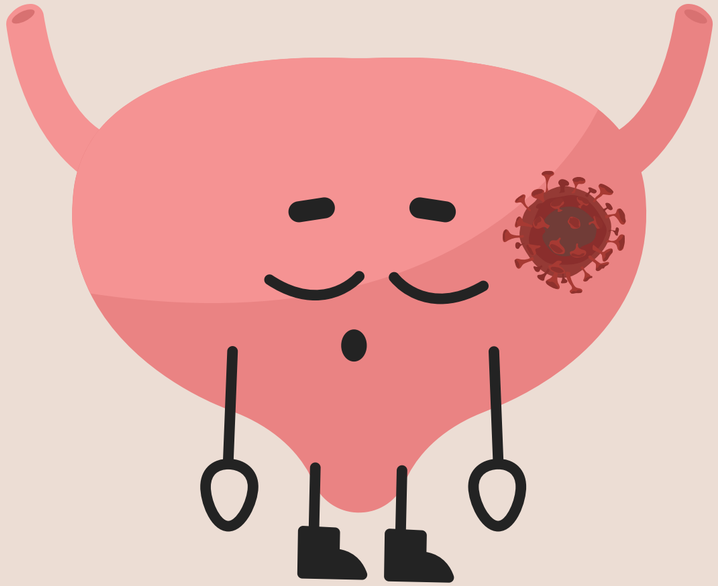
BLADDER CANCER



Introduction

Bladder cancer arises from the uncontrolled growth of cells in the bladder, a hollow organ responsible for storing urine produced by the kidneys. The urinary system comprises the kidneys, ureters, bladder, and urethra, working collectively to filter blood and excrete waste via urine. The most common type is urothelial carcinoma, originating from transitional cells lining the bladder and urinary tract, characterized by their capacity to stretch and contract. Less common forms include squamous cell carcinoma, adenocarcinoma, and small cell carcinoma, often linked to chronic irritation, infections (e.g., schistosomiasis), or neuroendocrine dysfunction. Bladder cancer is categorized as non-muscle-invasive or muscle-invasive, depending on its depth of invasion into the bladder wall. Major risk factors include tobacco use, occupational exposure to carcinogens, genetic mutations (e.g., HRAS, RB1, PTEN, NAT2, GSTM1), certain medications and herbal compounds, radiation exposure, and chronic infections or catheter use. The hallmark symptom is hematuria (blood in urine), often intermittent or microscopic. Other signs include urinary urgency, dysuria, nocturia, and, in advanced stages, pain, weight loss, edema, and fatigue. Early detection and risk stratification are vital for effective disease management [1] .

Incidence, Prevalence and Mortality

Category	Both Sexes	Male	Female
Incidence	614,298 cases	464,200 cases	150,098 cases
Mortality	220,596 deaths	157,000 deaths	63,596 deaths
5-Year Prevalence	1,952,000 cases	1,500,000 cases	452,000 cases

Source [2]

Diagnosis

Bladder cancer diagnosis relies on a combination of endoscopic, histological, and radiological techniques. Cystoscopy is the primary diagnostic tool, involving the insertion of a lighted cystoscope through the urethra to visualize the bladder lining. It enables real-time identification of abnormal areas and facilitates biopsy or resection of small tumors for pathological evaluation. CT urogram provides detailed cross-sectional imaging of the urinary tract using contrast-enhanced computed tomography to assess renal function, urothelial lesions, and metastatic spread. MRI, particularly triple-phase MRI, offers high-resolution imaging of bladder wall invasion and surrounding structures, aiding in local staging. Chest X-rays are performed to detect pulmonary metastases, while bone scans assess skeletal involvement using radiotracers that accumulate in sites of high osteoblastic activity, indicative of bone metastases. Together, these modalities form a comprehensive diagnostic framework essential for accurate staging and treatment planning in bladder cancer [3].

BIOMARKERS

A variety of urinary and tissue-based biomarkers support the diagnosis, prognosis, and monitoring of bladder cancer. Bladder Tumor Antigen (BTA) STAT and TRAK are used for screening and surveillance, with levels above 10 U/mL considered abnormal. Nuclear Matrix Protein 22 (NMP22) is commonly elevated (>10 U/mL) in patients with active disease or recurrence. Urokinase Plasminogen Activator (uPA), with abnormal values exceeding 0.5 ng/mL, serves as a prognostic marker linked to tumor aggressiveness. Cytokeratin 8 and 18 (UBC) levels above 0.15 ng/mL help monitor non-muscle invasive bladder cancer. Elevated Hyaluronic Acid (HA) and overexpression of Survivin, a known inhibitor of apoptosis, are associated with poor prognosis. The Epigenetic Profile Test, detecting abnormal gene methylation patterns, offers a non-invasive strategy for early bladder cancer detection. Collectively, these biomarkers enhance clinical decision-making and risk stratification in bladder cancer management [4-5].

