagnostic urinary biomarkers[119,120] might facilitate timely urological evaluation, and deployment in primary care could be particularly useful for the initial assessment of women presenting with haematuria.

Evidently, the relative contribution of delays in diagnosis and evaluation to differences in clinical outcomes is complex and difficult to dissect[121,122]. The data from NHS Digital (Cancer Survival in England, cancers diagnosed 2015 to 2019), although stratified by stage (Fig. 1b), do not take account of the difference in outcomes between stages T1a and T1b, T2a and T2b, and T3a and T3b, to which these factors will contribute. Similarly, the extent to which substantially increased sex differences in stage are related to biological differences, access to health care, or delays in diagnosis cannot easily be determined with the available data. Socio-economic factors influencing access to care could drive some of the differences[122]. For example, differences in the rate of MIBC at diagnosis between sexes according to Surveillance, Epidemiology, and End Results (SEER) data are strikingly greater among African Americans (30% in men versus 43% in women) than among white individuals (22% versus 25%). In addition to potential biological drivers

of these race differences, access to care is probably a major contributor based on similar data for other cancers[123]. Thus, addressing social barriers that limit access to care and timely referral is important. Bladder cancer disproportionately affects individuals with low socio-economic status and research from Canada suggests that this gap has broadened, particularly among women[124]. Similar research elsewhere can help to highlight regional and national deficiencies that can stimulate policy and funding changes at a higher level.

As part of health-care delivery, DSTs might be useful owing to their ability to be embedded within practice electronic medical systems so that they are easily accessible during consultation[125]. They can be automated to draw in background information on smoking status or family history to prompt clinicians to refer for investigation of a certain condition. In an evaluation of a seven-point checklist DST for the assessment of pigmented skin lesions, primary care physicians found such tools easy to use and particularly useful for borderline decision-making[126]. However, widespread use of DSTs relies on the levels of trust placed in the tools, compatibility of the DSTs with specific electronic care systems, and ease of use[125]. Furthermore, the ability of DSTs to affect change in cancer survival is uncertain and requires ongoing investigation. In the context of haematuria, models have been identified that could be used in primary care to guide referrals, with the potential to identify patients with visible haematuria who are at a low risk of bladder cancer and to stratify individuals who present with non-visible haematuria[127]. In a systematic review, 13 such models with good discrimination were identified for the diagnosis of bladder or kidney cancer (AUROC >0.8), although only 8 had been externally validated; all of the studies were at either a high or unclear risk of bias[127]. The authors concluded that external validations in appropriate populations were required before implementation in primary care[127].

Optimizing guideline-based care

The establishment and popularization of guidelines for the referral of women with haematuria are vital to promote standards of care for referral to cystoscopy. Accounting for different age-adjusted cancer risks, some referral guidelines for haematuria differ between men and women[128]. For example, the American Urological Association guidelines give greater weight to non-visible haematuria in men than in women during the 5th and 6th decades of life[129]. However, the relative paucity of research data to establish these recommendations and the variability of current recommendations between jurisdictions contribute to potential confusion and uncertainty among primary care providers[31].

Whether standard-of-care treatments for women with urothelial carcinoma should differ from those for men remains a challenging question, particularly as treatment patterns and practice evolve over time. Some historical data suggest that response to treatment might be inferior for women[11,15,55]. This evidence includes a meta-analysis, the results of which suggest that female sex is associated with poorer cancer-specific survival and inferior responses to BCG than male sex. For NMIBC, when evaluated critically, we believe that the most reliable and up-to-date data do not support the notion that treatment guidelines in men and women should differ. In metastatic urothelial cancer, men and women seem to have similar treatment outcomes across various studies[130]. Thus, despite the poorer outcomes reported for women with advanced bladder cancer than for men with the same, alternative standards of care are not clearly warranted.

Overall, accurate and reliable data are essential to identify the weak points in patients' journeys, for which improvements in care can translate into better outcomes. These data can be applied at both the health-system and the hospital level. Equality and diversity in recruitment to clinical trials is also essential, with appropriate instigation of meta-analyses when data gaps exist.

Harnessing biological differences to improve treatment

A meaningful assessment of the fundamental sex differences in urothelial transformation and subsequent cancer biology is challenging as it transects the complex interplay of sex hormones, environmental exposures, microenvironment, immunology, genetics and genomics, and the microbiome. Nonetheless, this research is crucial to identify specific differences that can be translated into clinical care — a call to action that has been emphasized[19]. However, in an era in which molecular classification, personalized medicines and targeted therapies are endlessly sought, this knowledge might remain years away — with studies including approximately 1 in 4 women patients, many are underpowered to answer the question of whether or not a certain biomarker or classifier or treatment is effective in women.

