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Clinicopathological Features and Survival Outcomes of Bladder Cancer: Evidence with Emphasis on the Egyptian Setting

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Abstract

Background: Bladder cancer is one of the most common genitourinary malignancies worldwide, with an estimated 614,298 new cases and over 220,000 deaths in 2022, and a major cause of cancer burden in Egypt with a high mortality-to-incidence ratio, where age-standardized incidence and mortality are 15.2 and 8.8 per 100,000. The disease spans a wide clinical spectrum, from non-muscle-invasive tumors characterized by frequent recurrence to muscle-invasive and metastatic disease with high mortality. Its epidemiology in Egypt has changed over recent decades, with declining schistosomiasis-associated squamous cell carcinoma and a growing predominance of smoking- and occupation-related urothelial carcinoma.

Clinicopathological characteristics such as stage, grade, histologic subtype, lymphovascular invasion, hydronephrosis, performance status, and nutritional status strongly influence treatment selection and survival. Management has evolved rapidly: transurethral resection and risk-adapted intravesical therapy for non-muscle-invasive disease, radical cystectomy or trimodality bladder preservation for muscle-invasive disease, and, more recently, immune checkpoint inhibitors, antibody-drug conjugates, and targeted agents across perioperative and advanced settings. Prognosis after radical cystectomy depends strongly on pathologic stage and nodal status, while cisplatin eligibility, based on renal function, performance status, hearing, and neuropathy, largely determines access to systemic therapy.

However, a considerable proportion of Egyptian patients still present with locally advanced or metastatic disease, and many are unfit for cisplatin-based therapy because of renal impairment or borderline performance status. Local survival data remain scattered across small, single-center retrospective series; in a South Egyptian cohort, 5-year overall survival was comparable after bladder preservation (56%) and radical cystectomy (60%), whereas survival for surgically managed muscle-invasive

schistosomiasis-associated disease has been reported at only 30% to 50%.

This review summarizes the epidemiology, risk factors, molecular biology, pathology, clinical presentation, diagnostic work-up, prognostic factors, treatment strategies, and survival outcomes of bladder cancer, together with practical considerations in diagnosis, bladder preservation, perioperative immunotherapy, and follow-up, with emphasis on the Egyptian setting. It also highlights current evidence gaps and directions for future research.

Keywords: Bladder Cancer, Clinicopathological Features, Survival Outcomes, Urothelial Carcinoma, Egypt

Introduction

Bladder cancer is a leading malignancy of the urinary tract. In 2022, an estimated 614,298 new cases were diagnosed worldwide, making it the ninth most commonly diagnosed cancer, with more than 220,000 deaths attributed to the disease in the same year [1]. In Egypt, the age-standardized incidence rate has been reported at 15.2 per 100,000 and the age-standardized mortality rate at 8.8 per 100,000, a relatively high mortality-to-incidence ratio [2].

The Egyptian epidemiologic profile has shifted considerably. Historically, chronic *Schistosoma haematobium* infection drove a high proportion of squamous cell carcinoma in younger patients. With successful control of schistosomiasis, urothelial carcinoma related to smoking and occupational exposures has become the predominant histology, bringing the national profile closer to that of Western countries [3]. Biologically, bladder cancer develops through two main pathways, producing non-muscle-invasive (NMIBC) and muscle-invasive (MIBC) disease with distinct molecular and clinical behavior.

Diagnosis rests on cystoscopy and transurethral resection of bladder tumor (TURBT), which establish histology, grade, and depth of invasion, and management is risk-adapted: intravesical therapy and surveillance for NMIBC [4], and radical cystectomy, perioperative systemic therapy, or trimodality bladder preservation for MIBC [5].

Treatment of advanced disease has changed substantially in recent years. Enfortumab vedotin combined with pembrolizumab has become a preferred first-line option in metastatic disease [6], and adjuvant nivolumab has become a standard option after cystectomy in high-risk patients [7]. Yet access to these agents, cisplatin eligibility, and late presentation continue to shape outcomes in many Egyptian centers.

Single-center Egyptian reports have described the clinicopathological pattern of the disease, including data from Zagazig University [8], but a consolidated synthesis linking clinicopathological features to treatment patterns and survival is lacking. This review therefore summarizes current evidence on bladder cancer with emphasis on prognostic clinicopathological factors and survival outcomes, and identifies gaps relevant to Egyptian practice.

