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Bladder Cancer treatment: New advances and remaining challenges

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ABSTRACT

The rising incidence of bladder cancer has been increasingly linked to environmental changes, particularly in regions burdened by pollution. Alarmingly, there is a growing trend of early-onset, aggressive, and treatment-resistant forms of bladder cancer, underscoring the urgent need for broader clinical awareness, especially as this disease has traditionally been considered a malignancy of older adults. This shift highlights the importance of educating younger populations, as early-life exposure to carcinogens such as tobacco, vaping chemicals, and industrial toxins may predispose individuals to bladder cancer later in life. Despite medical advances, the standard treatment for bladder cancer still largely depends on systemic DNA-damaging chemotherapies, which are associated with significant adverse events, high recurrence rates, and only incremental improvements in patient outcomes. This review summarizes the recent knowledge of bladder cancer therapies, with an emphasis on the mechanisms of resistance to conventional treatments and the innovative immune checkpoint inhibitors. We also examine the exposure of high school students to chemicals from smoking and vaping as potential risk factors for bladder cancer, aiming to raise public awareness and support prevention.

INTRODUCTION

Bladder cancer is currently a malignant cancer that affects the urinary system. Bladder cancer is prevalent in the world, with over 610,000 cases and 220,000 deaths in 2022 (1), which is a remarkable 7.1% increase compared to the number of case in 2020 (2). The growing issues of bladder cancer are becoming increasingly prevalent, an estimated of 84,000 new cases have been identified in 2025 (3). Global cases of bladder cancer are projected to increase by up to 73%, with an estimated 87% rise in related deaths by 2040 (4). The current clinical view of bladder cancer expresses a growing concern, from the surges in bladder cancer cases, resulting in many ongoing advancements in diagnosis, treatment and research for bladder cancer. Currently, the main treatment method for bladder cancer is surgery and chemotherapy. Although initial treatments can suppress tumor growth, bladder cancer frequently recurs, and the cancer cells often become more aggressive and spread rapidly to other parts of the body. In fact, nearly three-quarters of bladder cancer patients experience recurrence or disease progression within ten years of the initial diagnosis (5). Recent research works advised that somatic mutations, epigenetic alterations, metabolic variations and altered tumor micro-environments contribute to the resistance of the initial chemotherapy treatments (6). For this reason, improvement of precision medication for bladder cancer

patients who carry specific mutations, epigenetic alterations, metabolic vulnerability and immune suppressive tumor microenvironment is a must. Immune checkpoint inhibitors have expanded systemic treatment options for bladder cancer (7), but response rates remain modest, and the development of resistance to immunotherapy presents ongoing challenges. Continued efforts to refine immunotherapeutic strategies and overcome resistance mechanisms will be essential for improving patient outcomes.

METHODS

A comprehensive literature search was conducted in PubMed/MEDLINE to identify studies relevant to bladder cancer with a focus on smoking/tobacco exposure, chemotherapy resistance, and the tumor microenvironment/immune evasion [**Table 1**]. Searches were limited to publications from January 1, 2007 through December 31, 2025 and used a combination of Medical Subject Headings (MeSH) and free-text terms. A core bladder cancer query was applied to all searches and then combined with theme-specific keywords using Boolean operators (AND/OR). Eligible articles included peer-reviewed original studies, systematic reviews, meta-analyses, clinical practice guidelines, and expert consensus documents that address bladder cancer risk, mechanisms of resistance to systemic therapy (including cisplatin and gemcitabine-based regimens), or immune and microenvironmental mechanisms of disease progression and treatment failure.

Eligibility criteria: Peer-reviewed publications involving human subjects were selected, including (i) original research such as observational studies, translational investigations, and clinical trials; (ii) systematic reviews and meta-analyses; (iii) clinical guidelines and expert consensus statements; and (iv) key preclinical studies directly relevant to mechanisms or therapeutic development. Studies were considered eligible if they examined at least one of the following topics: incidence or mortality trends, established or emerging risk factors, molecular alterations and pathways, tumor microenvironment or immune evasion, treatment outcomes (surgery, intravesical therapy, chemotherapy, radiotherapy), immunotherapy (including immune checkpoint inhibitors), targeted therapies/antibody–drug conjugates, biomarkers, resistance mechanisms, or ongoing clinical trials.

Exclusion criteria**:** Non peer-reviewed material (e.g., editorials without substantive synthesis, news pieces), conference abstracts without full manuscripts (except when necessary to identify ongoing trials), case reports or small case series without broader relevance, studies not primarily focused on bladder cancer, and articles with insufficient methodological detail or unclear endpoints were excluded.

Screening and selection process: Titles and abstracts were first assessed for relevance to the review scope, followed by full-text evaluation of potentially eligible papers. Reference lists of key reviews, guidelines, and landmark clinical trials were hand-searched to identify additional relevant studies not captured by keyword searching. When multiple publications described overlapping cohorts, the most comprehensive and/or most recent report was prioritized.

Table 1. Search strategy employed for literature review.

Category	Search term
Therapy strategy	"immune checkpoint inhibitor" OR "chemotherapy" OR "radiation therapy" OR "targeted therapy" AND "bladder cancer"
Clinical trial	"clinical trial" OR "NCT number" AND "bladder cancer" AND "therapy"
Mechanisms	"chemo resistance" OR "tumor microenvironment" OR "immune evasion" AND "bladder cancer"
Research paper	"target gene" OR "key molecular mechanism" AND "bladder cancer"

RESULTS

Bladder cancer can be identified by symptoms like painful or frequent urination, Fatigue and tiredness, and hematuria (8). The most common symptoms being hematuria, gross and microscopic. They are characterized in 4 stages: In situ alone, carcinoma is present in cells where it starts. Localized, the carcinoma spread contained in bladder. Regionally, the carcinoma has spread to nearby structures or lymph nodes. Distant, the carcinoma has spread to distant parts of the body like the liver (**Figure 1**) (8). Carcinoma identified bladder cancer cases can reside in Non-Muscle Invasive Bladder Cancer (NMIBC) cases, where the urothelial carcinoma is confined to the layers of the epithelial cells, around 60-70% (9). The other 40-25% cases can be identified as Muscle-Invasive Bladder Cancer (MIBC) cases, where the carcinoma begins metastasis (**Figure 1**) (10). Symptom identification early on can lead to varying survival rates, compared to identification in a later stage of bladder cancer. According to the American Cancer Society (ACS), *Cancer Facts and Figures 2025*, Carcinoma cells in situ alone show a 97% 5-year relative survival rate, the localized stage expresses a 72% survival rate, the regional stage expresses a 40% survival rate, and the distant stage expresses a 9% survival rate. Hence, prevention and early detection of bladder cancer is essential to improve the outcome of bladder cancer patients.