To address some of these challenges, designing studies accordingly is important[19]. For example, in preclinical studies, attention is needed to account for the sex of origin of cell lines and to include studies in both male and female mice. In clinical trials, reporting of results should include sex-based analyses. Furthermore, evaluating prognostic and predictive biomarkers for outcomes and response to therapy according to sex is necessary in correlative analyses of clinical trials. Notably, the recruitment of women into clinical trials is an important

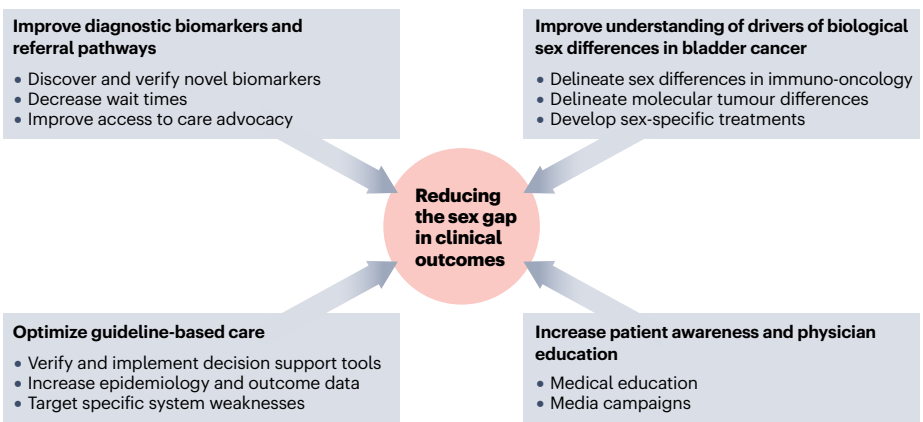


Fig. 4 | An overview of different approaches to decreasing the sex gap in bladder cancer outcomes. Each domain and sub-domain probably requires adequately powered prospective studies in order to validate and implement strategies that can reduce the sex gap in clinical outcomes.

pre-requisite for these analyses, as this has been a historical challenge. For instance, in a series of well-known trials investigating NMIBC in Spain, only 11% of all recruited patients were women[131].

Biological differences can present unique opportunities to tailor treatment according to sex. Preclinical studies suggest that alterations in sex steroids with AR antagonism could be a strategy for treating bladder tumours in men, alone or in combination with immunotherapy. Based on initial preclinical studies, AR antagonism might alter immune responsiveness to immunotherapy through alterations in the steroid milieu[96]. Hormonal differences are broadly recognized to influence the immune response[132], and AR suppressive therapy might improve bladder cancer outcomes through a hormonally mediated modulation of the TME[133]. Furthermore, a considerable amount of clinical data exists to suggest that 5α reductase inhibitors (5ARIs) could decrease the incidence and recurrence rates of low-grade bladder cancer in men. Results of a 2021 meta-analysis suggested a HR of 0.46 for recurrence for men with NMIBC receiving 5ARI therapy, and so prospective clinical trials are warranted. However, these trials should be adequately powered to avoid false negatives from the short-term evaluation of a long-acting mechanism of action[134].

Future directions

Research and advocacy are important in addressing the sex gaps in clinical care. Improved data collection on the natural history and epidemiological differences in haematuria between the sexes can drive the development of best practices and referral pathways[18]. Similarly, understanding the gaps in referral can facilitate targeted campaigns to raise awareness in both the populations at risk and their health-care providers.

At a fundamental level, many opportunities exist to expand our understanding of how sex differences affect the TME of bladder cancer and the immune interactions that contribute to anticancer activity and response to immune-targeted treatments. Understanding immune differences at the level of both urothelial and systemic interactions could facilitate increasingly effective and personalized therapies.

Clinical research is now emerging to evaluate whether sex-specific treatments are effective, such as suppression of the androgen axis in combination with existing treatments (for example, the 'BicaBCa' study, NCT05327647 (ref. 135)) in men. Further studies to target sex-specific strategies to decrease recurrences of NMIBC or progression of MIBC are similarly warranted given existing data[133], and increased reporting of sex-based analyses in clinical trials is to be welcomed. Importantly, improved awareness of the sex gap is also apparent, as illustrated by a number of presentations at the 2023 American Society of Clinical Oncology Genitourinary Cancers symposium[136,137].

Conclusions

In conclusion, addressing the sex gap in bladder cancer outcomes requires coordinated efforts to improve outcomes for women. Improved understanding of the sexual dimorphism of bladder cancer biology and immunology might enable personalized, sex-specific biomarkers. Development of sex-specific treatments through clinical trials is also needed, such as treatments targeting the androgen axis. In parallel, recognizing that implementation of best practices for referral, diagnosis and treatment of bladder cancer can provide rapid improvements in outcomes for which deficiencies exist is important. Further research is also needed to identify optimal strategies for the referral and evaluation of haematuria between sexes.

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Author contributions

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