Epidemiology of Bladder Cancer

Globally, bladder cancer ranks ninth among all cancers, and among men it is the sixth most common, with 523,674 new cases (5.4% of all cancers in men) recorded in 2022. Estimated new cases rose by about 7.1% compared with 2020 estimates, and roughly 1.95 million people were living with the disease within five years of diagnosis [1]. Incidence and mortality vary widely between regions, reflecting differences in tobacco exposure, occupational and environmental carcinogens, and access to care, which poses distinct challenges for public health and clinical practice.

In Egypt, bladder cancer remains one of the most frequent malignancies, particularly in men [8]. National estimates give an age-standardized incidence of 15.2 and a mortality of 8.8 per 100,000 [2]. The disease has undergone a marked histologic transition: with suppression of endemic schistosomiasis, the prevalence of squamous cell carcinoma has fallen while transitional (urothelial) carcinoma has increased [9,10].

Sex and age are strong demographic determinants. Men are approximately three to four times more likely than women to develop bladder cancer, a disparity attributed to higher smoking rates, greater occupational exposure, and hormonal and sex-chromosome differences. The median age at diagnosis in Western series is about 73 years, with more than 90% of cases occurring after age 55 [11]. Egyptian series report a male-to-female ratio of about 3:1 in the Zagazig experience [8], and other series describe a ratio near 5:1 with a median age at diagnosis of 59 to 60 years, roughly a decade younger than in Western populations [10].

Risk Factors for Bladder Cancer

Tobacco Smoking

Tobacco smoking is the most important modifiable risk factor for bladder cancer, increasing risk roughly threefold in current smokers compared with never-smokers [11]. Carcinogens such as aromatic amines and polycyclic aromatic hydrocarbons are excreted in urine and induce DNA damage in the urothelium, and the long latency of the disease explains its predominance in older patients.

Occupational and Environmental Exposures

Occupational exposure is considered the second most important risk factor after smoking, accounting for an estimated 7% to 20% of urothelial bladder cancers in men, with high-risk occupations including textile dyeing, painting, mining, and dry cleaning [12]. Exposure to aromatic amines, polycyclic aromatic hydrocarbons, metals, and solvents can form DNA adducts, and Egyptian data from textile dyeing workers have linked workplace exposures to biomarkers of bladder cancer [13]. Arsenic in drinking water is also an established risk factor [12], and chlorination by-products such as trihalomethanes have been estimated to contribute to a measurable fraction of cases in the United States.

Schistosomiasis and Chronic Inflammation

Chronic *S. haematobium* infection has long been linked to bladder cancer in Egypt. Egg deposition in the bladder wall causes granulomatous inflammation, fibrosis, and calcification, leading to squamous metaplasia and ultimately squamous cell carcinoma [3]. Mass

praziquantel treatment and public health efforts have reduced infection prevalence from 70-80% in the early twentieth century to very low levels in many areas, and the clinicopathologic profile has moved toward more urothelial histology, an older age at onset, and fewer squamous tumors [14]. Other chronic irritants, including recurrent urinary tract infections, stones, and long-term catheterization, also promote carcinogenesis [9].

Genetic Susceptibility, Diet, and Iatrogenic Causes

Lynch syndrome and polymorphisms in detoxification genes such as *NAT2* and *GSTM1* modify bladder cancer susceptibility. Lynch-related tumors typically show mismatch repair deficiency, which may predict response to immunotherapy. Western dietary patterns rich in red and processed meat have been associated with increased risk, while Mediterranean-type diets have been associated with lower risk. Iatrogenic exposures include cyclophosphamide, whose urinary metabolite acrolein injures the urothelium, and pelvic radiotherapy, which has been associated with an increased long-term risk of secondary bladder cancer [15].

Molecular Biology and Subtypes

Next-generation sequencing has expanded understanding of bladder cancer biology and established distinct molecular taxonomies [16]. Bladder cancer is among the most frequently mutated cancers, and *TERT* promoter mutations are among the commonest alterations, detected in a large majority of tumors.

