

STATISTICAL ANALYSIS OF THE FACTORS INFLUENCING THE RECURRENCE OF URINARY BLADDER CANCER AFTER RADICAL CYSTECTOMY

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Objective To evaluate the risk factors influencing the recurrence of urinary bladder cancer, and to predict the probability of recurrence within two years after radical cystectomy.

Patients and Methods Between 1986 and 1994, 857 patients were admitted at the Urology and Nephrology Center of Mansoura University, Egypt, for treatment of bladder malignancy by radical cystectomy. The number of male patients was 682 (80%) versus 175 females (20%) with a mean age of 49 years (range 18 – 90 years). The median follow-up period was 38 months (range 0.03–138 months). Histopathology revealed squamous carcinoma in 440 patients (51%), transitional carcinoma in 223 patients (26%), adenocarcinoma in 94 patients (11%) and mixed (two or more) types in 100 patients (11.7%). Most of the patients presented with advanced-stage disease (defined as P3 or P4): 611 patients (71%) had stage P3, 68 patients (6%) stage P4. Bilharzial ova were seen in 80% of the specimens, while regional lymph nodes were involved in 16% of the cases.

Results Cancer-related mortality was encountered in 199 patients (23.2%) and mortality from unknown causes in 54 patients (6.3%). Fifty-five patients (6.3%)

were alive with recurrence. Univariate and multivariate analysis of the survival rates showed that lymph node involvement ($P = 0.0000$), tumor grade ($P = 0.0017$), pathological stage ($P = 0.0008$), sex ($P = 0.0005$), urinary diversion ($P=0.0080$) and histopathology ($P=0.0253$) significantly influenced the recurrence-free survival after radical cystectomy. The 5-year survival rate was 61.7%, and the 5-year hazard rate was 48.3%. Using the logistic regression model for estimating and predicting the probability of recurrence within two years after radical cystectomy, we found that only one variable (lymph node involvement) had a significant effect on the prediction of the probability of recurrence.

Conclusion These findings suggest that positive lymph nodes, tumor grade, stage, sex, urinary diversion and histopathology of tumor cells are independent predictors of survival in patients with bladder cancer. Positive lymph nodes are the most important indicators for recurrence in general and especially for predicting the probability of recurrence within two years after radical cystectomy.

Key Words survival analysis, hazard function, logistic regression, bladder cancer

INTRODUCTION

Bladder cancer is a major health problem in Egypt and in many parts of the world including the Middle East. It represents approximately 20% of the total cancer incidence. The most common treatment in Egypt is radical cystectomy with urinary diversion.¹ Recurrence after surgery occurs in the pelvis, and 90.6% of

the recurrences occur during the first postoperative year.² In a critical analysis of the causes of the treatment failure, Ghoneim et al., (1979), observed that most of the recurrences developed within 24 months after operation and are largely local in distribution, and the incidence of post-operative mortality following cystectomy was 13.7%.³ The results of another study by Ghoneim et al.⁴ showed that

Table 1: Main Characteristics of the Studied Patients

Variables	Categories	No.	%
Sex	males	682	80.0%
	females	175	20.0%
Residence	rural	651	76.0%
	urban	206	24.0%
Occupation	farmers	348	40.6%
	workers	392	45.7%
	others	117	13.7%
Tumor histopathology	squamous	440	51.3%
	transitional	223	26.0%
	adenocarcinoma	94	11.0%
	mixed	100	11.7%
Tumor grade	GI	316	36.9%
	GII	393	45.9%
	GIII	148	17.2%
Tumor stage	P1	78	9.1%
	P2	120	14.0%
	P3	611	71.3%
	P4	68	5.6%
Bilharzial ova	No	169	20.0%
	Yes	688	80.0%
Lymph node inv. ^o	No	723	84.0%
	Yes	134	16.0%
Urinary diversion	Kock Pouch	238	27.8%
	W.N.B.*	82	9.5%
	M.R.B.**	102	11.9%
	Ileal conduit	198	23.1%
	Rectal bladder	197	23.0%
	Others	40	4.7%