Cytogenetics of Bladder Cancer

Bladder cancer exhibits diverse chromosomal abnormalities that reflect tumor type, stage, and progression. Early events often include loss of chromosome 9, particularly 9p21, affecting tumor suppressors like CDKN2A (p16) and contributing to cell cycle deregulation. High-grade and invasive tumors display complex karyotypes with structural rearrangements and genomic instability. Common findings include chromosome 7 and 17 polysomy, often linked to EGFR (7p11) and ERBB2 (17q12) amplification. Recurrent breakpoints (e.g., 11p15, 14q32) and isochromosomes such as i(8q) and i(17q) are frequently associated with aggressive disease. Deletions on 3p, 6q, 8p, 11p, 14q, and 17p often involve TP53 and other tumor suppressor genes. Gains and trisomies on 1q, 3q, 5p, 6p, 8q, and other regions promote oncogene activation and tumor progression. FISH (Fluorescence In Situ Hybridization) is a key diagnostic tool; the UroVysion probe set detects chromosomal gains (e.g., CEP3, CEP7, CEP17) and loss of 9p21, offering valuable insights into tumor grade and invasiveness. Overall, cytogenetic profiling aids in prognosis and understanding of bladder cancer pathogenesis [6].

Pharmacogenomics

Pharmacogenomic profiling plays a critical role in optimizing treatment for bladder cancer. ERCC1, involved in nucleotide excision repair, influences response to cisplatin-based chemotherapy; low ERCC1 expression predicts better outcomes in advanced or metastatic disease. FGFR3 activating mutations are found in a subset of tumors and confer sensitivity to FGFR inhibitors like investigational TYRA-300, offering a targeted option with improved tolerability. Overexpression of EGFR is associated with increased responsiveness to EGFR-targeted therapies such as gefitinib and erlotinib. Key regulators of the cell cycle—CCNA2, CCNB1, CDK1, PLK1, AURKA/B, FOXM1, CALML5—are often overexpressed in advanced stages, representing promising targets for investigational drugs like Volasertib (BI 6727). In the realm of immunotherapy, PD-L1 expression is an important biomarker for predicting response to immune checkpoint inhibitors, including Avelumab and Pembrolizumab, particularly in maintenance settings. These molecular insights support personalized therapy strategies, improving efficacy and reducing unnecessary toxicity [7-9].

TREATMENT

Bladder cancer treatment involves a multidisciplinary approach tailored to tumor stage, grade, and patient-specific factors. Primary modalities include surgery, radiation therapy, chemotherapy, immunotherapy, targeted therapy, and participation in clinical trials, followed by structured follow-up care. Surgical interventions range from transurethral resection (TUR) for superficial tumors, to partial or radical cystectomy with urinary diversion for invasive cancers. Radiation therapy, typically external beam, may be used independently or synergistically with chemotherapy. Systemic and intravesical chemotherapies, using agents like cisplatin, gemcitabine, and mitomycin, target both local and disseminated disease. Targeted therapies, such as enfortumab vedotin and erdafitinib, are guided by biomarker testing. Immunotherapy, with agents like nivolumab and pembrolizumab, enhances immune response via checkpoint inhibition. Clinical trials remain crucial for access to novel therapies. Post-treatment, routine surveillance testing ensures timely detection of recurrence and informs ongoing management [10-11].

Drugs for Bladder Cancer

Bladder cancer therapy employs a diverse arsenal of drugs across multiple classes, tailored to disease stage and patient tolerance. Cisplatin-based regimens (e.g., GemCis, MVAC) remain first-line for advanced/metastatic cases, with carboplatin as a substitute in cisplatin-ineligible patients. Gemcitabine, an antimetabolite, is widely used both systemically and intravesically. Intravesical agents like mitomycin, thiotepa, and BCG (Bacillus Calmette-Guérin) are key for non-muscle-invasive bladder cancer (NMIBC), leveraging direct cytotoxicity or immune activation. Novel agents include nivolumab, pembrolizumab, and avelumab—checkpoint inhibitors restoring T-cell function, approved for metastatic or BCG-unresponsive disease. Anktiva (IL-15 agonist) and nadofaragene firadenovec (gene therapy delivering IFN-α2b) offer promising immuno-gene therapy options for high-risk NMIBC. Enfortumab vedotin, an antibody-drug conjugate targeting Nectin-4, is indicated post-platinum and immunotherapy failure. Drug selection considers toxicity profiles—e.g., nephrotoxicity (cisplatin), immune-related adverse events (checkpoint inhibitors), and bladder irritation (intravesical therapies)—with alternatives guided by patient-specific tolerability and biomarkers [12-14].