NMIBC is generally genomically stable. Chromosome 9 deletions (involving *CDKN2A* and *TSC1*) occur in about half of cases, and oncogenic activation is frequently driven by *FGFR3* alterations together with *PIK3CA* mutations. Proteomic profiling has identified three NMIBC subtypes, ranging from a high-risk inflammatory group to a luminal group with the most favorable prognosis.

MIBC is more heterogeneous and genomically unstable, with frequent *TP53* and *RB1* inactivation. A consensus classification recognizes six subtypes: luminal papillary, luminal non-specified, luminal unstable, stroma-rich, basal/squamous, and neuroendocrine-like, the last being the most aggressive [17,18]. Subtype also relates to therapy response; for example, *ERCC2* mutations have been linked to cisplatin sensitivity. Papillary urothelial hyperplasia shares *TERT* and *FGFR3* mutations with papillary tumors, supporting a precursor relationship in the NMIBC pathway.

Pathology and Histologic Subtypes

Urothelial carcinoma accounts for more than 90% of bladder cancers in developed countries. The 2022 WHO classification recognizes multiple urothelial subtypes, including nested, micropapillary, plasmacytoid, sarcomatoid, giant cell, lipid-rich, and clear cell variants [19]. Histologic variants generally carry a poorer prognosis than conventional urothelial carcinoma. Plasmacytoid carcinoma, for example, typically presents at an advanced stage and warrants aggressive management.

Squamous cell carcinoma represents about 3% to 5% of bladder cancers in Western countries but up to 20% to 30% in schistosomiasis-endemic regions such as Egypt [3]. It usually presents at an advanced local stage, often after years of irritative symptoms, and tends to

extend locally rather than metastasize early [20]. Radical cystectomy with pelvic lymphadenectomy is the standard treatment, as these tumors respond poorly to urothelial-type chemotherapy. Primary adenocarcinoma is rare (0.5% to 2%) and may be urachal or non-urachal; it is often diagnosed late, and radical cystectomy with en bloc urachal resection is preferred for localized disease [21].

Staging follows the AJCC TNM system, which defines the primary tumor (Ta, Tis, T1 to T4), regional nodes (N0 to N3), and metastasis (M0 to M1b), and which separates NMIBC (Ta, T1, Tis) from MIBC (T2 to T4) to guide management [5].

Clinical Presentation

Painless gross hematuria is the most common presenting symptom worldwide, reported in 80% to 90% of patients [4]. In Egyptian series, gross hematuria with clots was reported in 72% of patients at Minia University Hospital, with a younger mean age at diagnosis (about 60 years) than in Western series (about 70 years) [10]. In schistosomiasis-endemic regions, patients tend to present earlier in life (often at 40 to 50 years) with mixed symptoms, including hematuria, dysuria, and suprapubic pain related to chronic inflammation and calcification [3].

Irritative voiding symptoms (frequency, urgency, dysuria) are more characteristic of carcinoma in situ and should prompt urologic assessment, while urinary tract infection must be excluded because it can mimic or coexist with bladder cancer. Reports have also linked the initial clinical presentation to histopathological and morphological tumor characteristics. Delays in diagnosis and limited screening in Egypt mean that advanced presentations with flank pain, pelvic mass, obstruction, or systemic symptoms remain relatively common [10].

Diagnostic Work-up and Staging

Cystoscopy, Cytology, and Biomarkers

Cystoscopy remains the cornerstone of diagnosis, since it allows direct visualization, biopsy, and resection in one procedure [22]. Blue-light cystoscopy detects about 15% more Ta tumors and about 41% more carcinoma in situ lesions than white-light cystoscopy, at the cost of a higher false-positive rate, and narrow-band imaging improves detection of flat lesions [23,24]. Urine cytology reported by the Paris System emphasizes detection of high-grade urothelial carcinoma. Urinary biomarkers (NMP22, BTA, UroVysion, ImmunoCyt) have higher sensitivity than cytology for some tumors but frequently give false-positive results in infection, stones, or hematuria, so they remain adjuncts rather than replacements for cystoscopy [25,26].