* W.N.B. = W-shaped neobladder

** M.R.B. = modified rectal bladder

^o lymph node inv. = lymph node involvement

treatment failure after radical cystectomy occurred in 331 patients (32%): in 198 patients (60%) with local recurrence, 107 patients (32%) with distant metastasis, and 26 patients (8%) with both.⁴

PATIENTS AND METHODS

In this retrospective study, data were taken from the archival medical files of patients who underwent radical cystectomy at the Urology and Nephrology Center, Mansoura University, Mansoura, Egypt, between January 1986 and April 1994 (the follow-up for all those patients was extended to 1996). The patients' age ranged from 18 to 90 years, 682 (80%) were males and 175 (20%) were females. Table 1 represents the main characteristics of the patients. For each patient, fourteen variables were registered from the medical files, i.e. age, sex, residence (rural or urban), governorate (from Dakahliya or others), occupation (farmers, workers, others), pathological stage of tumor (P1, P2, P3, P4), grade (GI, GII, GIII), the presence of bilharzial ova in the specimens, regional lymph node involvement, histopathological diagnosis (squamous, transitional, adenocarcinoma, mixed), multicentricity (solitary or multiple), types of urinary diversion (W-shaped neobladder, Kock pouch, modified rectal bladder, ileal conduit, rectal bladder, others), chemotherapy and radiotherapy.

Statistical Analysis

Three types of statistical analysis were applied: univariate and multivariate survival analysis, and logistic regression.

Univariate Survival Analysis

The data were initially analyzed by taking one variable at a time and testing it for any relationship with survival. Kaplan-Meier survival curves were plotted using the product limit method. The log-rank test was used to test the statistical differences between or among the recurrence-free survival curves in patients according to the different categories of each variable (P-values less than or equal to 0.05 were considered significant).^{5,6} The analysis of quantitative variables such as age was dichotomized (≤ 49 , >49 years).

Survival time (failure time) was defined as the time between the date of radical cystectomy and the date of first recurrence, death from cancer, or death from unknown cause (e.g. death from heart failure, pulmonary embolism, septic shock, intestinal obstruction or others).

Censored survival values refer to patients who were alive without clinical evidence of

Table 2: Results of Kaplan-Meier Estimates of 5-Year Recurrence-Free Survival and Median Survival for the Significant Variables by Using the Log-Rank Test

Variables	Categories	Median Survival (months)	5-Year Survival Rate	Pairwise Log-Rank Test for Significant Variables Log-Rank Statistics and (Significance)**					
Sex	Males	*	63.15	Males					
	Females	*	76.37	Females	42.11 (0.007)				
Histopathology	Squamous	*	69.03	SCC		Adenoca.	TCC		
	Adenoca.	*	71.80	Adenoca.	1.2 (0.273)	-	-		
	TCC	*	67.50	TCC	2.06 (0.1515)	3.81 (0.0508)	-		
	Mixed	24.5	43.30	Mixed	27 (0.0000)	20.3 (0.000)	12 (0.0005)		
Tumor Grade	G1	*	72.00	G1		GII			
	GII	*	67.50	GII	6.18 (0.0013)	-			
	GIII	37.43	47.48	GIII	35.36 (0.0000)	15.83 (0.0001)			
Tumor Stage	P1	*	66.53	P1		P2	P3		
	P2	*	79.80	P2	2.29 (0.1350)	-	-		
	P3	*	65.00	P3	2.07 (0.1500)	12.08 (0.0010)			
	P4	21.7	34.12	P4	17.86 (0.0000)	30.92 (0.0000)	14.89 (0.0000)		
Lymph node inv.	No	*	70.45	No					
	Yes	14.83	38.45	Yes	65.4 (0.0000)				
Urinary diversion	Kock P.	*	66.07	Kock P.		W.N.B.	M.R.B.	Il. Cond.	R.B.
	W.N.B.	*	80.22	W.N.B.	4.5 (0.073)	-	-	-	-
	M.R.B.	*	74.40	M.R.B.	0.29 (0.588)	2 (0.157)	-	-	-
	Ileal cond.	*	60.77	Il. Cond.	2.45 (0.177)	9.4 (0.002)	3.15 (0.076)	-	-
	R.B.	*	61.90	R.B.	4.68 (0.031)	12 (0.001)	4.68 (0.031)	0.39 (0.5319)	-
	Others	*	67.44	Others	0.08 (0.776)	2.28 (0.131)	0.01 (0.929)	1.07 (0.301)	2 (0.175)

