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A Classification After Radical Cystectomy of Patients With Bladder Cancer Associated With Schistosomiasis

M. Rafla, A.S. Ibrahim, A.J. Valleron and J.Y. Mary

The aim of this study was to classify the bilharzial bladder cancer patients after radical cystectomy into several prognostic strata with increasing risk of recurrence. 310 patients through the period 1977–1983 at the National Cancer Institute of Cairo were systematically analysed for 12 variables evaluated after radical cystectomy. Eight factors were shown to have a significant influence on the recurrence-free survival curve after radical cystectomy namely: tumour stage, size, grade and location in the bladder, lymph node involvement, metastasis, renal insufficiency and urinary diversion. Using the proportional hazard model, five factors were significantly related to a lower recurrence-free survival, one major prognostic factor, tumour grade (G2 or G3) (relative risk estimate of 5.5), and four minor prognostic factors (relative risk estimates around 2), namely tumour diameter greater than 5 cm, anterior or trigonal location of the tumour, tumour stage (T3 or T4) and presence of renal insufficiency before surgery. Four prognostic strata have been defined in relation to the presence of these prognostic factors. This classification was validated on a second sample of 122 patients by comparing for each prognostic stratum, the recurrence-free survival curve observed on this sample and the corresponding predicted curve by Cox model. No statistically significant difference could be detected. This classification of bladder cancer patients appears to be adequate for bilharzial bladder cancer patients after radical cystectomy, at least in the conditions they presented and were treated for at the NIC in Cairo.

Keywords: bladder cancer, schistosomiasis, radical cystectomy, prognosis, recurrence, classification
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INTRODUCTION

BLADDER CANCER occurs with high frequency in some parts of Africa and the Middle East. It is a major health problem in Egypt since it represents approximately 20% of the total cancer incidence. It is the most frequent cancer in males and the second most common neoplasm (after breast cancer) in females [1]. This cancer is almost always associated with schistosomiasis. The most common treatment in Egypt is radical cystectomy with urinary diversion [2]. Recurrence after surgery occurs locally in the pelvis and 90.6% of the recurrences occur during the first postoperative year [3].

In a previous study [4], we determined five prognositic factors

of recurrence by using a linear discriminant function of these factors to separate the patients who remain free of recurrence 1 year after the radical cystectomy from those who developed a recurrence during this period. This model was validated on a new sample of 122 patients, showing a sensitivity of 93% and a specificity of 80% [5]. Neverless, this model has some limitations. First, even if they are not numerous, patients whose recurrence occurred more than 1 year after the operation were analysed as patients without recurrence. Second, this criterion does not take into account the time at which the recurrence occurs during the 1-year period following the operation. Third, patients are classified in the 'good' or 'bad' prognosis groups according to their calculated score as compared to the cut-off point. Even if the procedure was validated [5], it may lead to a great loss of information. Indeed, a patient whose score is just under the cut-off point will be classified in the good prognosis group as will a patient with a score much lower than this value, whereas a patient with a score just over the cut-off value will be classified in the bad prognosis group. To overcome these limitations, we performed a new study using the same sample of patients, firstly to determine the prognostic factors which affect the recurrence-free survival curve after radical cystectomy and secondly to classify these patients in several strata with increasing risk.

PATIENTS AND METHODS

In this retrospective study, as described previously [4, 5], data were collected from patients aged more than 20 years with bladder cancer (as confirmed by histopathological analysis of biopsy) associated with schistosomiasis (as evidenced by urine detection of ova of *Schistosoma haematobium* or history), who underwent radical cystectomy in the period of January 1977 to December 1985 at the National Cancer Institute (NCI) of Cairo, and for whom a follow-up was feasible at the NCI.

For each patient, 12 factors were registered from the patient medical files, namely sex, age, pathological stage of the tumour (T1, T2, T3, T4) [6], tumour size (expressed as the largest diameter in cm), location (vault, anterior, posterior, lateral, trigone), histopathological diagnosis (squamous, transitional, adenocarcinoma), grade (G1, G2, G3) [6], the presence of ova of *Schistosoma haematobium* in the specimen, regional lymph node involvement, the existence of distant metastasis in other organs at the time of operation, renal insufficiency and the type of urinary diversion (rectal bladder, ileal conduit, ileo-cecal bladder, ureterocutaneous). Disease-free survival curves were calculated by the product-limit method [7], the event being defined by either recurrence, occurrence or death from any cause.