Cystoscopic appearance helps orient the diagnosis: carcinoma in situ appears as flat, reddish, velvety patches, non-muscle-invasive tumors as papillary, easily bleeding frond-like lesions, muscle-invasive tumors as flat, nodular, or sessile growths, and squamous cell carcinoma as nodular, necrotic, exophytic masses typically involving the lateral wall and trigone [23]. Among urinary biomarkers, NMP22 detects proteins released from tumor cells, BTA tests detect complement factor H-related protein, and UroVysion is a fluorescence in situ hybridization test that identifies changes in chromosomes 3, 7, and 17 and deletion of 9p21, making it more useful for high-grade tumors [25]. ImmunoCyt uses fluorescent antibodies

against tumor antigens on exfoliated urothelial cells and offers higher sensitivity than cytology, particularly for low-grade tumors, but false-positive results remain a limitation for most of these tests [26].

Imaging and Metastatic Evaluation

CT or MR urography is preferred for upper tract evaluation, while imaging plays a minor role in primary detection. In confirmed MIBC, CT or MRI is essential for local staging and detection of metastases, and FDG PET/CT has shown sensitivities of 48% to 87% and specificities of 90% to 97% for metastatic disease [27].

Transurethral Resection of Bladder Tumor

TURBT provides both a pathological diagnosis and complete removal of visible tumor. Documentation of tumor features and the presence of detrusor muscle in the specimen are key quality markers. En bloc resection keeps the tumor intact and may improve staging accuracy and reduce perforation risk [28]. Even with good technique, incomplete resection occurs in up to 50% of cases, and T1 tumors are upstaged to T2 in up to 20% of cases when muscle is present and up to 40% when it is absent, which is why repeat TURBT is recommended for T1 and incompletely resected high-grade disease [29]. Repeat TURBT in newly diagnosed T1 disease has been associated with improved 5-year recurrence-free survival (by 25%) and progression-free survival (by 14%) [4].

Complete resection can be achieved by conventional piecemeal resection or by en bloc resection, and detrusor muscle in the specimen is the key marker of TURBT quality because its absence is linked to residual tumor, early recurrence, and under-staging. Monopolar and bipolar resection show comparable efficacy and safety, although bipolar systems may reduce bleeding and obturator nerve stimulation [30]. Small papillary tumors discovered during transurethral resection of the prostate can be removed in the same session without increasing recurrence or progression, provided there is no perforation and postoperative intravesical chemotherapy is feasible [30]. The most common complications are bleeding and urinary tract infection; bladder perforation occurs in 1% to 5% of cases, may be intraperitoneal or extraperitoneal, and can require prolonged catheterization or surgical repair.

Prognostic Factors and Risk Stratification

Pathologic stage and grade remain the dominant determinants of prognosis. Ta lesions are usually indolent, whereas T1 tumors carry higher recurrence and progression risk, and muscle-invasive tumors are uniformly high-grade with a higher metastatic potential [4]. Five-year overall survival has been reported at about 75% for pT1, 50% for pT2, and 20% for pT3 disease [31]. Additional adverse factors include variant histology, lymphovascular invasion, carcinoma in situ, large or sessile tumors, multicentricity, incomplete resection, and positive margins.

Host-related factors are increasingly studied. Smoking status has been examined as a prognostic factor and in relation to neoadjuvant chemotherapy response and outcomes after cystectomy [32]. Body mass index has shown a complex relationship with outcomes, including an "obesity paradox" described in a large national database, and in older patients with bladder cancer. Low body weight may reflect frailty or occult malnutrition rather than a

direct effect of weight. Pretreatment hydronephrosis has been evaluated as a prognostic marker in both cystectomy series and radiotherapy-based bladder-preserving strategies [33]. Together, these factors help explain why stage and grade interact with patient fitness when treatment is selected.

Management of Non-Muscle-Invasive Bladder Cancer

Approximately 80% of patients present with NMIBC, which has a favorable survival but a high recurrence rate that makes it a considerable healthcare burden [4]. After TURBT, a single immediate intravesical instillation (mitomycin C or gemcitabine) within 24 hours reduces recurrence by roughly 10% to 15% at five years, mainly in low-grade Ta tumors, but it is contraindicated when perforation is suspected [34].