A. Treatment strategies for Bladder Cancer

The current standard-of-care for bladder cancer patients is listed in **Table 2**. The most common procedure for NMIBC is Transurethral resection of the bladder tumor (TURBT), however limitations do exist. In cases where residual cancer cells remain after TURBT, patients were instructed to repeat TURBT or begin administration for intravesical therapy (11). In cases where Bacillus Calmette-Guerin (BCG) therapy is ineffective, intravesical chemotherapy is recommended, and radical cystectomy may be considered for fit patients with persistent disease. MIBC patients may experience surgery procedures, radical cystectomy (RC) and partial cystectomy of the bladder. Treatments for MIBC include systematic chemotherapy,

which is considered as the current frontline to MIBC and metastasis in bladder cancer. For metastatic or advanced bladder cancer patients, second line therapy includes immune checkpoint inhibitors (12). Recently, alternative treatments to MIBC include radiation therapy and Antibody drug conjugates (ADCs) (13). The strongest solution to MIBC is considered to be RC, however many patients that undergo RC pass away within 5 years after completion. This had led to acceptance of perioperative chemotherapy, which has proven to increase patient lifespan. According to the NIAGARA trial in 2025, patients treated with neoadjuvant chemotherapy exhibited reduced risk of distant metastasis or death by 33% (14). Its widespread acceptance has collected attention as a possible frontline to MIBC treatments.

Table 2. Bladder Cancer Treatment by Stage

Disease Stage	**Treatment Modalities**	**Standard Options**
NMIBC	TURBT + Induction BCG	American Urological Association (AUA)/ Society of Urological Oncology (SUO) guidelines recommend TURBT followed by induction and maintenance BCG (15)
	Intravesical chemotherapy	Single postoperative chemotherapy instillation (e.g., mitomycin C, gemcitabine) can reduce recurrence in low-risk NMIBC (16)
	BCG-unresponsive NMIBC	Radical cystectomy for fit patients; alternatives include intravesical gemcitabine/docetaxel, or novel agents such as nadofaragene firadenovec (Adstiladrin), Anktiva, or pembrolizumab (17)
MIBC	Radical cystectomy + Neoadjuvant chemotherapy (NAC)	Standard of care includes radical cystectomy with pelvic lymph node dissection, often preceded by platinum-based neoadjuvant chemotherapy (per clinical consensus) (18)
Locally advanced / unresectable	Chemotherapy or chemoradiation	Cisplatin-based combination chemotherapy, or bladder preservation with concurrent chemoradiation (e.g., 5‑fluorouracil (5‑FU) + mitomycin) (clinical standard of practice) (19)
Metastatic / Advanced	Systemic chemotherapy	First-line: Gemcitabine + cisplatin (GC) remains standard for eligible patients (20)

	Immunotherapy	Second-line or cisplatin-ineligible patients: checkpoint inhibitors (e.g., pembrolizumab, atezolizumab) (widely endorsed) (20)
	Targeted / ADC therapies	Enfortumab vedotin (ADC targeting nectin-4) after platinum therapy (21)

B. The risk factors of Bladder Cancer

Bladder cancer has many risk factors, such as exposure to leather, textiles and paint products. Personal or family history, carrying genes linked to cancer: *HRAS, RB1, PTEN/ MMAC1, NAT2, GSMT1*, to name a few, may have higher incidence of bladder cancer (22). Bladder cancer's largest risk is smoking, which causes around 50% of all cases (23). Cigarette smoke carries over 60 known carcinogens, such as aromatic amines, including 4-aminobiphenyl and benzidine, polycyclic aromatic hydrocarbons (PAHs), and nitrosamines. These compounds are absorbed into the bloodstream, filtered through the kidneys, and concentrated in the urine, where these compounds come into direct touch with the urothelium (bladder lining) (24). Prolonged exposure leads to DNA damage, mutations, and ultimately malignant transformation of bladder epithelial cells (25). Emerging data suggests that e-cigarettes and vaping effects may contribute to bladder cancer risk but further long term evaluation is needed (26). Studies using mouse models suggested that over 57% of animals exposed to E-cigarette vaping chemicals developed bladder cancer (27). Studies suggested that detected nicotine-derived nitrosamine ketone (NNK) and formaldehyde in e-cigarette vapor has been suggested to promote urothelial carcinogenicity (28). Moreover, the solvents and flavoring agents in vape liquids can degrade into reactive compounds that produce oxidative stress and inflammation in our bodies, processes known to promote tumor development (29). Unlike traditional tobacco, vaping is often perceived as safer and more socially appropriate, particularly among teens and young adults. Early concern can raise awareness to chronic exposure to bladder cancer during a teens developmental window.

C. Mechanisms of Bladder Cancer chemoresistance

Despite the improved survival of bladder cancer patients subjected to chemotherapies, with genetic complexity and adaptation to chemotherapies, treatments are rendered ineffective. According to Weill Cornell medicine, within months of any initial platinum containing chemotherapies, most patients begin to build chemoresistance (30). Chemoresistance causes many patients to relapse, as well as creating limitations for therapeutic alternatives. Hence, the major challenge to chemotherapy treatments to applicable bladder cancer cases is the eventual development of chemoresistance. As of currently, a few mechanisms have been suggested to contribute to the chemoresistance of bladder cancer. These mechanisms involve the generation of somatic mutations and the cancer clone evolutionary selection, the

epigenetic alteration and related transcriptional regulation, the metabolic adaptation and altered tumor microenvironment (**Figure 2**), which are summarized in the following 4 sections.

C-1. Genetic mutation and evolutionary selection.

Chemotherapy applies pressures to all cells, during treatment chemotherapy is administered into the body. As a result, the fast-growing tumor cells, which are identified with high presence of mitochondria, fast cell division, and DNA replication are sensitive to the chemotherapy reagents (31). However, slow growth tumor cells, the cells with low mitochondria number are less likely to be killed by chemotherapy reagents, remaining after the cycles of treatment. The remaining tumor cells leads to recurrence, muscular invasive subtype, and even the spreading metastasis of bladder cancer.

The presence and accumulation of somatic mutation of bladder cancer cells have been suggested to contribute to the resistance to chemotherapies (**Figure 2A**). Recent studies indicated that the presence of mutation of *ERCC2* (32)*, TP53 (33)* or *PIK3CA (34)* are observed in bladder cancer. *ERCC2* is involved in nucleotide excision repair (NER), a process that repairs damaged DNA. Mutations in ERCC2 can prevent NER procedure occurring (32). *TP53* and *PIK3CA*, are involved in cell cycle control and growth signaling, are frequently mutated in bladder cancer. Their mutation can result in the advance in growth of tumor cells, leading to chemoresistance.