Two different patients' samples were available. The first sample of 310 patients underwent radical cystectomy from January 1977 to December 1983. This sample was used to determine the prognostic factors (step one) and to derive the corresponding new classification (step two). The total number of bladder cancers in this period at the NCI of Cairo was 4163. Radical cystectomy with urinary diversion was performed for 1773 patients. Subjects with incomplete follow-up and those with one or more of the variables not registered were excluded from the study. From among the approved subjects we selected at random our first sample (learning sample).

Out of 691 patients undergoing radical cystectomy during the period 1984–1985, a sample of 150 consecutive patients was selected; 122 patients had complete data and were retained for analysis as the second sample. This second sample (test sample) was used to validate the new classification obtained on the first sample (step three).

In a first step the role of each factor was studied separately (univariate analysis). The log rank method [8] was used to compare the recurrence-free survival curves in patients according to the different categories of each factor. For this analysis, quantitative factors, such as tumour size or patient age, were dichotomised (below or equal to the median, above the median). For qualitative factors presenting more than two categories, this analysis allows us to group successive categories either on logical grounds or on evident similarities. So, T1 and T2 tumour stages were combined due to the small number of patients with T1, tumour grade G1 was distinguished from G2 or G3 and anterior or trigonal location from other locations (see Figure 1), and ureterocutaneous diversion from the three other diversions. To quantify the possible role of a risk factor, the relative risk (RR) of recurrence (point estimate, 95% confidence interval) in patients presenting the factor as compared to patients who do not present the factor was estimated. [9].

In a second step, all the binary factors were studied together, taking into consideration their relationships by using the Cox model, which is a semi-parametric model of the instantaneous recurrence rate [10]. According to the number of prognostic binary factors (k) selected by this method, it defines a fixed number of patient categories, i.e. 2^k combinations. To determine prognostic strata, the rationale was the following: a weight (score) was attributed to the presence of a risk factor proportionaly to the logarithm of its relative risk determined through the Cox model. For that purpose, coefficients in the Cox model for each factor were rounded and standardised by division by the smallest one. Each combination of factors (presence or absence) was assigned a total score, the sum of the scores assigned to each factor present in the combination. In this way, combinations with the same score formed a unique class. Then for each class, survival curves without recurrence were obtained from the Cox model and consecutive classes with similar curves defined a stratum. All strata corresponded to the new proposed prognosis classification.

In a third step, the derived prognostic classification was applied to the second sample (test sample) which was composed of patients whose data were not used for the construction of the classification. This validation was based on the comparison for each stratum between the survival curve without recurrence observed on this sample and the survival curves predicted by the Cox model.

All the analyses were performed on Microvax II by using BMDP software [11].

RESULTS

Table 1 presents the main characteristics of the patients in the first (learning) and second (test) samples, respectively.

Univariate analysis

Among the 12 factors studied, eight factors had a significant influence on the recurrence-free survival curves after radical

