

Is survival after radical cystectomy for bladder cancer in Saudi patients different from that of Western patients?

Alaa Mokhtar,^a Mohamed Matar Al Alawi,^b Waleed Mohamad Al Taweel,^a Khalid Al Othman,^a Said A. Kattan,^a Mohammed Faihan Al Otaibi^a

From the ^aDepartment of Urology, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia; ^bUrology Unit, Surgical Department, Salmaniya Medical Center, Manama, Bahrain

Correspondence: Dr. Mohammed Faihan Al Otaibi · Consultant Urology, Department of Urology, King Faisal Specialist Hospital & Research Centre, PO Box 3354, Riyadh 11211, Saudi Arabia · T: +966555787885 F: +966114424301 · otaibim@kfsrhc.edu.sa

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BACKGROUND: Although radical cystectomy (RC) is considered the gold standard treatment of muscle invasive bladder cancer, nearly half of patients develop metastases and ultimately die within 2 years.

OBJECTIVE: To assess survival, evaluate different prognostic factors that may affect disease-free survival (DFS) in Saudi patients after RC for carcinoma of the bladder and to compare our results with those of Western countries.

DESIGN: Retrospective chart review.

SETTING: A tertiary care center in Saudi Arabia.

PATIENTS AND METHODS: We collected data on patients who underwent RC for bladder cancer in the period between 1979 and 2014. Demographic, clinical and pathological variables and the application of perioperative chemotherapy were reviewed. Univariate and multivariate analyses were done with DFS as the end point.

MAIN OUTCOME MEASURE: Disease-specific survival.

RESULTS: On 328 patients for whom data was available, the median follow up was 23 months (range, 2 month-28 years) and median age was 58 years (range, 21-90). Of these patients, 268 were males (81.7%), 235 (71.7%) had urothelial carcinoma (UC), 79 (24.1%) had squamous cell carcinoma (SCC), and 208 (63.4%) had pathological tumor stage 3 or more. The 5-year overall survival (OS) and DFS were 52% and 48%, respectively. There was no statistically significant difference in DFS of patients with UC and pure SCC. On univariate analysis, lymph node status and pathological tumor stage were significant predictors of DFS. Both variables sustained statistical significance in a multivariate analysis.

CONCLUSION: Survival following RC is almost the same as others. Moreover, pathological tumor stage and lymph node metastasis were the only independent predictors for survival following RC. Future cooperative prospective studies are required to gain data on our region.

LIMITATIONS: Relatively small sample size and retrospective.

Bladder cancer accounts for approximately 450 000 new cases and 165 000 deaths worldwide in 2014.¹ In Saudi Arabia, bladder cancer is the ninth most common cancer among men of all ages, and it accounted for 3.8% and 0.9% of all newly diagnosed cancer cases among males and females in 2012, respectively.²

Histologically, urothelial carcinomas (UC) represent the majority of all epithelial bladder cancer (about 95%)

whereas non-urothelial carcinomas represent about 5% of all epithelial bladder cancer.³ In some areas including Egypt, Saudi Arabia (particularly the Jizan region), Iraq, Yemen, Sudan, and South Africa pure squamous cell carcinoma (SCC) cases comprise a larger proportion of the total bladder carcinoma burden because of the prevalence of schistosomiasis.⁴ Radical cystectomy (RC) is considered the standard of care for patients with organ-confined carcinoma of the bladder. It offers the

best long-term survival rates coupled with the lowest local recurrence.⁵⁻¹³

Owing to the variability in the clinical behavior of this malignancy after RC, an evaluation of prognostic factors is required to select candidates who should receive adjuvant therapies. In this retrospective analysis, we assessed survival and identified possible independent prognostic variables in Saudi patients with adequate follow up after RC for bladder cancer. These patients were treated in a tertiary care center to which most patients with bladder cancer are referred. Furthermore, we compared our data with that of Western countries. To the best of our knowledge, this is the largest series that has evaluated this issue among Saudi patients.