Recent studies suggested that Apolipoprotein B mRNA Editing Catalytic Subunit (APOBEC) enzymes are associated with the chemoresistance of bladder cancer (35). APOBEC enzymes introduce mutations into the tumor genome, some of which can confer resistance to chemotherapy drugs. However, the introduction of additional somatic mutation to the tumor genome leads to neo-antigen generation, which consequently trigger the anti-tumor immunity (35). Recent studies also suggest that the elevated APOBEC mediated mutation is linked to increased immune cell infiltration of bladder cancer tissues (36). However, mutations can also promote evolution and drug resistance, further outcomes of tumor mutation must be tested precisely.

C-2. Epigenetic reprogramming of chemo-resistant bladder cancer

Recent evidence suggests that epigenetic reprogramming, including changes in DNA methylation, histone modifications, and non-coding RNA expression, plays a critical role in driving chemotherapy resistance (37). In chemotherapy resistant bladder cancer tumors, tumor cells may undergo transcriptional reprogramming before or after chemotherapy treatment (**Figure 2B**). Referred to as primary resistance (before chemotherapy) and acquired resistance (after chemotherapy), Transcriptional reprogramming is frequently modulated by the regulation of DNA methylation and histone modification, rather than the alteration of genetic alterations.

DNA methylation is one of the major mechanisms of suppressing pro-apoptotic genes: genes control cell death when in response to DNA damage response (38). Through the addition of the DNA methyltransferase to DNA methylation for the promoter regions of corresponding genes, bladder tumor cells may achieve the suppression of the genes that promote tumor cells apoptosis; consequently, resulting in the resistance of the tumor cell from the chemotherapy reagent induced cell death.

Histone modifications regulate the expression of target genes. Histone deacetylases (HDACs), which increase histone deacetylation, leads to suppression of pro-apoptotic genes in favor for enhanced expression of genes that promote cell cycle progression and DNA repair processes (39). Cell cycle and DNA repair modifications allow tumor cells to evade cytotoxic effects of platinum-based chemotherapy. Similarly, dysregulated histone methylation such as elevated levels of H3K27me3 that are catalyzed by the methyltransferase Enhancer of Zeste Homolog 2 (EZH2), have been identified to be associated with repression of tumor suppressor genes and tumor cell acquisition of a stem-like quiescent phenotype, which are underlying the recurrence of post chemotherapies (40). Hence, targeting DNA methylation and histone modification enzymes are actively explored as innovative therapeutic strategies of bladder cancer that resist the standard-of-care chemotherapies.

C-3. Metabolic adaptation of chemo-resistant bladder cancer

Recent studies show that tumor cells with chemoresistance exhibit altered metabolic pathways when compared to tumor cells that are sensitive to chemotherapy reagents (41) (**Figure 2C**). As a response to chemotherapy, bladder tumor cells undergo metabolic reprogramming to match the increased demand of energy required, manage oxidative stress and the demand of cell division (41). One example of an adaptation is the shift from oxidative phosphorylation, to the glycolysis (the Warburg effect) (42). The increased shift of glycolysis provides rapid ATP production and the intermediates of nucleotide synthesis, which are essential for cell proliferation and DNA replication (42). Additionally, chemo-resistant bladder tumor cells upregulate the pentose phosphate pathway, which are the important steps for the biosynthesis of nucleotide (43). The pentose phosphate pathway (PPP) is an essential metabolic process that operates with glycolysis. Its upregulation is a characteristic of adaptation in chemotherapy resistant bladder cancer. The PPP has two main functions: it generates nicotinamide adenine dinucleotide phosphate (NADPH), which maintains redox homeostasis by neutralizing the reactive oxygen species (ROS) (43). Its second function is to produce ribose-5 phosphates, which is essential for rapid cell proliferation and DNA repair. In terms of chemotherapy, bladder cancer cells experience increased oxidative stress. To combat this, resistance cells enhance PPP activity to produce more NADPH and allowing them to detoxify ROS and resist chemotherapy-induced cell death (43). Glucose-6-phosphate dehydrogenase (G6PD), a rate-limiting enzyme is frequently overexpressed in drug-resistant cancer cells, correlating its activity with enhanced survival, DNA repair capacity, and apoptosis resistance.

Furthermore, metabolic adaptability of bladder tumor cells under chemotherapy also contribute to the immune evasion and any following recurrence post treatment (**Figure 2D**), which is further described blow. Targeting metabolic vulnerability, including the small molecular inhibitors, that weaken essential

enzymes governing glycolytic or PPP pathways, serve as one of the promising strategies to overcome the metabolic adaption and chemotherapy resistance in bladder cancer patients.

D. The innovative Immunotherapies for advanced Bladder Cancer

Recent research advancements lead to the development of immunotherapy, using immune checkpoint inhibitors as a treatment strategy. Immune checkpoint inhibitor (ICI) therapy has become an essential part in treating advanced bladder cancer cases (7). These therapies target immune checkpoint molecules, attempting to attack tumors that have evaded immune detection (**Figure 3A**). Immune checkpoint molecules include Programmed death-1 (PD-1), Programmed death-ligand (PD-L1), and Cytotoxic T-lymphocyte associated protein 4 (CTLA-4), and other less characterized components (44). By blocking these inhibitory signals, ICIs restore cell–mediated anti-tumor immunity, leading to anti-tumor effect (**Figure 3A**). Below is a summary of the current FDA approved immune checkpoint inhibitors for bladder cancer or more general urothelial cancer patients (**Table 3**).

Table 3. FDA-approved immune checkpoint inhibitors for bladder cancer (urothelial carcinoma).

Drug Name	**Target**	**Brand Name**	**FDA-Approved Indications for Bladder Cancer**	**Approval Status**
Atezolizumab	PD-L1	Tecentriq	Previously approved for metastatic urothelial carcinoma after platinum-based chemotherapy (withdrawn by manufacturer)	Approval withdrawn (as of 2021)
Nivolumab	PD-1	Opdivo	Adjuvant treatment for patients with high-risk urothelial carcinoma after radical cystectomy	Approved
Pembrolizumab	PD-1	Keytruda	- Metastatic urothelial carcinoma after platinum chemotherapy - First-line in cisplatin-ineligible, PD-L1+ patients - BCG-unresponsive, high-risk NMIBC with carcinoma in situ	Approved for multiple bladder cancer settings
Avelumab	PD-L1	Bavencio	Maintenance therapy for locally advanced or metastatic urothelial carcinoma that has not progressed after platinum chemotherapy	Approved
Durvalumab	PD-L1	Imfinzi	Investigated in urothelial carcinoma but not FDA-approved for bladder cancer (as of current status)	Not approved for bladder cancer

Despite these advancements, only a small portion of patients show benefit from ICI therapy. Resistance mechanisms of bladder cancer, such as immune exclusion, impaired antigen presentation, and an immunosuppressive tumor microenvironment, limit the overall response rates of patients (7). As a result, ongoing efforts are focused on improving immunotherapy effects for bladder cancer patients. Examples of these efforts include identifying predictive biomarkers, optimizing patient selections, and developing combinations with chemotherapy, radiation, or metabolic modulators. Currently, there are many active tests showing the effects of ICI strategies alone and in combination of chemotherapy. The current active clinical trials of combination strategies in treating bladder cancer, ranging from prevention, early-stage bladder cancer, to advanced metastatic bladder cancer can be found as below (**Table 4**).