Correspondence to M. Rafla at 1 Fawzi El Motei Street, Heliopolis, C.P. 11361, Cairo, Egypt.
M. Rafla, A.J. Valleron and J.Y. Mary are at the Unite de Recherches Biomathematiques et Biostatistiques, INSERM U 263, Universite Paris 7, 2 place Jussieu, 75251 Paris Cedex 05, France; and A.S. Ibrahim is at the Cancer Statistics and Epidemiology Unit, National Cancer Institute, Cairo, Egypt.
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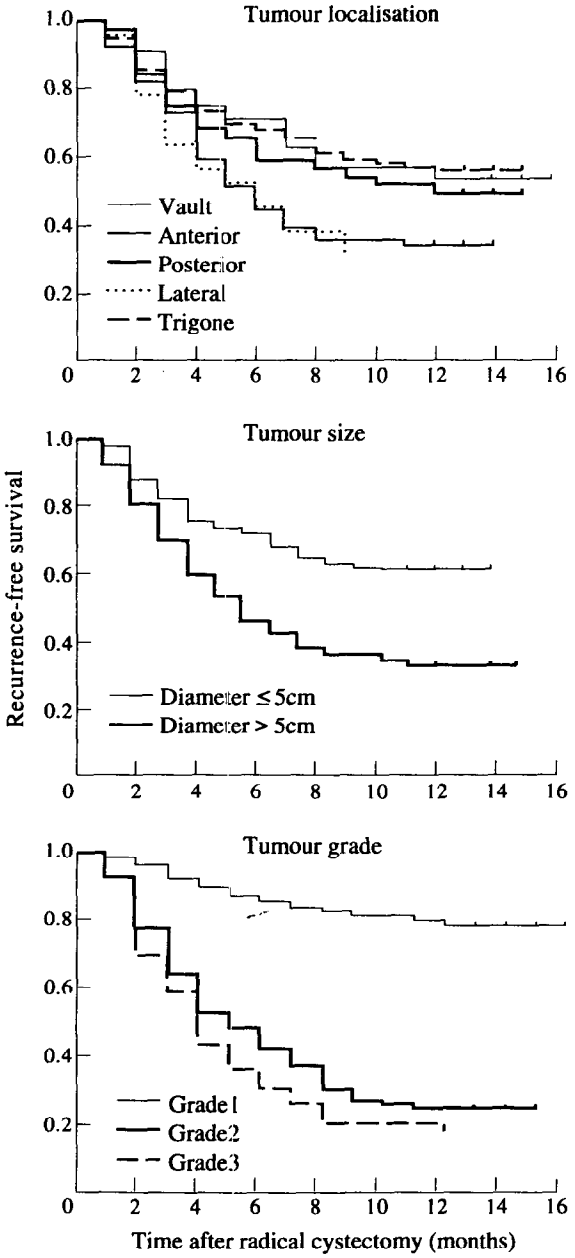

Figure 1. Recurrence-free survival curves according to tumour localisation, tumour size and tumour grade.

cystectomy. Table 2 presents the relative risk (point estimate, 95% confidence interval) of each prognostic factor. To visualise the role of prognostic factors, examples of recurrence-free survival curves are displayed in Figure 1 as a function of time after operation for three of those factors.

Multivariate analysis

When using the Cox model, only tumour grade, renal insufficiency, tumour diameter, anterior/trigone location and tumour stage had a prognostic role on the recurrence-free survival curve after radical cystectomy (Table 3). As shown in Table 4, unselected factors were no longer related to the recurrence-free survival curve once these five risk factors were included in the Cox model. A scoring system was developed, as shown in Table 5, based on relative risk in the Cox model of each factor. According to the total score of factors included, a patient is

Table 1. Main patients' characteristics in first (learning) and second (test) samples

Variable	First sample (310 patients) Number	%	Second sample (122 patients) Number	%
Sex				
Males	253	82	91	75
Females	57	18	31	25
Tumour location				
Vault	36	12	24	20
Anterior	57	18	32	26
Posterior	45	15	42	34
Lateral	144	46	19	16
Trigone	28	9	5	4
Tumour stage				
T1	1	0.3	0	0
T2	29	9.4	3	2
T3	242	78.1	102	84
T4	38	12.3	17	14
Histopathology of the tumour				
Squamous	272	88	100	82
Transitional	30	9	16	13
Adenocarcinoma	8	3	6	5
Tumour grade				
G1	149	48	42	34
G2	122	39	52	43
G3	39	13	28	23
Presence of ova of *Sch.h.*				
No	70	23	45	37
Yes	240	77	77	63
Lymph node involvement				
No	294	95	103	84
Yes	16	5	19	16
Metastasis				
No	299	96	120	98
Yes	11	4	2	2
Renal insufficiency				
No	185	60	84	69
Yes	125	40	38	31
Type of urinary diversion				
Rectal bladder	208	67	83	68
Ileal conduit	63	20	10	8
Ileo-caecal conduit	13	4	7	6
Ureterocutaneous	26	8	22	18
Age (years)				
Range	20–75		23–70	
Mean	45.0		48.0	
S.D.	9.7		9.8	
Median	45.0		49.0	
Diameter of the tumour (cm)				
Range	1–12		1–14	
Mean	5.0		6.0	
S.D.	1.9		2.1	
Median	5.0		6.0	

Sch. h., Schistosoma haematobium.

Table 2. Factors related to recurrence or death occurrence as assessed by the log rank method on the first (learning) sample: level of significance, P, point estimate of relative risk (RR) with its 95% confidence interval (95% C.I.)

