

# Pathological factors and associated clinical outcomes of patients with urothelial neoplasms treated at King Abdulaziz University Hospital : a single center experience

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## Abstract

**Objectives:** To evaluate the operative and pathologic factors associated with long-term survival and local recurrence in patients treated for urothelial tumors.

**Methods:** A retrospective study was performed that included 47 patients with resected urothelial tumors at King Abdulaziz University Hospital, Jeddah, Saudi Arabia from 2009 to 2017.

**Results:** In this study, 89.36% of patients had bladder tumors, and most were diagnosed based on transurethral resection of bladder tumor (TURBT). The histological grade was high in 74.47% of patients; in patients who underwent surgery, 17.39% had positive margins, 45.45% had perineural invasion, and 38.10% had lymphovascular/perivascular invasion. The median recurrence time was 40.2 months, and recurrence-free survival rates were 85.5%, 71.6%, and 44% for one, two, and five years, respectively.

**Conclusion:** Our outcomes are comparable to those in the literature; however, more accurate data collection and future national collaboration are essential to improve patient outcomes.

**Key words:** long-term, survival, recurrence, urothelial, tumors, Saudi Arabia

## Introduction

Bladder cancer is the 11th most common cancer in Saudi adult men and 12th in women according to the 2020 Cancer Registry Report(1). Urothelial carcinoma, also known as transitional cell carcinoma, is the most common histological variant of bladder cancer. It most commonly involves the bladder, however, other urinary tract sites lined by transitional epithelium, namely the renal pelvis, ureters, and urethra, could also be involved (2,3).

Less common variants of bladder cancer include adenocarcinomas, squamous cell carcinomas, mixed histologies, neuroendocrine tumors, and sarcomas. Collectively, these cancers account for less than 5%–10% of all bladder cancers in the United States (4). Tumors of the upper urinary tract are almost twice as common in men compared to women, with a mean age of 73 years at diagnosis (5). The age-adjusted annual incidence rates of ureteral and renal pelvis cancer in the Surveillance, Epidemiology, and End (SEER) database was 0.91 and 1.15/100,000 person-years during the period from 1997 to 2005 (6).

The most commonly used staging system is the tumor, node, and metastasis (TNM) staging system by the The American Joint Committee on Cancer (AJCC). Treatment recommendations for urothelial carcinoma of the bladder are based on many factors, but the most important is the presence or absence of muscle invasion, which is categorically divided into non-muscle-invasive disease (Ta, T1, and Tis) and muscle-invasive disease ( $\geq$ T2 disease). Other factors affecting management include histology, grade, and depth of invasion, and this information can be obtained through biopsy and TURBT specimens. These factors are used to estimate the probability of recurrence and progression to a more advanced stage. Patient bladder function, comorbidities, and life expectancy are also important considerations (7).

For muscle invasive bladder cancer (MIBC) with limited or no nodal metastasis, the standard of care is to offer neoadjuvant cisplatin-based chemotherapy (NAC) followed by radical cystectomy (RC) and lymph node dissection(8). The addition of NAC has been shown in multiple randomized prospective trials and a large meta-analysis to improve survival as well as complete response rate in MIBC (9). The role of lymph node dissection at the time of RC has been controversial. Multiple retrospective trials have found that lymph node dissection plays an important prognostic and therapeutic role. A recent review of the SEER database and the database of the Changhi Tenth People's Hospital in China demonstrated that the number of lymph nodes dissected was independently associated with prolonged survival (10). However, a European trial has recently failed to prove the advantage of extended lymphadenectomy over a limited lymphadenectomy in all oncologic outcomes measured (11). An ongoing large phase 2 randomized trial by the Southwest Oncology Group (SWOG) examining the role of extended lymph node dissection at the time of RC is currently underway (12).

Since bladder cancer is a common malignancy in old age with comorbid diseases and potential renal impairment, the standard approach with NEC and RC may not be feasible.

Treatment options for patients with MIBC who are not candidates for NAC or RC or who refuse the RC approach include RC alone; bladder preservation with radiation therapy, with or without chemotherapy and/or prior TURBT; and, for select patients, TURBT alone (7). There is an increasing interest in organ preservation approaches with trimodal therapy (TURBT, radiation, and chemotherapy), even for RC candidates (13).