Table 4. The current active clinical trials investigating the combinatorial strategies of bladder cancer.

Disease Setting	**Agent(s)**	**Trial ID / Phase**	**Status / Notes**
High-risk NMIBC	Sasanlimab ± BCG	CREST (Phase III)	Completes primary endpoints ~Dec 2024
NMIBC (BCG-refractory)	Pembrolizumab + BCG	KEYNOTE-676 (Phase III)	Recruiting until Nov 2024
NMIBC (BCG-naïve)	Atezolizumab + BCG	ALBAN (Phase III)	Recruiting through Feb 2028
NMIBC personalized vaccine	mRNA-4157/V940 + BCG	INTerpath-011	Early phase, exploring efficacy
High-risk NMIBC	Anktiva + BCG	–	FDA breakthrough designation in refractory carcinoma in situ (CIS)
MIBC (adjuvant)	Nivolumab	CheckMate-274 (III)	FDA-approved; improved disease-free survival (DFS)
MIBC (perioperative)	Durvalumab + chemo	NIAGARA (III)	Led to March 2025 FDA perioperative approval

Advanced/metastatic UC	Enfortumab vedotin + Pembrolizumab	EV-302 (III)	OS ~31.5 mo vs 16.1; practice-changing results
First-line metastatic UC	Nivolumab + Ipilimumab	CheckMate-901 (III)	Comparing double ICI vs chemo combos
First-line metastatic UC	Durvalumab + chemo ± tremelimumab	NILE (III)	Multi-arm study, global enrollment ongoing

Hence, understanding the crosstalk between chemotherapies and immunotherapies, and the effect of these systematic treatment to both tumors and the immune system will be essential to develop effective treatment strategies to overcome resistance, leading to improved outcomes for bladder cancer patients.

E. Factors contribute to the immune suppressive tumor microenvironment.

In bladder cancer, particularly muscle-invasive and advanced urothelial carcinoma, tumor microenvironments (TMEs) often develop mechanisms to evade immune detection and resist immunotherapy. The TME are composed with a variety of tumor infiltrating immune cells and the extra-cellular matrix, including fibroblast. The interplay between tumor cells, immune cell and extra cellular matrix (ECMs) contribute to the complex TME and fine tune the response of bladder cancer patients to immunotherapies.

E-1. The diverse expression of immune checkpoints

Currently, only anti-PD-1 antibodies have been approved by the FDA for patients with advanced bladder cancer. However, tumor cells can exploit the diverse expression of immune checkpoint molecules to deactivate effector cells in the immune system. In bladder cancer, PD-L1 expressions in tumor cells are frequently upregulated, particularly in metastatic bladder cancer (45). The expression of PD-L1 interacts with PD-1, inhibiting the activation of cytokine production and the tumor-killing cytotoxic activity in T cells. Tumor cells may develop additional mechanisms in deactivating T cells, bypassing the inhibitory role of the current anti-PD-1 strategy.

Cytotoxic T-Lymphocyte–associated protein 4 (CTLA-4) is a frequent immune checkpoint target. CTLA-4 competes with CD28 for binding to CD80/CD86 on antigen-presenting cells (APCs) (46). The expression of CTLA-4 in the immune regulatory cells inhibits the early T cell activation and impairs the effects of anti-tumor immunity (46). CTLA-4 blockade (like Ipilimumab) is under investigation in

combination with PD-1/PD-L1 inhibitors for bladder cancer, however, it has not been approved by the FDA yet. Currently, clinical trials are investigating the combination of anti-PD-1 and anti-CTLA-4 antibodies to improve immune response and treatment outcomes for patients.

T-cell Immunoreceptor with Ig and ITIM Domains (TIGIT) is another immune checkpoint that has been studies frequently. TIGIT is found on various immune cells, including activated CD8+ T cells, regulatory T cells (Tregs), and natural killer (NK) cells (47). TIGIT primary interacts with CD155 (aka PVR, poliovirus receptor) (47), which is often upregulated on antigen-presenting cells and bladder tumor cells (48). This interaction suppresses the T cell proliferation and cytokine production. Currently, many clinical trials are studying the anti-TIGIT agents (Tiragolumab) alone or in combination with anti-PD-1 in bladder cancer.

E-2. Extracellular matrix in immune resistance of Bladder Cancer

The ECMs in bladder cancer play vital roles in the tumor response and resistance to therapies. The state of ECM regulates the tumor microenvironment and contributes to immune resistance. A dense and remodeled ECM creates a physical barrier to limit the infiltration of effector cells, including activated CD8+ T cells and NK cells into the tumor. In addition, ECM may interact with and inhibit the distribution of cytokines and chemokines, which impairs the recruitment of immune cells to the tumor tissues (49). Certain ECM enzymes, such as matrix metalloproteinases (MMPs), have been shown to promote tumor cell growth (50).

Activated cancer-associated fibroblasts (CAFs) are a major producer of ECM and serve as an important factor in regulating immune suppressive cytokines. The high abundance of CAFs has been associated with reduced effectiveness of therapy in blader cancer patients receiving immunotherapies (51). The presence of CAFs has been suggested to produce cytokines that weaken responses to immune checkpoint inhibitors, therefore, targeting the ECM and CAFs is actively being explored to enhance the effectiveness of immunotherapy (51). Strategies such as the reprograming of CAFs to quiescent or immune supportive cell types have shown promising results: mitigating the stromal barriers of bladder tumor to immune cell infiltration and reactivating the anti-tumor immunity to enhance the success of ICI treatment (52).