PATIENTS AND METHODS

After institutional review board approval, a retrospective chart review was conducted for patients who underwent RC for primary carcinoma of the bladder, with the intent to cure, at our tertiary care hospital from 1979 to 2014. Patients without adequate follow up or with postoperative death within 30 days were excluded. Follow-up time was defined as the time from RC to the date of death or to the date of the last follow up. Censored survival values represent patients who were alive without clinical evidence of disease at the last follow up.

Bladder cancer cases were diagnosed by transurethral resection. Patients were staged preoperatively with abdominal/pelvic computerized tomography (CT) and chest x-ray. Whole body bone scan was performed if clinical symptoms or laboratory findings were suggestive of osseous metastases.

The indication for RC and bilateral pelvic lymphadenectomy (PLND) was nonmetastatic muscle invasive bladder cancer and high risk nonmuscle invasive bladder cancer. Concomitant urethrectomy was done if there was an evidence of carcinoma of the urethra. The tumors were pathologically staged according to the 2002 TNM system of the International Union Against Cancer,¹⁴ and graded according to the 2004 World Health Organization system.¹⁵ The patients were initially examined 2 months after surgery, and then every 3 months for 1 year, semi-annually for the second year, and annually thereafter until disease progression or death. Follow-up examinations consisted of laboratory studies, chest radiography, and abdominal/pelvic CT. Treatment failure was defined as any radiological evidence of tumor relapse regardless of the presence of symptoms. Percutaneous, laparoscopic, or open biopsy confirmation of recurrence was only performed in those patients for whom the diagnostic uncertainty

could not be resolved by imaging. Treatment failure was categorized as local recurrence (cystectomy bed), or distant metastases (including lung, liver, bone, peritoneal lymph nodes, or brain). In addition, a group of patients with clinically localized urothelial tumors received neoadjuvant chemotherapy (NAC). Adjuvant chemotherapy (AC) was given to patients with histologically diagnosed urothelial carcinoma stage T3 or more, and/or node-positive patients (except for those who were medically intolerant or refused this treatment). AC was initiated, if indicated, within 3 months of surgery.

For this retrospective study, all the statistical analysis of data was evaluated by using the software package SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). Descriptive statistics for age are reported as median and range and categorical variables were summarized as frequencies and percentages. Continuous variables were compared by the *t* test, while categorical variables were compared by chi-square test. The Kaplan-Meier product limit method was used to find the survival estimates. The equality of survival distributions in the univariate analysis was tested using the 2-sided log rank test.¹⁶ Multivariate survival models were constructed using the Cox hazard regression with *P* < .05 being considered statistically significant.¹⁷ All *P* values were 2-sided. The analyzed parameters were patient age, gender, place of residence, tumor cell type, stage, grade, nodal involvement, presence of schistosomiasis, presence of ureteral obstruction, and administration of neoadjuvant or adjuvant chemotherapy.

RESULTS

Between 1979 and 2014, 651 patients were admitted to our hospital with a diagnosis of invasive bladder tumor. RC was performed in 419 patients (**Table 1**). Twenty-one patients (5%) died within 30 days of RC. The causes of death were pulmonary embolism in 11 patients, intestinal obstruction in 6, and cardiac failure in 4. Complete data for review was available for 328 patients. The median follow up was 23 months (range, 2 month-28 years). The condition of patients at last follow up is summarized in **Table 2**. During the period of follow up, 139 cases (42.3%) were identified as definitive treatment failure (alive but with disease or died of disease). Treatment failures were due to local recurrences in 44 cases (13.4%), distant metastases in 53 (16.1%), or both in 42 (12.1%).

The clinicopathological characteristics of the 328 patients are shown in **Table 3**, along with estimates of 5-year DFS in relation to tumor and patient characteristics. The median age was 58 years (range, 21-90) and 268 patients (81.7%) were men. The study included 119 patients (36%) who were from the southern region of