For non-muscle invasive bladder cancer (NMIBC), the management of choice is TURBT. Depending on the tumor grade, the clinical stage (T0, Ta, Tis, or T1), presence of residual tumor, a combination of the above, intravesical chemotherapy, Bacille Calmette-Guerin (BCG), or even cystectomy could be recommended (14).

The risk of recurrence in patients with non-muscle invasive urothelial bladder carcinoma depends on multiple factors. Tumor grade is the most important prognostic factor for progression. T category, tumor size, tumor number, concurrent CIS, intravesical therapy, response to bacillus Calmette-Guerin at 3- or 6-month follow-up, prior recurrence rate, age, sex, lymphovascular invasion, and depth of lamina propria invasion are other important clinical and pathological parameters to predict recurrence and progression in patients with NMIBC (15).

For most patients with upper urinary tract urothelial cancers, nephroureterectomy with excision of a cuff of normal bladder and bladder mucosa is the preferred procedure; the frequent occurrence of synchronous or metachronous multifocal tumors makes a less extensive resection contraindicated (16,17,18).

Open and laparoscopic surgical approaches appear to be equally safe and effective, assuming adequate expertise is available and complete resection of the intramural ureter with bladder cuff is performed (19). Some patients with particular conditions may benefit from renal-sparing surgery, such as those with a single kidney, impaired renal function, bilateral lesions, or other nephropathies (20). In addition, those with low-grade, low-stage tumors of the ureter or renal pelvis may also be candidates for this approach (19). Treatment options in these settings include retrograde uretero-pyeloscopy alone or in conjunction with antegrade percutaneous resection (21,22,23).

This study aimed to identify the operative and pathologic factors affecting long-term survival and local recurrence in a tertiary center in Jeddah, Saudi Arabia, for urothelial tumors.

## Subjects and Methods

**Study design and time frame:** A retrospective study was conducted at King Abdulaziz University Hospital (KAUH), Jeddah, Saudi Arabia during 2018-2020.

**Sampling methodology:** We collected data for all patients treated at our center between 2009 and 2017.

**Study instrument:** Data were obtained from the electronic medical records through a data collection sheet for every patient that included items about sex, date of birth, death

and date of death, site of tumor, date of first pathological diagnosis, method of diagnosis, metastasis, site of metastasis, transurethral resection of bladder tumor procedure and the date, the presence of muscle invasion, any procedures (nephrectomy, urethrectomy, Ureterectomy, cystectomy), chemotherapy treatment and the date of first cycle, cytology and histological type and grade, margin, perineural invasion, lymphovascular or perivascular invasion, recurrence or progression and the date, TNM staging, and last follow-up date.

**Ethical considerations:** Ethical clearance was obtained from the research ethics committee of KAUH, Saudi Arabia.

**Data analysis:** Stata SE, version 15.0, (StataCorp LLC, TX) was used for data analysis, and survival analysis was performed using the Kaplan–Meier method.

## Results

### Patients' demographics

A total of 47 patients with resected urothelial tumors were identified and included in this study. The mean age was  $62.97 \pm 2.1$  years, with a predominance of male patients (85.11%). Most patients (89.36%) had a bladder tumor, and the majority were diagnosed based on transurethral resection of bladder tumor (TURBT), with only 4.26% diagnosed via biopsy. Of those who underwent TURBT, 85.11% were curative. The number of patients who underwent other surgical procedures was 62.5% (29), of which 36.96% underwent cystectomy. The other patient characteristics are shown in Table 1.

### Tumor characteristics and treatment

Cytology was performed in 34 patients, 21 of whom showed atypical cells, and nine patients had clear malignant changes. Moreover, the histological grade was high in 35 patients (74.47%). Among those who underwent surgery, 17.39% had positive margins, 45.45% had perineural invasion, and 38.10% had lymphovascular/perivascular invasion.