Nutrigenomics of Bladder Cancer

A range of plant- and animal-based compounds exhibit significant nutrigenomic potential in modulating bladder cancer risk via key gene targets such as Nrf2, p53, NF-κB, MAPK, and PPAR. Phytochemicals like betalains, polyphenols, flavonoids, isothiocyanates, curcumin, and withanolides from sources such as prickly pear, pomegranate, moringa, turmeric, and ashwagandha show antioxidant, anti-inflammatory, and pro-apoptotic effects. These compounds activate detoxification pathways and support DNA repair mechanisms, particularly through the Nrf2 and p53 pathways. Whole foods like figs, sweet potatoes, carrots, pumpkin, and millets contribute fiber and polyphenols that modulate the gut microbiome and systemic inflammation. Animal-based nutrients such as omega-3 fatty acids and selenium from fish (e.g., seer and red snapper) further enhance anti-inflammatory gene responses via PPAR. Importantly, compounds like piperine from black pepper may enhance the bioavailability of other anticancer agents. Collectively, these dietary factors hold promise in cancer prevention, especially in genotypes vulnerable to oxidative stress (e.g., GSTM1 null). Continued integration of nutrigenomics into cancer therapeutics may enable more personalized dietary strategies for bladder cancer management [15-16].

NUTRITIONAL VALUES

A diverse range of plant and marine-based foods contribute essential nutrients and bioactives that support cellular defense mechanisms relevant to bladder cancer prevention. Dietary fiber, abundant in guava (5 g/fruit), fox millet (8 g/100g cooked), and spleen amaranth, meets up to 14% of daily recommended values (DV), aiding gut health and detoxification. Vitamin C-rich sources like guava (126 mg/fruit) and lemon significantly exceed daily needs, providing up to 168% DV for women and over 500% for children, enhancing antioxidant defenses. Carrots, pumpkin, and sweet potatoes offer high vitamin A content (up to 961 mcg/serving), covering over 100% of daily needs and supporting cell differentiation. Magnesium, crucial for cellular signaling, is supplied by cactus fruit and moringa leaves, meeting 10–28% DV per serving. Omega-3 fatty acids from seer and red snapper meet 63–143% of daily requirements, modulating inflammation and gene expression. Fish also supplies high-quality protein (22 g/100g), contributing ~40–50% of daily protein needs. Phytocompounds like curcumin (200 mg/tsp turmeric), withanolides (5–10 mg/g ashwagandha), piperine (5–10 mg/g black pepper), berberine (50–100 mg/g daur haldi), and volatile oils from vach, nagarmotha, and gajpipal, though lacking formal RDA, exhibit functional bioactivity such as apoptosis induction, inflammation modulation, and enhanced nutrient bioavailability. These data underscore the integrative role of diet in supporting genomic stability and chemoprevention [17-19].