Factor Categories	P	RR	95% C.I.
Tumour grade			
G3	<0.001	7.3	4.45–11.9
G2		5.7	1.49–8.45
G1		1.0	
G2 or G3	<0.001	6.0	4.06–8.83
G1		1.0	
Tumour size			
Diameter >5 cm	<0.001	2.0	1.53–2.86
Diameter ≤5 cm		1.0	
Renal insufficiency			
Yes	<0.001	2.1	1.51–2.83
No		1.0	
Tumour stage			
T4	<0.001	8.8	3.14–22.65
T3		3.8	1.54–9.22
T1 or T2		1.0	
T3 or T4	<0.001	4.2	1.74–10.34
T1 or T2		1.0	
Lymph node involvement			
Yes	<0.001	2.6	1.51–4.56
No		1.0	
Type of urinary diversion			
Ureterocutaneous	0.0176	2.4	1.34–4.23
Rectal bladder		1.2	0.81–1.86
Ileo-caecal conduit		1.1	0.44–2.57
Ileo-conduit		1.0	
Ureterocutaneous	0.0024	2.0	1.27–3.26
Others		1.0	
Metastasis			
Yes	0.006	2.4	1.26–4.56
No		1.0	
Tumour location			
Trigone	0.0085	1.9	1.17–3.26
Anterior		1.8	1.24–2.77
Posterior		1.2	0.74–1.94
Vault		1.0	0.59–1.76
Lateral		1.0	
Anterior/trigone	<0.001	1.8	1.31–2.51
Others		1.0	

considered in class A if he/she has a score <3, class B if the score is 3 or 4, class C if the score if 5, class D if the score is >5. Table 6 gives, for each stratum, its relative risk of recurrence when compared to stratum A. Figure 2 presents the expected recurrence-free survival curves after radical cystectomy derived from the Cox model ($P < 0.0001$).

Table 3. Prognostic factors of recurrence or death as assessed by the Cox model; rank of selection, χ^2 of selection and degree of significance P at selection, final relative risk: point estimate (RR) and 95% confidence interval (95% C.I.)

Rank	Prognostic factor	χ^2	P	RR	95% C.I.
1	Grade 2 or 3	104.01	0.000	5.5	3.7–8.1
2	Renal insufficiency	17.45	0.000	1.9	1.4–2.6
3	Diameter >5 cm	11.82	0.001	1.6	1.1–2.2
4	Anterior or trigone location	9.70	0.002	1.7	1.2–2.3
5	Stage T3 or T4	4.87	0.027	2.4	1.0–6.0

Table 4. Relationship between unselected factors and the recurrence-free survival curve before any selection of prognostic factors (univariate analysis) and after selection through the Cox model of the five factors described in Table 3

	Before any selection		After selection of the five factors	
Unselected factors	χ^2	P	χ^2	P
Lymph node involvement	9.12	0.003	1.54	0.214
Metastasis	5.57	0.018	1.69	0.193
Ureterocutaneous or urinary diversion	7.39	0.007	1.28	0.257
Age ≥44 years	2.78	0.095	3.22	0.073
Male	1.29	0.255	0.02	0.887
Ova	1.43	0.232	0.48	0.489
Squamous or transitional	0.72	0.395	0.34	0.559

The factors lose their prognostic value when the five selected factors are taken in consideration by the Cox model.

Table 5. Scoring system used for prognostic factors of bladder cancer associated with schistosomiasis

Factor	Score
Tumour grade	
Grade I	0
Grade II or III	3
Tumour stage	
T1 or T2	0
T3 or T4	1
Tumour diameter	
≤5 cm	0
>5 cm	1
Tumour location	
Anterior or trigonal	1
Other location	0
Renal insufficiency	
No	0
Yes	1

Table 6. Prognostic strata and their relative risk of recurrence or death calculated from the Cox model

Stratum	Relative risk of recurrence or death	95% C.I.
A	1	
B	8.7	4.5–16.9
C	14.8	7.6–28.7
D	23.3	12.1–45.1