PERSPECTIVE AND CURRENT CHALLENGE

Bladder cancer is transforming, with rapid growing cases among younger individuals and increasingly complex patterns of therapeutic resistance. This trend raises emerging questions about prevention and early detection, including whether these trends reflect evolving environmental exposures, lifestyle factors, or improved diagnostic practices. Regardless of the underlying cause, the growing instance of bladder cancer patients calls for innovation to strategy that includes both stronger prevention and the development of treatment therapies. Clinically, management is increasingly challenged by heterogeneity

across disease states (NMIBC, MIBC and metastatic diseases), long-term surveillance burden, and the high prevalence comorbidities (e.g., renal dysfunction) that limit standard options such as cisplatin. In NMIBC, patients often require repeated transurethral resections, intravesical therapies, and intensive cystoscopic surveillance. These treatments carry cumulative physical and psychological burdens, increase healthcare utilization, and still fail to prevent progression in a significant proportion of high-risk cases (53). For MIBC, coordinating multimodality care, whether radical cystectomy, bladder-preserving chemoradiation, or the integration of perioperative systemic therapy, remains challenging. Many Practice variation persists because patients differ widely in health, tumor biology, and access to specialized multidisciplinary teams. In the metastatic setting, therapeutic treatments has rapidly expanded, including platinum-based chemotherapy, immune checkpoint blockade, antibody-drug conjugates, and targeted agents for selected molecular subsets. However, choosing the optimal sequencing is difficult in the absence of universally validated predictive biomarkers and given frequent early resistance (54). In addition to these challenges, many patients are older and have renal impairment, frailty, cardiovascular disease, or poor performance status, which restricts eligibility for cisplatin-based regimens and narrows treatment choices (55).

From a therapeutic view, the limitations of standard chemotherapy have driven research into immune-based, metabolic, and epigenetic treatment strategies. An existing treatment paradox is that, although bladder cancer can be immunogenic, it frequently remains refractory to immunotherapy: immune checkpoint inhibitors benefit only a subset of patients, and many tumors develop resistance or relapse despite evidence of immune infiltration. Immune checkpoint inhibitors provide a promising foundation, yet their effects remain restricted by the immunosuppressive tumor microenvironment. This has led to ongoing field controversies regarding optimal sequencing and combination strategies, balancing improved response rates against additive toxicity, and the absence of universally reliable biomarkers to guide patient selection and treatment choices. Future progress will likely depend on rational combinations of immunotherapy with stromal-targeting agents, metabolic regulators, and advanced cellular therapies such as genetically modified Chimeric Antigen Receptor T-cell (CAR-T) therapy and engineered NK cell therapies. However, achieving durable clinical benefit will require overcoming resistance programs created by the microenvironment, clarifying which patients should receive intensified combinations, and addressing practical implementation challenges in routine oncology care.

A major strength of this review is its integration of recent epidemiologic trends, mechanistic insights, and therapeutic developments across a 20-year time frame, creating a comprehensive synthesis of how bladder cancer biology and treatment have evolved. By combining discussions of environmental risk factors, chemoresistance mechanisms, and development of immunotherapeutic strategies, the review provides a broad yet cohesive overview that reflects current scientific and clinical priorities. However, this work is limited by its narrative scope. It does not include a formal systematic review process because certain topics, such as long-term outcomes of newer therapies or the clinical utility of new biomarkers, remain constrained by the availability of published data. Additionally, while mechanistic studies are included, the rapidly growing number of studies means that some recent findings may not yet be fully represented. These limitations highlight the need for continued research and updated synthesis as the field progresses.

CONCLUSION

In summary, the evidence reviewed in this work demonstrates that bladder cancer progression and treatment failure come from the combined influence of environmental exposure, adaptive resistance mechanisms, and the diversity in clinical frontlines. Despite significant advances in surgery, chemotherapy, and immunotherapy, long-term disease management remains challenging for many patients because of early recurrence, varied treatment responses, and the absence of universally reliable predictive biomarkers. The future of bladder cancer care lies in prevention in youth, public education and precision based therapeutic approaches that are driven by chemotherapy improvements, tumor resistance suppression and innovative strategies. These key targets hold the greatest promise for transforming outcomes in battling bladder cancer.

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REFERENCES

1. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: a cancer journal for clinicians. 2024;74(3):229-63.

2. Zhang Y, Zhang H, Li Y, Ma X, Tan H, Gao J, et al. Disease burden and trends of bladder cancer in the world and BRICS from 1990 to 2021 and its projection until 2036: analysis based on the global burden of disease study 2021. Discov Oncol. 2025;16(1):1319.

3. Siegel RL, Kratzer TB, Giaquinto AN, Sung H, Jemal A. Cancer statistics, 2025. CA: a cancer journal for clinicians. 2025;75(1):10-45.

4. Zhang Y, Rumgay H, Li M, Yu H, Pan H, Ni J. The global landscape of bladder cancer incidence and mortality in 2020 and projections to 2040. J Glob Health. 2023;13:04109.

5. Chamie K, Litwin MS, Bassett JC, Daskivich TJ, Lai J, Hanley JM, et al. Recurrence of high-risk bladder cancer: a population-based analysis. Cancer. 2013;119(17):3219-27.

6. Liu S, Chen X, Lin T. Emerging strategies for the improvement of chemotherapy in bladder cancer: Current knowledge and future perspectives. J Adv Res. 2022;39:187-202.

7. Okobi TJ, Uhomoibhi TO, Akahara DE, Odoma VA, Sanusi IA, Okobi OE, et al. Immune Checkpoint Inhibitors as a Treatment Option for Bladder Cancer: Current Evidence. Cureus. 2023;15(6):e40031.

8. Leslie SW, Soon-Sutton TL, Aeddula NR. Bladder Cancer. StatPearls. Treasure Island (FL)2025.

9. Anastasiadis A, de Reijke TM. Best practice in the treatment of nonmuscle invasive bladder cancer. Ther Adv Urol. 2012;4(1):13-32.

10. Kulkarni GS, Black PC, Sridhar SS, Zlotta AR, Shayegan B, Rendon RA, et al. 2025 Canadian Urological Association Expert Report: Muscle-invasive bladder cancer. Can Urol Assoc J. 2025;19(1):E1-E16.

11. Kim LHC, Patel MI. Transurethral resection of bladder tumour (TURBT). Transl Androl Urol. 2020;9(6):3056-72.

12. Ghatalia P, Zibelman M, Geynisman DM, Plimack E. Approved checkpoint inhibitors in bladder cancer: which drug should be used when? Therapeutic advances in medical oncology. 2018;10:1758835918788310.

13. Wei Q, Li P, Yang T, Zhu J, Sun L, Zhang Z, et al. The promise and challenges of combination therapies with antibody-drug conjugates in solid tumors. J Hematol Oncol. 2024;17(1):1.