* Median Survival has not been reached; ** P-Value ≤ 0.05 is considered significant

SCC = squamous cell carcinoma, TCC = transitional cell carcinoma, W.N.B. = W-shaped neobladder, M.R.B. = modified rectal bladder, R.B. = rectal bladder, Il. Cond. = ileal conduit

disease at the time of the last follow-up, and also patients who were lost to follow-up and free from recurrence.

Multivariate Survival Analysis

Cox's proportional hazard model was applied with a stepwise regression analysis (forward or step-up method), where the variables, which had no effect, were removed from the model to assess the effect of the previous variables on survival and to estimate the relative risk, survival rates, and hazard rates.⁷⁻¹⁷

Logistic Regression Model

Before using the logistic regression model for estimating and predicting the probability of recurrence, we followed two steps to overcome the censored data.¹⁸⁻²⁰

The first step was to exclude censored data like patients who were alive without clinical evidence of disease at the time of the last follow-up, and patients who were lost to follow-up and free of recurrence.

The second step was to include in the logistic model only the significant variables obtained from Cox's proportional hazard model and the interactions between some of those variables, like the interactions among tumor stage and lymph node involvement, tumor grade; tumor grade with lymph node involvement; and histopathology diagnosis with tumor stage, tumor grade, and with lymph node involvement. The dependent variable was defined as follows:

$Y = 1$ if failure time (survival time) ≤ 24 months;
 $Y = 0$ if failure time > 24 months.

RESULTS

Univariate Survival Analysis

Among the fourteen variables studied, six variables had a significant influence on recurrence-free survival after radical cystectomy. These variables were lymph node involvement, tumor grade, tumor stage, sex, urinary diversion and histopathology. The log-rank test showed that patients with tumor stage P4 had a significantly worse prognosis than those with P3 ($P = 0.0000$), P2 (0.0000) and P1 (0.0000) tumor stages (Table 2). The 5-year survival rates for stages P1, P2, P3 and P4 were 66.5%, 79.8%, 65%, 34.1% respectively. There

was no significant difference in survival when comparing P1 with P2. However, the advanced stages (P3, P4) caused a significant reduction in the probability of survival.

The 5-year survival rates for grades GI, GII, and GIII were 72%, 67.5%, and 47.5%, respectively. Patients with GIII tumors had a significantly worse prognosis than those with GI ($P = 0.0000$) and with GII (0.0001) tumor grades. The median survival for patients with GIII was 37.43 months.

The 5-year survival rate was 70.5% for patients with negative nodes and 38.5% for those with positive nodes ($P = 0.0000$). The median survival for patients with positive nodes was 14.83 months.

The 5-year survival rates for squamous carcinoma, adenocarcinoma, transitional cell carcinoma, and mixed cell tumors were 69.03%, 71.8%, 67.5%, and 43.3%, respectively. The median survival for patients with mixed cell tumors was 24.5 months.

The sex of the patients was also a significant variable in survival ($P = 0.0007$) (Table2).

Multivariate Survival Analysis

When using Cox's proportional hazard model, we found similar results to those obtained by Kaplan-Meier for the analysis of recurrence-free survival. Six variables proved to be associated with a bad prognosis for recurrence. Those variables were: positive lymph nodes, an aggressive tumor grade (GII, GIII), an advanced tumor stage (P3, P4), the gender of the patients (male), the type of urinary diversion (rectal bladder) and histopathology of the tumor cell (mixed, T.C.C). The relative risk for negative nodes compared to positive nodes was 0.42 (this means that the estimated risk of recurrence is 0.42 times less for a patient with negative nodes, adjusted for the other variables in the model). The relative risk estimates for GI, GII to GIII were 0.61 and 0.60, respectively. Table 3 presents further details on the results of Cox's proportional hazard model.