Data from 31 patients documented muscle invasion by the tumor. Of these, 20 patients underwent TURBT as a curative modality of management, 11 underwent TURBT for biopsy purposes, and 8 underwent cystectomy. For those who underwent TURBT, none of the patients who received TURBT as curative management had muscle invasion, while 10 of 11 patients who received TURBT for diagnostic purposes had muscle invasion. In contrast, the majority (7 of 8 patients) who underwent cystectomy had muscle invasion.

Regarding neoadjuvant and adjuvant treatment, unfortunately, a significant amount of data was missing, and no correlation between outcomes and adjuvant therapy could be performed.

### Recurrence and survival data

The data showed that the overall median recurrence time was 40.2 months. Recurrence-free survival (RFS) was 85.5% for one year, 71.6% for two years, and 44% for five years (Figure 1). The univariate analysis results showed a higher risk of death with increased age (hazard ratio, 1.089; 95% confidence interval;  $p$  value = 0.014), and further analysis revealed no significant difference between mortality risk and sex, tumor site, histopathology details, and invasion (Table 2).

Table 1: Patient demographics and clinical information

	Summary statistics
<b>Characteristics</b>	
Total number of patients	47 (100%)
Age (mean $\pm$ SD), years	62.97 $\pm$ 2.1
<b>Sex</b>	
Female	7 (14.89%)
Male	40 (85.11%)
<b>Clinical information</b>	
<b>Site of tumor</b>	
Pelvic ureter	5 (10.64%)
Bladder	42 (89.36%)
<b>Method of diagnosis</b>	
TURBT	40 (85.11%)
Biopsy	2 (4.26%)
Surgical resection	5 (10.64%)
<b>TURBT</b>	
Yes	39 (82.98%)
No	8 (17.02%)
<b>TURBT type</b>	
Curative	21 (53.85%)
Biopsy	18 (46.15%)
<b>Nephrectomy</b>	
Yes	6 (12.77%)
No	41 (87.23%)
<b>Ureterectomy</b>	
Yes	5 (10.64%)
No	42 (89.36%)
<b>Cystectomy</b>	
Yes	17 (36.96%)
No	29 (63.04%)
<b>Urethrectomy</b>	
Yes	1 (2.13%)
No	46 (97.87%)
<b>Cytology</b>	
Malignant	9 (19.15%)
Atypical	21 (44.68%)
No malignancy	4 (6.38%)
Not done	14 (29.79%)
<b>Histological grade</b>	
Low grade	12 (25.53%)
High grade	35 (74.47%)
<b>Margin</b>	
Positive	4 (17.39%)
Negative	19 (82.61%)
<b>Perineural invasion</b>	
Yes	5 (45.45%)
No	6 (54.55%)