14. You C, Zhang J, Lei J, Fu W, Liu M, Cai H, et al. Cost-effectiveness of perioperative durvalumab plus neoadjuvant chemotherapy for muscle invasive bladder cancer in the United States. Therapeutic advances in medical oncology. 2025;17:17588359251357519.

15. Strope SA, Elliott SP, Saigal CS, Smith A, Wilt TJ, Wei JT, et al. Urologist compliance with AUA best practice guidelines for benign prostatic hyperplasia in Medicare population. Urology. 2011;78(1):3-9.

16. Kang M, Jeong CW, Kwak C, Kim HH, Ku JH. Single, immediate postoperative instillation of chemotherapy in non-muscle invasive bladder cancer: a systematic review and network meta-analysis of randomized clinical trials using different drugs. Oncotarget. 2016;7(29):45479-88.

17. Escobar D, Doshi C, Zahir M, Daneshmand S. Modern management of BCG-refractory non-muscle-invasive urothelial carcinoma of the urinary bladder. Urologie. 2025.

18. Lee HW, Kwon WA, Nguyen NT, Phan DTT, Seo HK. Approaches to Clinical Complete Response after Neoadjuvant Chemotherapy in Muscle-Invasive Bladder Cancer: Possibilities and Limitations. Cancers (Basel). 2023;15(4).

19. Teply BA, Kim JJ. Systemic therapy for bladder cancer - a medical oncologist's perspective. J Solid Tumors. 2014;4(2):25-35.

20. Yafi FA, North S, Kassouf W. First- and second-line therapy for metastatic urothelial carcinoma of the bladder. Curr Oncol. 2011;18(1):e25-34.

21. Hoffman-Censits J, Maldonado L. Targeted Treatment of Locally Advanced and Metastatic Urothelial Cancer: Enfortumab Vedotin in Context. Onco Targets Ther. 2022;15:1519-29.

22. Gu J, Wu X. Genetic susceptibility to bladder cancer risk and outcome. Per Med. 2011;8(3):365-74.

23. Freedman ND, Silverman DT, Hollenbeck AR, Schatzkin A, Abnet CC. Association between smoking and risk of bladder cancer among men and women. JAMA. 2011;306(7):737-45.

24. Li Y, Hecht SS. Carcinogenic components of tobacco and tobacco smoke: A 2022 update. Food Chem Toxicol. 2022;165:113179.

25. Wnek SM, Medeiros MK, Eblin KE, Gandolfi AJ. Persistence of DNA damage following exposure of human bladder cells to chronic monomethylarsonous acid. Toxicol Appl Pharmacol. 2009;241(2):202-9.

26. Sahu R, Shah K, Malviya R, Paliwal D, Sagar S, Singh S, et al. E-Cigarettes and Associated Health Risks: An Update on Cancer Potential. Adv Respir Med. 2023;91(6):516-31.

27. Molony RD, Wu CH, Lee YF. E-liquid exposure induces bladder cancer cells to release extracellular vesicles that promote non-malignant urothelial cell transformation. Sci Rep. 2023;13(1):142.

28. Tang MS, Lee HW, Weng MW, Wang HT, Hu Y, Chen LC, et al. DNA damage, DNA repair and carcinogenicity: Tobacco smoke versus electronic cigarette aerosol. Mutat Res Rev Mutat Res. 2022;789:108409.

29. Muthumalage T, Prinz M, Ansah KO, Gerloff J, Sundar IK, Rahman I. Inflammatory and Oxidative Responses Induced by Exposure to Commonly Used e-Cigarette Flavoring Chemicals and Flavored e-Liquids without Nicotine. Front Physiol. 2017;8:1130.

30. Faltas BM, Prandi D, Tagawa ST, Molina AM, Nanus DM, Sternberg C, et al. Clonal evolution of chemotherapy-resistant urothelial carcinoma. Nature genetics. 2016;48(12):1490-9.

31. Tilsed CM, Fisher SA, Nowak AK, Lake RA, Lesterhuis WJ. Cancer chemotherapy: insights into cellular and tumor microenvironmental mechanisms of action. Front Oncol. 2022;12:960317.

32. Li Q, Damish AW, Frazier Z, Liu D, Reznichenko E, Kamburov A, et al. ERCC2 Helicase Domain Mutations Confer Nucleotide Excision Repair Deficiency and Drive Cisplatin Sensitivity in Muscle-Invasive Bladder Cancer. Clinical cancer research : an official journal of the American Association for Cancer Research. 2019;25(3):977-88.

33. Wu G, Wang F, Li K, Li S, Zhao C, Fan C, et al. Significance of TP53 mutation in bladder cancer disease progression and drug selection. PeerJ. 2019;7:e8261.

34. Ross RL, McPherson HR, Kettlewell L, Shnyder SD, Hurst CD, Alder O, et al. PIK3CA dependence and sensitivity to therapeutic targeting in urothelial carcinoma. BMC Cancer. 2016;16:553.

35. Glaser AP, Fantini D, Wang Y, Yu Y, Rimar KJ, Podojil JR, et al. APOBEC-mediated mutagenesis in urothelial carcinoma is associated with improved survival, mutations in DNA damage response genes, and immune response. Oncotarget. 2018;9(4):4537-48.

36. Shi R, Wang X, Wu Y, Xu B, Zhao T, Trapp C, et al. APOBEC-mediated mutagenesis is a favorable predictor of prognosis and immunotherapy for bladder cancer patients: evidence from pan-cancer analysis and multiple databases. Theranostics. 2022;12(9):4181-99.

37. Wang N, Ma T, Yu B. Targeting epigenetic regulators to overcome drug resistance in cancers. Signal Transduct Target Ther. 2023;8(1):69.

38. Hervouet E, Cheray M, Vallette FM, Cartron PF. DNA methylation and apoptosis resistance in cancer cells. Cells. 2013;2(3):545-73.

39. Gallinari P, Di Marco S, Jones P, Pallaoro M, Steinkuhler C. HDACs, histone deacetylation and gene transcription: from molecular biology to cancer therapeutics. Cell Res. 2007;17(3):195-211.

40. Marei HE. Epigenetic regulators in cancer therapy and progression. NPJ Precis Oncol. 2025;9(1):206.

41. Liu F, Li K, Zhu Q. Targeting Metabolic Reprogramming in Bladder Cancer Immunotherapy: A Precision Medicine Approach. Biomedicines. 2025;13(5).

42. Burns JE, Hurst CD, Knowles MA, Phillips RM, Allison SJ. The Warburg effect as a therapeutic target for bladder cancers and intratumoral heterogeneity in associated molecular targets. Cancer Sci. 2021;112(9):3822-34.