the country, a known endemic area for schistosomiasis. Histopathological analysis demonstrated that 235 patients (71.7%) had urothelial carcinoma (UC) and 79 (24.1%) had squamous cell carcinoma (SCC). Of the total, 208 (63.4%) had pathological tumor stage \geq pT3 and 317 (96.6%) had high tumor grade. A total of 49 participants (14.94%) were in the pT4a category. The most common site for extravesical extension in men was to the prostate, and in women to the vagina or uterus. Histological evidence of regional lymph node involvement was found in 82 patients (25%). Schistosomal eggs were present in 80 (24%) of the excised specimens and their relative frequency was higher among squamous tumors (55.7% of SCC tumors versus 15% of UC) ($P<.001$). Further analysis comparing patients with SCC and UC histological subtypes revealed that other patients and tumor characteristics were comparable. The 5-year OS of patients having SCC and UC were 55.5% and 50%, respectively ($P=.589$). The 5-year DFS of patients having SCC and UC were 51% and 46%, respectively ($P=.727$). Incidental prostatic adenocarcinoma was found in 23 (8.5%) male cysto-prostatectomy specimens. The median age of these patients was 65 (range, 32-80) years while male patients with no histological evidence of prostatic adenocarcinoma had a median age of 58 (range, 20-91) years, a difference of no statistical significance. There were 24 patients who received neoadjuvant chemotherapy (NAC), and 37 patients who received adjuvant chemotherapy (AC).

Kaplan-Meier estimates of the 5-year overall survival (OS) and disease-free survival (DFS) of the entire group were 52% and 48%, respectively (**Figures 1a, 1b**). The estimates of 5-year DFS in relation to tumor and patient characteristics are summarized in **Table 3**. Tumor pathological stage and lymph node involvement had a significant impact on survival. Survival was directly related to the final pathological stage (**Figures 2a, 2b**). As tumor stage progressed, there was a significant stepwise decrease in the 5-year DFS ($P<.001$). The 5-year OS and DFS were significantly decreased for patients with positive results from lymph node examinations compared to those without nodal involvement ($P<.001$) (**Figures 3a, 3b**).

In contrast, there were no statistically significant differences observed in the 5-year DFS according to patient age ($P=.973$), gender ($P=.590$), tumor histology ($P=.716$), tumor grade ($P=.446$), patient area of residence ($P=.333$), or presence of schistosomal involvement ($P=.327$). Patients with unilateral or bilateral ureteral obstruction showed a trend towards poor survival ($P=.06$). Patients who received NAC or AC did not show significant survival benefits over RC alone ($P=.440$ and

$P=.368$ respectively).

Overall univariate analysis revealed that pathological tumor stage and nodal involvement were predictors of poor survival. A Cox multivariate regression showed that only pathological stage ($P<.001$, HR: 2.391, CI 1.1759-3.252) and malignant nodal involvement ($P<.001$, HR: 2.448, CI 1.777-3.374) were significant independent factors predictive of survival in patients undergoing RC, PLND, and urinary diversion.

DISCUSSION

The optimal goals of treatment for any invasive bladder cancer include long-term survival, prevention of pelvic recurrence or development of metastatic bladder cancer, and an excellent quality of life.

The technique of RC with PLND can be performed safely, with excellent bladder tumor control and a low incidence of local pelvic recurrence.⁵⁻¹³ However, even if muscle invasive bladder cancer is shown to be organ-confined at RC, up to 50% of patients develop metastases and ultimately die of disease, despite apparently complete surgical removal, due to the aggressive na-

Table 1. Surgery for invasive bladder cancer.

	Number of cases (%)
Radical cystectomy	419 (64)
Partial cystectomy	42 (6.5)
Simple cystectomy	70 (10.8)
Salvage cystectomy	22 (3.4)
Diversion only	58 (9)
Abdominal exploration	40 (6)
Total	651 (100)

Table 2. Condition at last follow up.

	Number of patients
Living free of disease	165
Living with disease	14
Died of disease	120
Died of unknown cause	5
Died of unrelated cause	24
Not followed	70
Postoperative mortality	21
Total	419

ture of the disease.¹² This fact prompted us to evaluate retrospectively a series of Saudi patients treated with RC, with a long period of follow up, in a single tertiary care hospital.