The Logistic Regression Model

Using the logistic regression model for estimating the probability of recurrence and predicting it (under the previous conditions), we found that the only variable influencing the probability of recurrence within two years after

Table 3: Variables Shown to be Significant after Stepwise Regression in Cox's Proportional Hazard Model

Variables	B	S.E. (B)	P-value*	R.R.** Exp. (B)	95% CI for R.R.**
<u>Sex</u>					
Male	0			1.00	
Female	-0.72	0.21	0.0005	0.48	(0.32, 0.73)
<u>Histopathologic Type</u>					
Squamous Cell Carcinoma	-0.54	0.17	0.0019	0.58	(0.42, 0.82)
Adenocarcinoma	-0.52	0.26	0.0450	0.59	(0.35, 0.99)
Transitional Cell Carcinoma	-0.34	0.18	0.0627	0.71	(0.49, 1.08)
Mixed	0			1.00	
<u>Stage</u>					
P1	-0.67	0.28	0.0183	0.51	(0.29, 0.89)
P2	-1.05	0.29	0.0002	0.35	(0.20, 0.61)
P3	-0.39	0.21	0.0653	0.68	(0.45, 1.02)
P4	0			1.00	
<u>Grade</u>					
GI	-0.49	0.18	0.0058	0.61	(0.43, 0.87)
GII	-0.52	0.14	0.0003	0.60	(0.44, 0.79)
GIII	0			1.00	
<u>Lymph Node Involvement</u>					
Negative Lymph Nodes	-0.86	0.14	0.0000	0.42	(0.32, 0.56)
Positive Lymph Nodes	0			1.00	
<u>Urinary Diversion</u>					
Kock	-0.20	0.30	0.5068	0.82	(0.45, 1.48)
W-Shaped Neobladder	-0.77	0.39	0.0493	0.46	(0.21, 0.998)
Modified Rectal Bladder	0.21	0.34	0.5325	1.24	(0.63, 2.43)
Ileal Conduit	-0.02	0.31	0.9556	0.98	(0.54, 1.80)
Rectal Bladder	0.19	0.30	0.5261	1.21	(0.67, 2.19)
Others	0			1.00	

* Significance = $P \leq 0.05$, ** R.R. = relative risk

radical cystectomy was the lymph node involvement ($P = 0.0506$). This probability was estimated 92.1% for positive nodes and 82.6% for negative nodes. The probability of recurrence for the patients with positive nodes was increased by 0.095 compared with patients who had negative nodes.

DISCUSSION

The purpose of this retrospective study was to evaluate the risk factors influencing urinary bladder cancer and to predict the probability of recurrence after radical cystectomy. As shown in Tables 2 and 3, the univariate analysis of

recurrence-free survival curves yielded results similar to those obtained by the multivariate analysis. The same risk factors which had a significant impact on survival were: lymph node involvement, a high tumor stage (P3, P4), a high tumor grade (GII, GIII), the gender of the patient (male), the type of urinary diversion (rectal bladder) and the histopathological diagnosis (TCC, mixed). These results are consistent with those of Ghoneim et al. who concluded that tumor stage, tumor grade, and lymph node involvement only had a significant impact on survival following radical cystectomy.⁴

In this study, the 5-year survival rates for stages P1, P2, P3 and P4 were 66.5%, 79.8%, 65%, 34.1% respectively. Other studies reported that for tumors with superficial muscle invasion (P2) the 5-years survival rate ranged between 65% and 76%.²¹⁻²³ Frazier et al. reported that 5-year disease-free survival was 39% for patients with stages PT3 or greater.²⁴

While Ghoneim et al. reported a 5-year disease-free survival of 23.4% for patients with positive nodes and of 53.1% for patients with negative nodes³, the 5-year survival rate in our study was 38.5% for patients with positive nodes and 70.5% for patients with negative nodes ($P = 0.0000$). The median survival for patients with positive nodes was 14.83 months.

To our knowledge, this study is the first one to concentrate on the prediction of the probability of recurrence within two years after radical cystectomy. To achieve this, we used the logistic regression model and found that a positive node was the only risk factor that had a significant influence on this probability.