43. Giacomini I, Ragazzi E, Pasut G, Montopoli M. The Pentose Phosphate Pathway and Its Involvement in Cisplatin Resistance. Int J Mol Sci. 2020;21(3).

44. Grywalska E, Pasiarski M, Gozdz S, Rolinski J. Immune-checkpoint inhibitors for combating T-cell dysfunction in cancer. Onco Targets Ther. 2018;11:6505-24.

45. Pichler R, Heidegger I, Fritz J, Danzl M, Sprung S, Zelger B, et al. PD-L1 expression in bladder cancer and metastasis and its influence on oncologic outcome after cystectomy. Oncotarget. 2017;8(40):66849-64.

46. Rowshanravan B, Halliday N, Sansom DM. CTLA-4: a moving target in immunotherapy. Blood. 2018;131(1):58-67.

47. Chauvin JM, Zarour HM. TIGIT in cancer immunotherapy. J Immunother Cancer. 2020;8(2).

48. Mori K, Matsumoto K, Amano N, Koguchi D, Shimura S, Hagiwara M, et al. Expression of Membranous CD155 Is Associated with Aggressive Phenotypes and a Poor Prognosis in Patients with Bladder Cancer. Cancers (Basel). 2022;14(6).

49. Mai Z, Lin Y, Lin P, Zhao X, Cui L. Modulating extracellular matrix stiffness: a strategic approach to boost cancer immunotherapy. Cell Death Dis. 2024;15(5):307.

50. Rodriguez Faba O, Palou-Redorta J, Fernandez-Gomez JM, Algaba F, Eiro N, Villavicencio H, et al. Matrix Metalloproteinases and Bladder Cancer: What is New? ISRN Urol. 2012;2012:581539.

51. Caramelo B, Zagorac S, Corral S, Marques M, Real FX. Cancer-associated Fibroblasts in Bladder Cancer: Origin, Biology, and Therapeutic Opportunities. Eur Urol Oncol. 2023;6(4):366-75.

52. Li M, Wu B, Li L, Lv C, Tian Y. Reprogramming of cancer-associated fibroblasts combined with immune checkpoint inhibitors: A potential therapeutic strategy for cancers. Biochim Biophys Acta Rev Cancer. 2023;1878(5):188945.

53. Holzbeierlein JM, Bixler BR, Buckley DI, Chang SS, Holmes R, James AC, et al. Diagnosis and Treatment of Non-Muscle Invasive Bladder Cancer: AUA/SUO Guideline: 2024 Amendment. J Urol. 2024;211(4):533-8.

54. Powles T, Bellmunt J, Comperat E, De Santis M, Huddart R, Loriot Y, et al. ESMO Clinical Practice Guideline interim update on first-line therapy in advanced urothelial carcinoma. Ann Oncol. 2024;35(6):485-90.

55. Galsky MD, Hahn NM, Rosenberg J, Sonpavde G, Hutson T, Oh WK, et al. A consensus definition of patients with metastatic urothelial carcinoma who are unfit for cisplatin-based chemotherapy. Lancet Oncol. 2011;12(3):211-4.

FIGURES AND FIGURE LEGEND

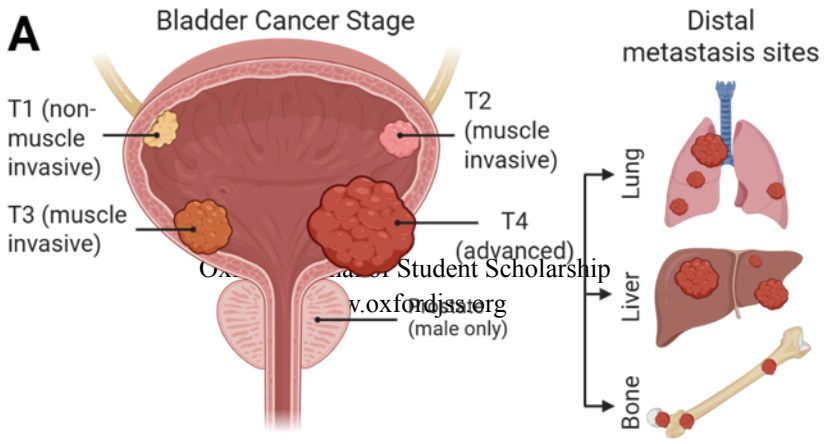

Figure 1. The pathological and molecular features of bladder cancer. **A:** Bladder cancer is categorized as four major tumor stages: In situ alone, carcinoma is present in cells where it starts. Localized, the carcinoma is contained within the bladder (T1). Regional (T2-T3), the carcinoma has spread to nearby structures or lymph nodes. Distant, the carcinoma has spread to distant parts of the body including lungs, liver, and/or bones (T4). Right: the frequent sites of distal metastasis in bladder cancer include the lungs, liver, and bones. **B**: the non-muscle invasive bladder cancer is the urothelial carcinoma that is confined to the layers of epithelial cells. The muscle invasive bladder cancer is the urothelial carcinoma that invades the muscle layer and begins to metastasize.