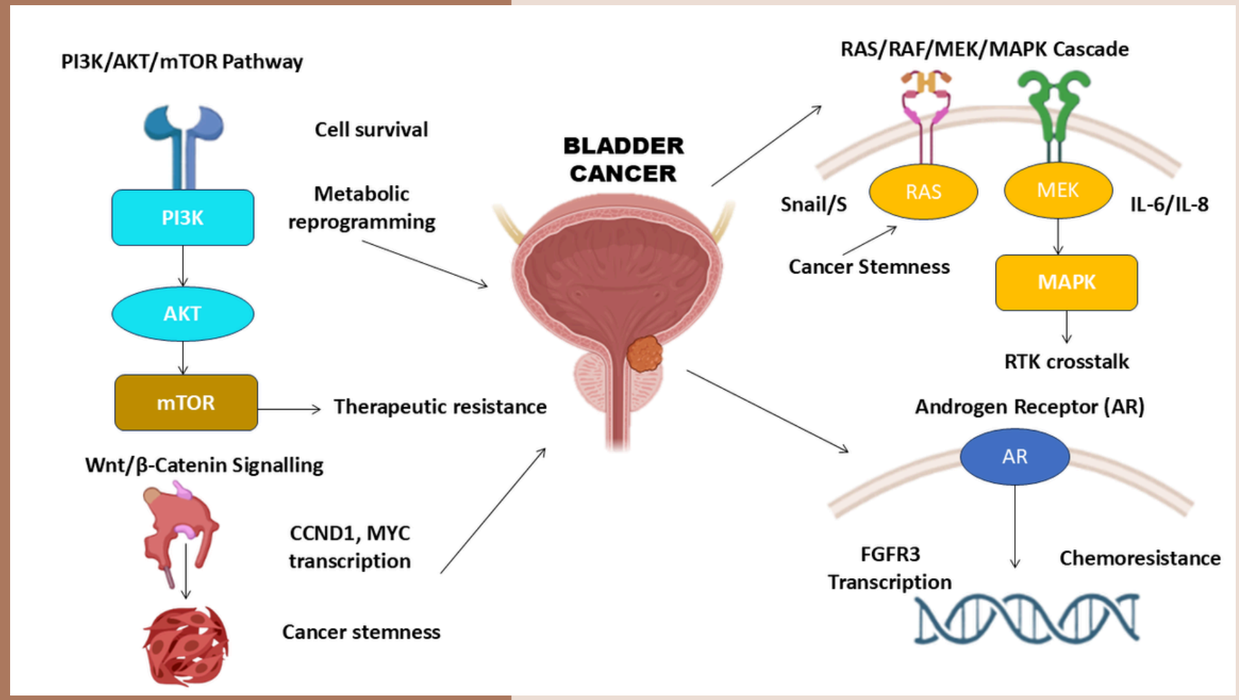
Genes associated in Bladder Cancer

Bladder cancer pathogenesis is driven by dysregulation of critical genes involved in cell cycle control, chromatin remodeling, and inflammation. Oncogenes such as CCNA2, CCNB1, CDK1, PLK1, AURKA, and AURKB are frequently overexpressed, facilitating unchecked proliferation and mitotic errors. Notably, AURKB serves as a strong diagnostic marker (AUC = 0.90), while FOXM1 enhances proliferation and modulates DNA repair via MSH2/MSH6. Pro-inflammatory signaling from IL6 contributes to immune evasion and tumor microenvironment remodeling. CALML5 and CDC20 further enhance metastatic potential and mitotic progression. DNA replication and repair genes like TOP2A and EP300 are altered, with implications in chemoresistance. Tumor suppressors TP53, CDKN2A, and ARID1A are frequently mutated or deleted in advanced disease stages, correlating with poor prognosis and genomic instability. Epigenetic regulators KDM6A and EP300 disrupt histone modifications, further enhancing tumor heterogeneity. This molecular landscape highlights diagnostic and therapeutic targets essential for stratified bladder cancer management [20-22].

Polymorphisms of Bladder Cancer

Genetic polymorphisms in DNA repair and inflammatory response genes significantly influence susceptibility to bladder cancer. Inflammatory SNPs such as TNF +488A and TNF -859T show increased frequency in patients (28.1% vs. 14.9%, P=0.0012), correlating with tumor grade and progression. Polymorphisms in DNA repair genes like XPC Lys939Gln, XPD Lys751Gln, and ERCC2 Asp312Asn disrupt nucleotide excision repair, elevating cancer risk (e.g., XPC, P=0.001). XRCC1 Arg399Gln, affecting base excision repair, and NBS1 Glu185Gln, involved in DNA damage response, also show associations with disease susceptibility (P=0.03). Detoxification gene deletion GSTT1 null exhibits strong risk association (OR 2.54, P=0.003). Furthermore, haplotypes such as POLB GATG and FANCA TAA are linked to 4-fold increased risk and higher disease prevalence. These genetic variations underscore the importance of polymorphism profiling in understanding individual risk and tailoring preventive strategies in bladder cancer [23-26].

Signalling Pathways



Bladder cancer pathogenesis involves the dysregulation of several oncogenic signaling pathways, contributing to tumor progression, metastasis, and therapeutic resistance:

1. **PI3K/AKT/mTOR Pathway:** Dysregulated in >50% of cases, promoting cell survival through AKT-mediated inhibition of apoptosis, and metabolic reprogramming via mTOR activation. Prevalence of PIK3CA mutations (20%) results in resistance to EGFR/HER2 inhibitors.
2. **Ras/Raf/MEK/MAPK Cascade:** Affected in >50% of non-Hodgkin's lymphomas, this pathway is activated by PTEN deletions, HRAS mutations (15-20%), and EGFR/HER2 overexpression. It induces epithelial-mesenchymal transition (EMT) and stimulates pro-inflammatory cytokines (IL-6/IL-8), enhancing invasiveness.
3. **Wnt/β-Catenin Signaling:** Aberrant activation in 30-40% of tumors drives nuclear β-catenin accumulation, upregulating transcription factors (CCND1, MYC), promoting cancer stemness, and correlating with cisplatin resistance (HR=2.1).
4. **Androgen Receptor (AR) Pathway:** AR overexpression in 60% of urothelial carcinomas enhances FGFR3 transcription in non-muscle-invasive tumors and mediates chemoresistance through efflux pumps, with higher activity observed in males [27-30].

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THANK YOU