The all-cause mortality rate and the cancer related mortality rate were 40.5% and 29% respectively which were comparable to recent published data.⁹ The 30 days mortality rate in our study was 5% which was higher than others (1.3-3%).^{7,11,13} The number of SCC cases in our study is significantly higher than that reported in Western series¹⁸⁻²⁵ but lower than a large Egyptian series²⁶ (Table 4). Nearly half of SCC patients (48%) referred to our hospital were from the Jizan region. Moreover, 71 (90%) of these cases presented and were treated before the year 2007. This finding can be explained by prevention and early treatment of risk factors like schistosomiasis. However, these findings have to be interpreted cautiously because of the possible presence of other factors. Despite the high incidence of SCC in our group of patients, the 5-year OS and DFS of all 328 patients was 52% and 48%, respectively, which are within the range of most published reports.⁵⁻¹³ Table 4 demonstrates the published survival outcomes after RC with or without preoperative radiotherapy (RT) or NAC for patients with pure SCC.

The pathological stage progression has a significant negative impact on survival in patients undergoing RC for bladder cancer as shown in many published series as well as in our study.^{13,26-31} Metastases of bladder cancer to pelvic nodes varied between 14% and 27% and has been proven to be a highly, prejudicial variable that affect the DFS. In our series, 82 (25%) of the patients had metastatic lymph node involvement. The 5-year DFS following RC and PLND was 54.3% in patients without lymph node metastases and 26.9% in patients with lymph node metastases; these results were comparable to other series.^{8,11,26,27,31-34}

Previous studies have reported a significant role for tumor grade in predicting the outcome after RC,^{23,28} while other studies including ours have found tumor grade to be a non-independent predictor of survival.³⁵ Most of our cases were with high-grade tumors; however, bias may exist as early cases were classified according to the old grading system, and we considered grade 2 tumors as high grade according to the new grading system.

A debate exists whether ureteral obstruction at the time of RC has an impact on patient OS.³⁵⁻³⁹ Ureteral obstructions were encountered in about 42% of cases, which may be related to the fact that about two-thirds of our patients had advanced tumor stage (pT3 and above). Univariate analysis demonstrated a trend to-

Table 3. Kaplan-Meier estimates of 5-year disease-free survival in relation to tumor and patient characteristics.

	Number of patients (%)	5-year disease-free survival rate (%)	P value*
Overall	328 (100)	48.27	
Gender			
Male	268 (81.7)	47.74	.590
Female	60 (18.3)	49.50	
Age groups (years)			
≤60	179 (54.6)	47.77	.973
>60	149 (45.4)	49.31	
Stage			
T1 or less	29 (8.8)	55.54	<.001*
T2	91 (27.74)	52.95	
T3	159 (48.48)	50.49	
T4	49 (14.94)	17.85	
Histology			
UC	235 (71.7)	46.00	.727
SCC	79 (24.1)	51.00	
Adenocarcinoma	9 (2.7)	35.56	
Mixed/undifferentiated	5 (1.5)	53.00	
Schistosomiasis			
Yes	80 (24.4)	0.4830	.327
No	248 (75.6)	0.4152	
Grade			
Low	11 (2.3)	0.4605	.446
High	317 (96.7)	0.4173	
Hydronephrosis			
None	191 (58.2)	0.4995	.066
Bilateral/Unilateral	137 (41.8)	0.4454	
Place of residence			
Central	89 (27.1)	0.4801	.333
Eastern	46 (14)	0.4353	
Western	53 (16.2)	0.4845	
Northern	21 (6.4)	0.4813	
Southern	119 (36.3)	0.4580	
Lymph nodes			
Positive	82 (25)	26.92	<.001*
Negative	246 (75)	54.31	
Prostate cancer			
Yes	23 (7)	50.21	.245
No	245 (93)	50.32	

Data are number and percentage. *Log rank test statistic P<.05 is considered significant.