Risk stratification (low, intermediate, high) guides further therapy and follow-up [35]. Low-risk patients need no adjuvant therapy beyond the single instillation, with early cystoscopic surveillance. Intermediate-risk patients receive a six-week induction course of BCG or mitomycin C with maintenance [36], and high-risk patients (high-grade Ta/T1, carcinoma in situ, variant histology, lymphovascular invasion) receive induction BCG followed by maintenance for up to three years [4].

BCG-unresponsive disease is defined as persistent or recurrent high-grade NMIBC within twelve months of an adequate BCG course [37]. Radical cystectomy remains the preferred option, while bladder-sparing alternatives include nadofaragene firadenovec (complete response of 53% at three months) [38], sequential intravesical gemcitabine and docetaxel (one-year recurrence-free survival of 65%), the TAR-200 delivery system (76% complete response in carcinoma in situ in SunRISe-1) [39], the oncolytic adenovirus CG0070 (about 75% complete response in BOND-003) [40], and systemic pembrolizumab for carcinoma in situ [37]. The global shortage of BCG adds urgency to these developments [40].

Combination strategies are also under study. The QUILT-3.032 trial of nogapendekin alfa inbakicept plus BCG reported a 71% complete response rate, with durable responses of 45% at 12 months and 33% at 18 months [41]. Management of BCG-unresponsive disease nevertheless remains a major therapeutic challenge, and a well-performed TURBT with optically enhanced cystoscopy and meticulous pathological evaluation is the essential first step [40].

Management of Muscle-Invasive Bladder Cancer

Surgery

Radical cystectomy with pelvic lymph node dissection is the standard of care for resectable MIBC (cT2 to T4a, N0/1, M0). Robot-assisted techniques offer comparable oncologic outcomes with reduced blood loss and shorter hospital stay [34]. The SWOG S1011 trial found that extended lymphadenectomy did not improve survival compared with standard dissection but increased morbidity [42]. Urinary diversion may be incontinent (ileal conduit) or continent (neobladder, Indiana pouch) according to patient selection, and enhanced recovery protocols have improved postoperative recovery [43]. Survival after cystectomy depends strongly on pathologic stage and nodal status [43].

Ten-year recurrence-free survival after cystectomy ranges from 86% in pT0 tumors without nodal involvement to 45% in pT4 disease, and falls to approximately 34% when lymph nodes are positive. Robot-assisted cystectomy with intracorporeal urinary diversion has increased the number of days alive and out of hospital compared with open surgery, highlighting perioperative benefits [43]. Pelvic organ-preserving cystectomy in women and prostate-sparing cystectomy in men have also been explored, and both require careful patient selection [34].

Perioperative Systemic Therapy

Neoadjuvant cisplatin-based chemotherapy is recommended for eligible patients with cT2N0 or higher disease. In the VESPER trial, dose-dense MVAC gave higher 5-year overall survival than gemcitabine-cisplatin (66% vs 57%), at the price of more grade 3 or higher toxicity [44]. Up to half of patients are cisplatin-ineligible because of renal impairment or other comorbidities, and a creatinine clearance of 60 mL/min or more is conventionally required [45].

Chemoimmunotherapy has produced high pathologic response rates in phase II studies: pT0 in 42% with neoadjuvant pembrolizumab, 36% with pembrolizumab plus gemcitabine and split-dose cisplatin, 43% clinical complete response with nivolumab plus gemcitabine-cisplatin, and 33% with durvalumab plus chemotherapy. A phase III trial of perioperative durvalumab with neoadjuvant chemotherapy reported 24-month event-free survival of 67.8% versus 59.8% and overall survival of 82.2% versus 75.2% [46]. In cisplatin-ineligible patients, perioperative enfortumab vedotin plus pembrolizumab improved 2-year event-free survival to 74.7% versus 39.4% with surgery alone (HR 0.40) [47].

When adjuvant therapy is needed, cisplatin-based chemotherapy is given within 12 to 14 weeks to eligible patients with pT3 or higher or node-positive disease [48]. Adjuvant nivolumab improves disease-free survival in patients who are ineligible for or decline cisplatin, with benefit shown in the chemotherapy-naïve subgroup [49] and after prior neoadjuvant chemotherapy [7]. Adjuvant atezolizumab, in contrast, did not improve disease-free survival in IMvigor010 [50].