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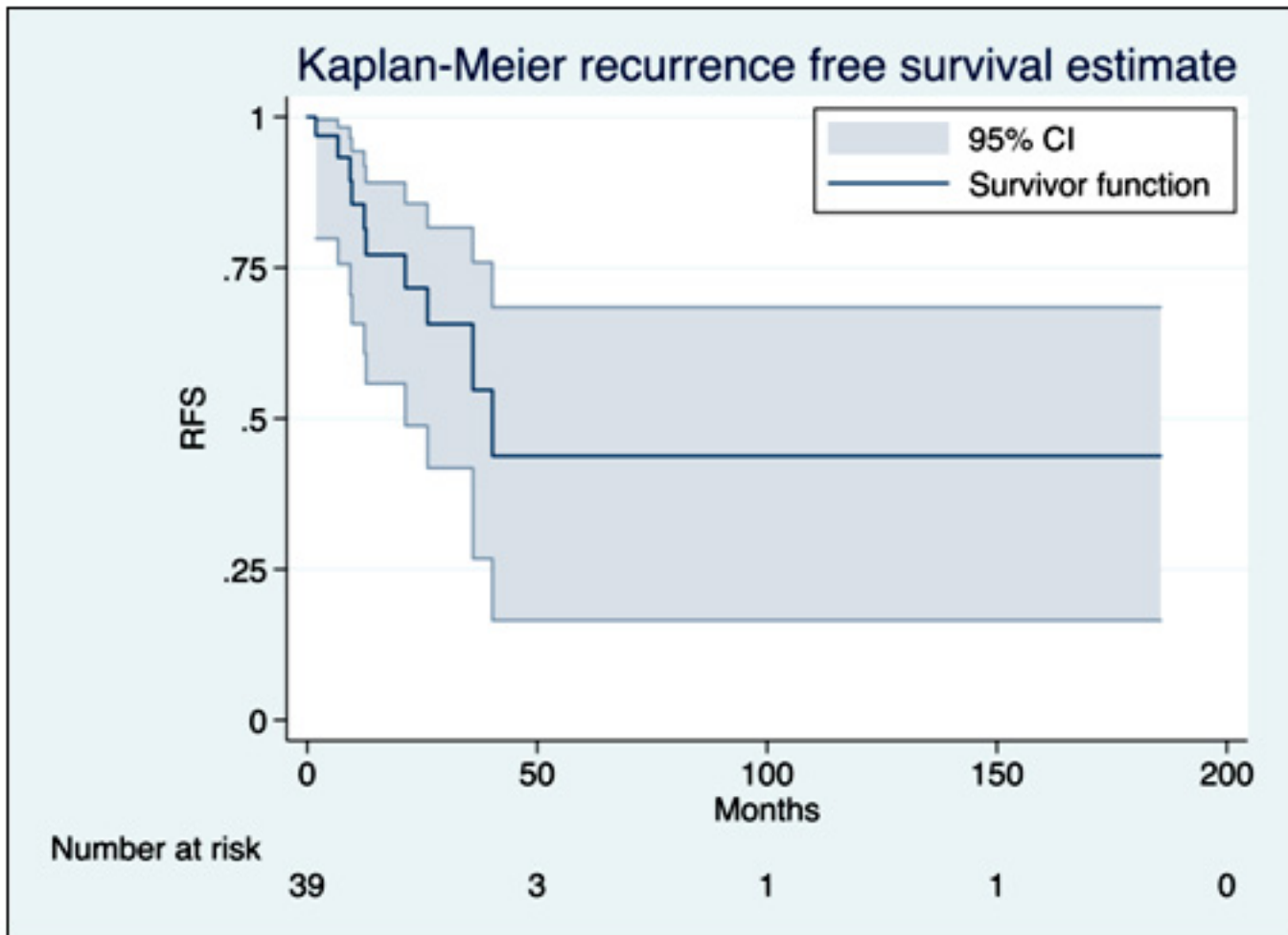
**Table 1: Patient demographics and clinical information (continued)**

Lymphovascular/Perivascular invasion	
Yes	8 (38.10%)
No	13 (61.90%)
Muscle invasion	
Yes	10 (32.26%)
No	21 (67.74%)
TNM staging	
T staging	
T1	9 (45%)
T2	5 (25%)
T3	4 (20%)
T4	2 (10%)
N staging	
N+	5 (23.81%)
N0	15 (71.43%)
Unknown	1 (4.76)

**Table 2: Univariate analysis for variables related to recurrence in patient with resected bladder tumor**

Variable	Hazard Ratio (95% CI)	P-value
Age	1.089 (1.017–1.166)	0.014
Sex	0.6991 (0.179–2.718)	0.605
Site of tumor	0.972 (0.120–7.871)	0.980
Histological grade	1.220 (0.314–4.735)	0.773
Margin	0.756 (0.073–7.830)	0.815
T stage	1.119 (0.3625–3.4530)	0.845
N stage	0.4553 (0.0844–2.456)	0.360
Perineural invasion	2.392 (0.2134–26.82)	0.479
Lymphovascular/Perivascular invasion	4.699 (0.4854–45.48)	0.182

Figure 1: Kaplan- Meier recurrence free survival estimate



## Discussion

This study was performed to evaluate operative and pathologic factors associated with long-term survival and local recurrence in patients treated for urothelial tumors in a tertiary center in Jeddah, Saudi Arabia. The data of patients who were treated for urothelial tumors in our cohort showed that the mean age at diagnosis was 63 years. This finding is consistent with those of another study, in which the median age of patients was 66 years (24). While urothelial tumor can occur at any age, it is generally a disease in middle-aged and elderly people. Not surprisingly, age is now widely accepted as the greatest single risk factor for developing urothelial bladder cancer (UBC) (25). Various descriptive studies have shown that individuals aged  $\geq 65$  years have 11 times the incidence of cancer in general. In fact, the median age at diagnosis is approximately 70 years (26).