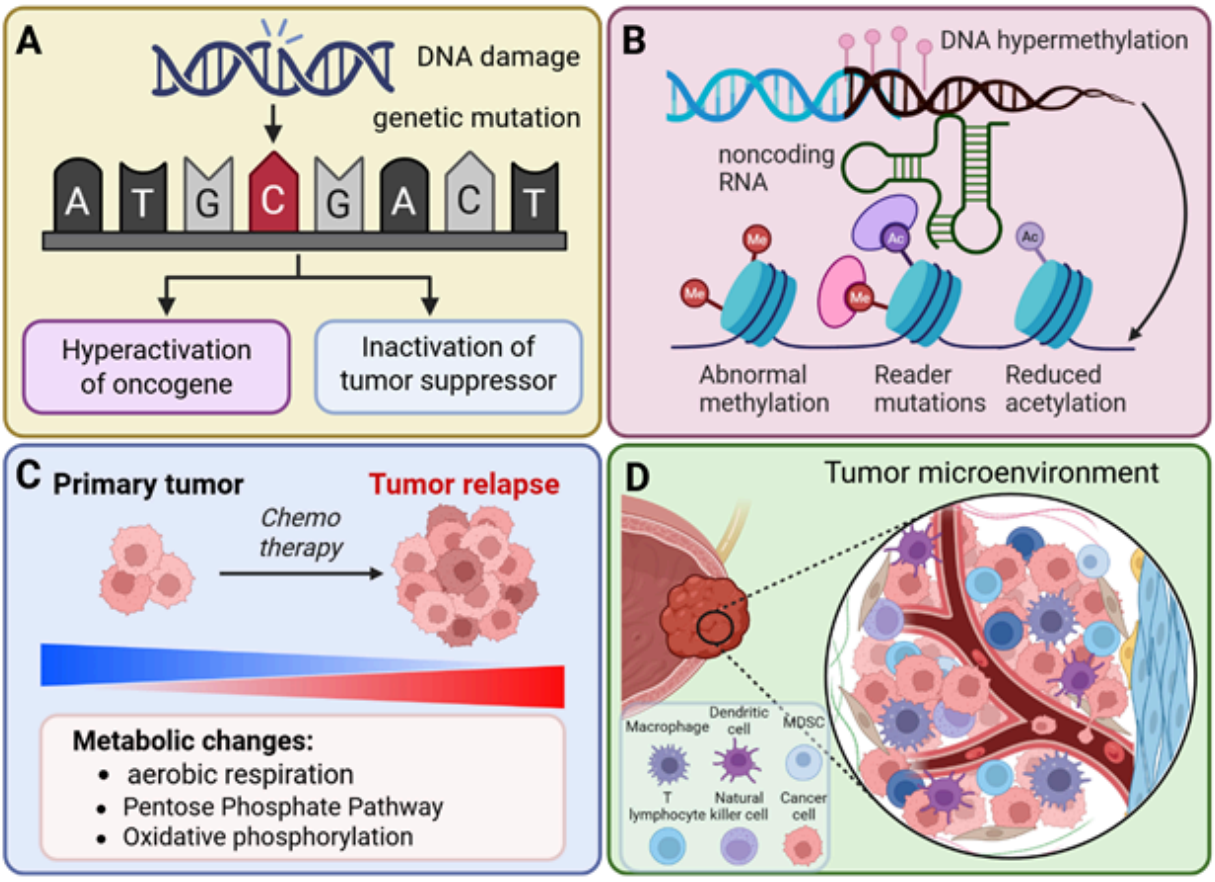

Figure 2. The molecular mechanism of chemoresistance of bladder cancer. A: DNA damage and genetic mutation may lead to generation of somatic mutations, which lead to hyperactivation of a given oncogene or inactivation of certain tumor suppressors. As a consequence, the tumor cells achieve a growth advantage under the treatment of chemotherapies. **B**: without alteration of genetic information, the altered epigenetic modifications including DNA methylation and histone modification contribute,

including abnormal acetylation, reader mutation or reduced acetylation that may lead to gene dysregulation and a growth advantage for tumor cells. The expression of noncoding RNAs also contributes to the transcriptional regulation of target genes. **C**: tumor relapse post chemotherapy may exhibit altered metabolic features, including increased or reduced aerobic respiration, pentose phosphate pathway, or oxidative phosphorylation. These metabolic changes facilitate tumor cells in adapting to metabolic alterations upon the treatment of chemotherapy. **D**: the tumor cells are surrounded by the presence of a variety of stromal cells and immune cells, which in combination, modulate the characteristics of tumor cells for survival or cell death during chemotherapy administration.

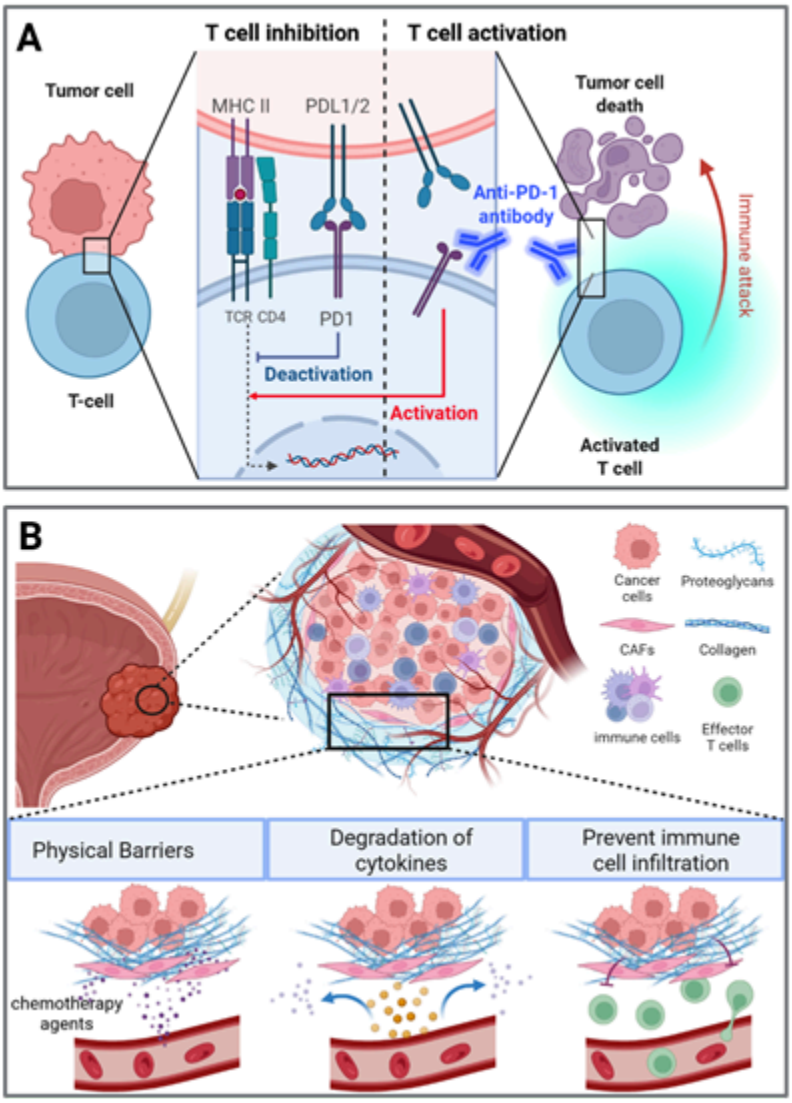

Figure 3. The underlying factors contributed to the resistance of bladder cancer to immunotherapies. A: Tumor cell expressing PD-1, which in turn interacts with the PD-1 that is expressed in T cells. This interaction inactivates T cells from tumor cell killing. The administration of

anti-PD-1 antibody blocks the PD-L1/PD-1 interaction, attenuating the tumor cells induced inactivation of T cells, resulting in the immune attack and tumor cell death. B: The presence of extracellular matrix (ECM) modulates the efficacy of cancer treatment in multiple ways: ECM serves as a physical barrier, preventing the tumor infiltration of chemotherapy agents. ECM may produce peptidase to degrade the tumor resident cytokines, mitigating the efficacy of immunotherapies. The presence of ECM may also prevent the tumor infiltration of immune cells, resulting in tumor resistance to immune checkpoint inhibitors.