Bladder Preservation

Trimodality therapy (maximal TURBT, radiosensitizing chemotherapy, and radiotherapy) is the most accepted bladder-preserving approach, with an institutional experience reporting 5-year overall survival of about 61% and salvage cystectomy in about 9% [51]. Partial cystectomy suits only highly selected patients with small solitary tumors [52]. Long-term randomized evidence supports chemoradiotherapy, and real-world cohorts treated with definitive concurrent chemoradiotherapy show comparable feasibility in daily practice; pooled analyses have compared bladder-preservation alternatives in non-metastatic MIBC.

Bladder preservation is intended for carefully selected patients who are unsuitable for, or refuse, radical cystectomy, and its foundation is a maximal TURBT that removes all visible tumor while limiting the risk of perforation [51]. In the same institutional experience, 5-year disease-free survival was about 61% and bladder-preserved disease-free survival about 60% [51]. Partial cystectomy may be considered for small (under 3 cm), solitary tumors that do

not involve the trigone, are not associated with carcinoma in situ, and do not arise in a diverticulum, but the risk of recurrence is significantly higher and strict follow-up is required [52].

Systemic Treatment of Advanced Disease

In first-line treatment of metastatic disease, enfortumab vedotin plus pembrolizumab improved median overall survival from 16.1 to 31.5 months compared with platinum-based chemotherapy [6]. Nivolumab plus gemcitabine-cisplatin is an alternative, improving median overall survival from 18.9 to 21.7 months [53]. Atezolizumab plus chemotherapy and pembrolizumab plus chemotherapy did not improve overall survival. When these options are unsuitable, gemcitabine-cisplatin or MVAC remains available, with similar efficacy and better tolerability for gemcitabine-cisplatin [48]. Cisplatin ineligibility is commonly defined by ECOG performance status of 2 or higher, creatinine clearance below 60 mL/min, grade 2 or higher hearing loss, or grade 2 or higher neuropathy [54]. For these patients, pembrolizumab monotherapy achieved a 29% response rate [55], and avelumab maintenance after platinum chemotherapy improved survival in responders [56].

Because cisplatin-based chemotherapy is limited by nephrotoxicity, ototoxicity, and peripheral neuropathy, careful pretreatment assessment of renal function, performance status, hearing, and neurological status is essential [54]. In Egyptian practice, where renal impairment and borderline performance status are common at presentation, this assessment largely determines whether patients can receive platinum-based or immunotherapy-based regimens.

For patients with *FGFR3* mutations or *FGFR2/3* fusions, erdafitinib improved overall survival compared with chemotherapy (12.1 vs 7.8 months) [57], although it was not superior to pembrolizumab in a randomized comparison. Enfortumab vedotin improved median overall survival from 8.97 to 12.88 months after platinum and checkpoint inhibitor therapy [58], and pembrolizumab prolonged survival over chemotherapy in the second-line setting. Atezolizumab showed improved long-term survival in updated analyses, and sacituzumab govitecan combined with pembrolizumab achieved a 41% response rate. Later-line options include platinum rechallenge, taxanes, gemcitabine, and vinflunine [59]. Palliative radiotherapy and surgery provide symptom control [48].

Follow-up

Follow-up is tailored to disease category. For low-risk NMIBC, cystoscopy is performed at 3 and 9 months and then annually up to five years, after which surveillance may be discontinued because late recurrence risk is very low [60]. For intermediate- and high-risk NMIBC, cystoscopy with cytology every 3 months for the first two years, then every 6 months to year 5 and annually thereafter, reflects a persistent lifelong risk [4]. For MIBC treated by cystectomy or trimodality therapy, most relapses occur in the first two years, and follow-up combines clinical review, renal function, cytology, and cross-sectional imaging every 3 to 6 months, de-escalating to every 6 to 12 months up to year 5; no single standardized schedule exists [5].

Survival Outcomes in Bladder Cancer

Survival endpoints in the literature capture different aspects of disease control: overall survival is the most meaningful but requires long follow-up and is diluted by non-cancer deaths, progression-free survival is used mainly in advanced disease, disease-free or recurrence-free survival after complete resection, and cancer-specific survival to isolate disease-related mortality [4,5]. In NMIBC, many more patients die with the disease than of it.