There was a male predominance (85%) in our study. Fajkovic et al. found that men have up to a four-fold higher UBC incidence than do women (27). A retrospective study of the Netherlands Cancer Registry spanning the period 1989–1994 identified 20,541 patients diagnosed with UBC, of whom 80% were male and 20% female (28).

Another study was conducted in 17 Spanish hospitals with 615 patients with newly diagnosed UBC and found

a 6.7-fold greater risk of diagnosing UBC in men than in women for both non-muscle-invasive and muscle-invasive disease (29). While there is no uniform theory to explain the sex differences in UBC presentation and behaviors, a suggested explanation could be related to excessive environmental exposure to carcinogens such as tobacco and industrial chemicals in men compared to that in women(30). Moreover, the historically lower smoking prevalence in women may also play a role(31).

Most of our patients underwent TURBT for initial diagnosis and treatment. TURBT is the 'gold standard' for the diagnosis and therapy of non-muscle-invasive bladder cancer (32). The aim of TURBT in bladder cancer is twofold. On the one hand, TURBT aims to provide a potential cure of selected bladder tumors. On the other hand, TURBT is important for accurate staging of high-risk tumors and particularly muscle-invasive lesions, which require additional therapy including radical cystectomy or radio-chemotherapy(33). Successful surgical therapy for low-risk, non-muscle-invasive tumors depends on the completeness of the performed TURBT. However, despite all surgical efforts aimed at achieving complete tumor removal, the high recurrence rate (35%–70%) and thus the propensity of these lesions to eventually progress (10%–50%) represent the major obstacles of TURBT(32).

As for the recurrence of cancer, the median time of recurrence for our patients was more than 3 years. In comparison to previous studies, a retrospective review demonstrated a 5-year disease-free survival reaching up to 50%–60% when using TURBT (33). The 2-years RFS for our patients was 71.6%, which agrees relatively well with a study conducted in Germany that found the overall recurrence rate after TURBT was 14.4% (33). In addition to tumor cell implantation, insufficient resection has also been discussed as a cause of relapse, particularly at the primary resection site. Numerous trials investigating routine re-TURBT, as a diagnostic approach, have reported detection rates of 30%–75% of residual tumor cells across all tumor stages (34).

In a previous Korean study, the median bladder recurrence-free survival, disease progression-free survival, and cancer-specific survival values were 19.0 months, 38.5 months, and 67.0 months, respectively (35).

The univariate predictor for survival showed a higher risk of death with increased age, which is consistent with the findings of other studies that predicted a longer survival in patients younger than 65 years (36). The ratio of cancer-specific mortality to incidence for men and women in the USA aged 65–69 years is 14% and 18%, respectively, whereas that for men and women aged 80–84 years is 30% and 37%, respectively (26). There have been several studies on the biological and clinical aggressiveness of UBC in young and old patients, but these have been relatively inconclusive (26).

Studies have found that cigarette smoking is significantly associated with advanced disease stages, recurrence, and survival among patients who underwent RNU for UTUC (37). This can be explained by the effect of aromatic amine-like chemicals that promote carcinogenesis, causing recurrence and progression, and reducing survival (38). In a previous Saudi study, pathological tumor stage and lymph node metastasis were the only independent predictors of survival following radical cystectomy (14).

### Limitations

Because of the retrospective nature of our study, certain data elements were not available, as were some missing data in the old medical records. In particular, limitations in the data regarding neoadjuvant and adjuvant therapies have limited the possibility of correlating the clinical outcomes with the treatment received.

### Conclusion

Limited data are available pertaining to the management of urothelial neoplasms in Saudi Arabia. Future prospective data collection, institutional and national data registries, and research collaboration are needed to improve the clinical outcomes of our patients and to dictate future management approaches.

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