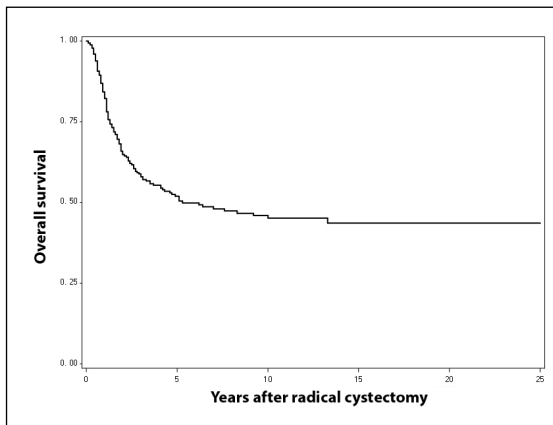


Figure 1a. Kaplan-Meier estimates of overall survival. Five-year overall survival was 52% (of 327 observations 179 [54.7%] were censored).

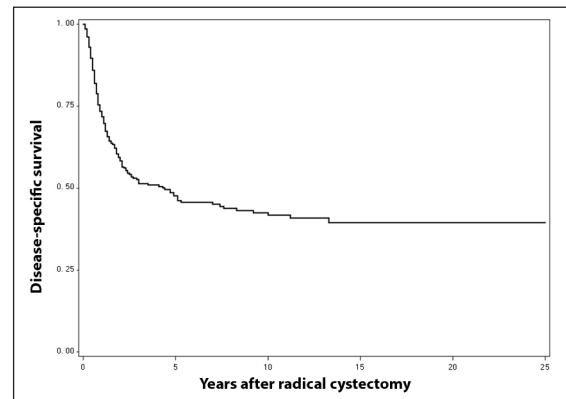


Figure 1b. Kaplan-Meier estimates of disease-free survival. Five-year disease-free survival was 48% (of 328 observations 164 [50.0%] were censored).

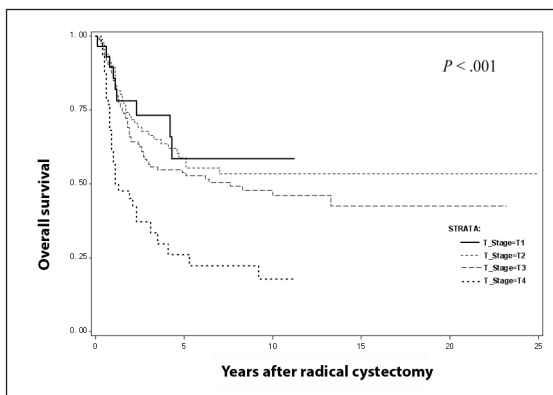


Figure 2a. Overall survival estimates relative to tumor pathological stage (of 327 observations 179 [54.7%] were censored).

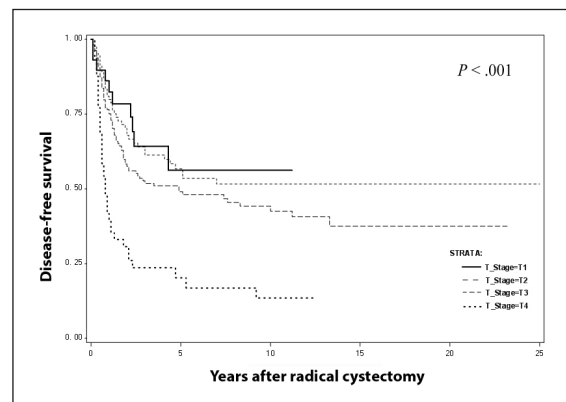


Figure 2b. Disease-free survival estimates relative to tumor pathological stage (of 328 observations 164 [50.0%] were censored).

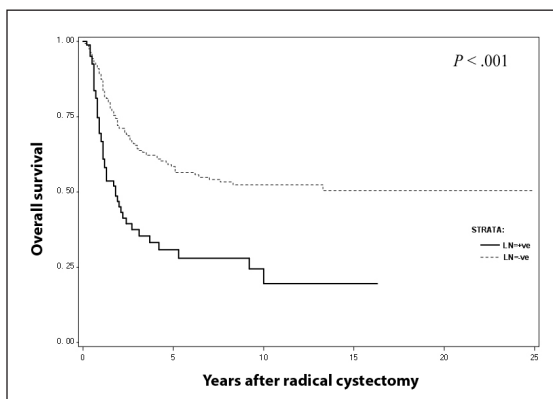


Figure 3a. Overall survival estimates relative to nodal status (of 327 observations 179 [54.7%] were censored).