Population data from the SEER database report 5-year relative survival of 97% for carcinoma in situ, 71% for localized disease, 39% for regional disease, and 8% for metastatic disease [31]. Egyptian data are more limited. In a cohort from the South Egypt Cancer Institute (166 patients, T1-4N0M0), 5-year overall survival was comparable between bladder preservation (56%) and radical cystectomy (60%), with 5-year disease-free survival of 45% and 53% respectively [61]. At the National Cancer Institute in Cairo, patients undergoing radical cystectomy for muscle-invasive urothelial carcinoma had a 3-year disease-free survival of 56% [62]. A regional review of schistosomiasis-associated bladder cancer reported 5-year survival of 30% to 50% for surgically managed muscle-invasive disease, reflecting advanced stage at presentation and a historically higher proportion of squamous histology [3].

Table 1. Selected clinical trials informing current treatment and survival outcomes in urothelial carcinoma.

Trial / study	Setting	Key finding	Ref.
EV-302	First-line metastatic disease	Enfortumab vedotin plus pembrolizumab improved median overall survival from 16.1 to 31.5 months versus platinum chemotherapy	[6]
CheckMate-901	First-line metastatic disease	Nivolumab plus gemcitabine-cisplatin improved median overall survival from 18.9 to 21.7 months	[53]
THOR	FGFR-altered, pretreated	Erdafitinib improved overall survival versus chemotherapy (12.1 vs 7.8 months)	[57]
EV-301	Second-line metastatic disease	Enfortumab vedotin improved median overall survival from 8.97 to 12.88 months	[58]
KEYNOTE-905 / EV-303	Perioperative, cisplatin-ineligible MIBC	Two-year event-free survival 74.7% with enfortumab vedotin plus pembrolizumab versus 39.4% with surgery alone (HR 0.40)	[47]
NIAGARA	Perioperative, cisplatin-eligible MIBC	Durvalumab added to gemcitabine-cisplatin: 24-month event-free survival 67.8% vs 59.8% and overall survival 82.2% vs 75.2%	[46]
CheckMate 274	Adjuvant after cystectomy	Adjuvant nivolumab prolonged disease-free survival (median 25.9 vs 13.7 months in the chemotherapy-naive subgroup)	[7,49]
SWOG S1011	Radical cystectomy	Extended lymphadenectomy did not improve survival over standard dissection and increased morbidity	[42]
SunRISe-1	BCG-unresponsive carcinoma in situ	TAR-200 produced a 76% complete response rate	[39]

Evidence Gaps and Future Directions

Several gaps limit the application of international evidence to Egyptian patients. Most pivotal trials enrolled predominantly cisplatin-eligible patients treated in high-resource settings, whereas a considerable proportion of Egyptian patients present with locally advanced disease, renal impairment, or borderline performance status. Local survival data are largely derived from small single-center retrospective series with heterogeneous staging, treatment, and follow-up, which makes comparison between centers difficult [61,62].

Priorities for future research include multicenter prospective registries with standardized reporting of stage, grade, histologic subtype, lymphovascular invasion, hydronephrosis, performance status, and nutritional variables; confirmation of schistosomiasis exposure; evaluation of bladder-preserving strategies and perioperative immunotherapy in the Egyptian population; and assessment of access, cost, and feasibility of antibody-drug conjugates and checkpoint inhibitors within national treatment pathways.

Conclusion

Bladder cancer is a heterogeneous disease whose outcome is determined mainly by stage and grade, with histologic subtype, host factors, and treatment selection modifying prognosis. In Egypt, the epidemiologic shift from schistosomiasis-associated squamous carcinoma toward smoking- and occupation-related urothelial carcinoma has changed the clinical profile, yet late presentation, cisplatin ineligibility, and limited access to newer agents continue to limit outcomes.

Modern management offers a growing range of options, from risk-adapted intravesical therapy and bladder-preserving trimodality treatment to perioperative immunotherapy and antibody-drug conjugates. Egyptian evidence on survival is still derived largely from small retrospective series. Future research should focus on multicenter prospective registries, standardized reporting of clinicopathological and nutritional variables, confirmation of schistosomiasis exposure, and the integration of molecular subtyping and novel agents into regional treatment pathways.

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