Our findings suggest that positive lymph nodes, tumor grade (GII, GIII), stage (P3, P4), sex (Male), type of urinary diversion (R.B), and histopathology of tumor cells (Mixed, TCC) are independent predictors of survival in patients with bladder cancer and might be useful in selecting those who would benefit from adjuvant therapy. The only risk variable influencing the probability of recurrence within two years after radical cystectomy are positive lymph nodes, which, therefore, may be considered the best indicators for recurrence in general and especially for predicting the probability of recurrence within two years after radical cystectomy.

Recently, Ghoneim et al. reported a predictive model of survival after radical cystectomy in a cohort of patients and concluded that tumor stage, grade and lymph node involvement were independent prognostic factors. They estimated a 5-year survival.²⁵ In this study the patients were evaluated at an end point after at least two years of follow up as most of the treatment failures occur within this period. The difference between the two studies may be due to the different follow-up periods or the design of the statistical model used. However, both studies showed that stage, grade and lymph node involvement were among the most important prognostic factors after radical cystectomy for invasive bladder cancer.

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RESUME

Analyse Statistique des Facteurs Influençant la Récidive du Cancer de la Vessie après Cystectomie Radicale

Objectifs: Evaluer les facteurs de risque influençant la récurrence de cancer de vessie et prévoir la probabilité de récurrence dans les 2 ans post cystectomie radicale. **Patients et Méthodes:** Entre 1986 et 1994, 857 patients avaient été admis pour traitement de tumeur maligne de vessie par cystectomie radicale au centre d'Urologie-Néphrologie de l'Hôpital Universitaire de Mansoura en Egypte. Le nombre d'hommes était de 682 (80%) contre 175 femmes (20%) avec une moyenne d'âge de 49 ans (extrêmes de 18 et 90 ans). La durée médiane du suivi était de 38 mois (extrêmes de 0.03 et 138 mois). L'histopathologie avait révélé un carcinome à cellules squameuses chez 440 patients (51%), un carcinome urothélial chez 223 patients (26%), un adénocarcinome chez 94 patients (11%) et un aspect mixte (2 ou plus de 2 types) chez 100 patients (11.7%). La plupart des patients présentaient un stade avancé (défini comme P3 ou P4) : 611 patients (71%) avaient un stade P3 et 68 patients (6%) un stade P4. Des œufs de Bilharzie ont été retrouvés dans 80% des échantillons, tandis qu'un envahissement ganglionnaire régional a été retrouvé dans 16% des cas. **Résultats:** Le nombre de décès par cancer était de 199 cas (23.2%) et le nombre de décès de cause inconnue était de 54 patients (6.3%). Cinquante cinq patients (6.3%) étaient vivants avec une récurrence. L'analyse univariée et multivariée du taux de survie avait montré que l'envahissement ganglionnaire ($P = 0.0000$), le grade tumoral ($P = 0.0017$), le stade pathologique ($P = 0.0008$), le sexe ($P = 0.0005$), la dérivation urinaire ($P = 0.0080$) et l'histopathologie influençaient significativement la survie sans récurrence après cystectomie radicale. Le taux de survie à 5 ans était de 61.7% et le risque de récurrence à 5 ans était de 48.3%. En utilisant le modèle de régression logistique pour estimer et prédire la probabilité de récurrence dans les 2 ans post cystectomie radicale, nous avons trouvé que seul l'envahissement ganglionnaire avait un effet significatif dans la prédiction de la probabilité de récurrence dans les 2 ans post cystectomie radicale. **Conclusions :** Ces constatations suggèrent que l'envahissement ganglionnaire, le grade tumoral, le stade tumoral, le sexe, la dérivation urinaire, et l'histopathologie des cellules tumorales sont des prédicteurs indépendants de la survie dans le cancer de la vessie. L'envahissement ganglionnaire est le plus grand indicateur de récurrence en général, et en particulier c'est le plus grand prédicteur de la probabilité de récurrence dans les 2 ans après cystectomie radicale.