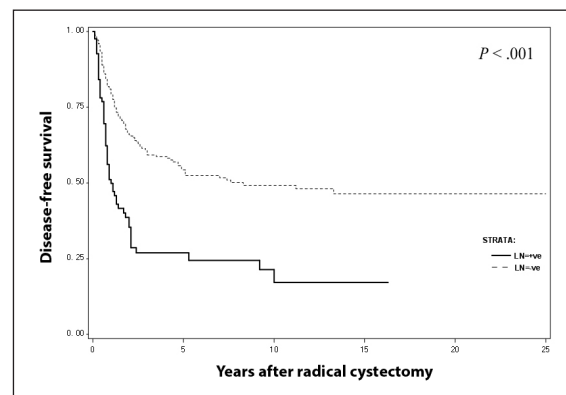


Figure 3b. Disease-free survival estimates relative to nodal status (of 328 observations 164 [50.0%] were censored).

Table 4. Published reports of patients with squamous cell carcinoma, including treatment modality, and survival rates.

Reference	Center	Year	N	Treatment modality	5-year OS (%)	DFS (%)
Richie et al ¹⁸	Inapplicable	1976	33	RC	48	NR
Johnson et al ¹⁹	Inapplicable	1976	90	RC+preoperative RT	34	NR
Kassouf et al ²⁰	MD Anderson	2007	27	RC+NAC or preoperative RT 47.6 (at 2 years)	NR	32.8
Prempre et al ²¹	University Hospital of Jacksonville	1984	52	RC+preoperative RT	NR	40
Swanson et al ²²	MD Anderson	1990	25	RC+preoperative RT	50	NR
Rausch et al ²³	Klinikum Fulda	2012	31	RC±NAC, chemoirradiation	26	46
Balci et al ²⁴	Ataturk Training and Research Center	2013	60	RC	NR	39.1
Izard et al ²⁵	Queen University	2015	178	RC	33	57
Ghoneim et al ²⁶	Mansoura	2008	1345	RC	NR	57.7
Current study	King Faisal Specialist Hospital	2017	79	RC	55.5	51

RC: radical cystectomy, NAC: neoadjuvant chemotherapy, RT: radiotherapy, NR: not reported.

wards poor survival in patients with unilateral or bilateral ureteral obstruction ($P=.06$).

In our series, incidental findings of prostatic adenocarcinoma occurred in 8.5% (23 out of the 268 males) of the cystoprostatectomy specimens. This is similar to China (6.8%)⁴⁰ but still lower than in Western countries (25-46%).^{41,42} Furthermore, whether the presence of prostatic adenocarcinoma is clinically significant is still controversial.⁴³⁻⁴⁵ In fact, the impact of prostatic adenocarcinoma on survival was not statistically significant in our patients.

Treatment with NAC was recommended for patients with T2 to T4a bladder cancer, for whom RC is indicated with an absolute survival benefit of 5% and 6% for 5-year and 10-year OS, respectively.⁴⁶ Our study, with the limitations of being retrospective and having only a few patients treated with NAC, revealed no significant survival benefit of NAC compared to RC monotherapy. Similar results were encountered with the use of AC for high-risk patients, such as pT3/4 and/or lymph node-positive (N+) disease. Many studies have shown a trend

towards increased OS especially in the presence of extravesical extension and nodal involvement.⁴⁶

This study is the largest to address oncological outcomes in a Saudi population following RC performed in a single center. However, there are limitations to this study. First, it was retrospective. Second, the sample size was not large compared to other reports.^{11,26,33} Despite that squamous cell carcinoma and advanced tumor stage comprise a relatively large proportion of our cases, the present study revealed that survival is the same after RC. Moreover, pathological tumor stage and lymph node metastasis are the only independent predictors for survival. However, careful follow-up and aggressive adjuvant therapy in patients with advanced stage and/or lymph node involvement should be considered. However, future cooperative prospective studies are required to provide more data related to our region.

Conflict of interest

The authors declare no conflict of interest.

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