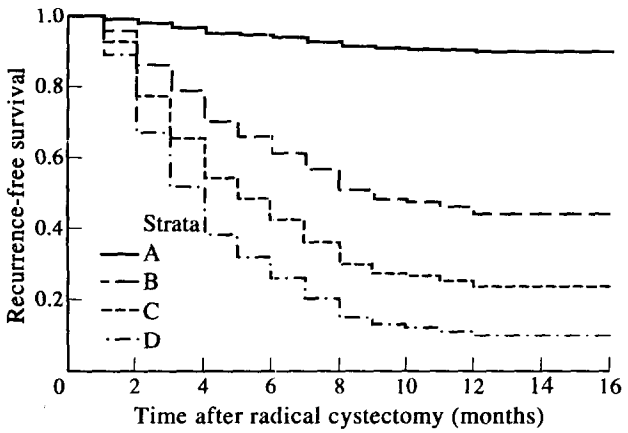

Figure 2. Recurrence-free survival curves after radical cystectomy of the four strata derived from the Cox model.

Validation

Each patient of the second sample was classified in his stratum according to the total score calculated from Table 5. For example, a patient with tumour grade I, tumour diameter 6 cm, lateral location, tumour extension T3 and normal renal function has a score of 2 and thus is classified in stratum A. The observed recurrence-free survival curve is described for each statum in Figure 3. No statistically significant difference could be detected between the observed and predicted recurrence-free survival curve of each stratum (Table 7, Figure 3) [12].

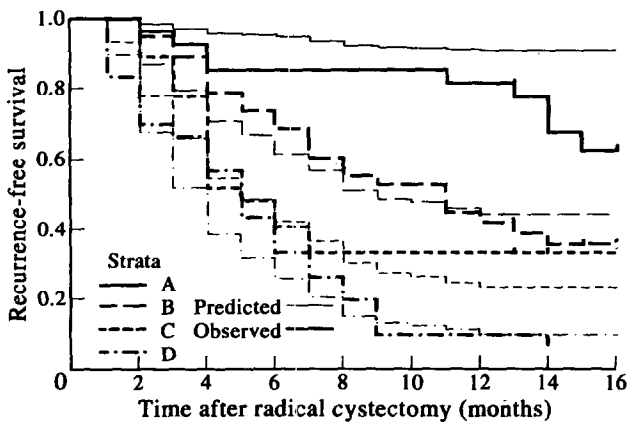

Figure 3. Observed and expected recurrence-free survival curves after radical cystectomy of the four strata on the second sample.

DISCUSSION

The purpose of this study was to derive a classification of bilharzial bladder cancer after radical cystectomy into several prognostic strata with increasing risk of recurrence. As shown in Table 1, the association of bladder cancer with schistosomiasis defines a distinct clinicopathological entity of bladder cancer quite different from that experienced in the western world [2]. It is commonly a well differentiated squamous carcinoma with a limited tendency to lymphatic and blood stream spread.

The univariate analysis of recurrence-free survival curves gave similar results to those obtained by analysis recurrence occurrence 1 year after radical cystectomy as previously published [4]. In multivariate analysis, indeed, the same prognostic factors were selected by both analyses; five factors were proved to be associated with bad prognosis for recurrence in our study [tumour grade (G2 or G3), anterior or trigonal location of the tumour, tumour diameter >5 cm, tumour stage T3 or T4 and renal insufficiency], factors identical to those derived by a discriminant function [4] apart from anterior or trigonal location which replaced lymph node involvement in the previous study.

When we classify patients from a second sample according to the previously published discriminant function [4] and the new proposed prognostic classification, a two-way table can be constructed (Table 8). It shows clearly that a more sensitive prognostic classification has been obtained through the Cox model than through linear discrimination.

When the patients of the second sample are classified according to the pTNM classification [6] from data obtained after radical cystectomy, a very poor agreement (Kappa coefficient estimate of 0.01) [13] was observed between the two classifications (Table 9). Most of the studied patients were classified in group III or VI of pTNM classification. Moreover, within these two pTNM groups these patients were almost equally distributed among the four prognostic strata of the new proposed classification. The apparent defect of classical pTNM classification was not suprising, since pTNM classification has been derived from data obtained from cystoscopy and biopsy at first assessment and completed or modified by supplementary observation during the operation and histopathological examination. Therefore, the use of pTNM classification from data of radical cystectomy specimens was clearly out of scope of this classification.

In conclusion, our classification appears to be suitable for classification of bilharzial bladder cancer patients after radical cystectomy into several prognostic strata. In spite of this narrow

Table 7. Comparison between the recurrence-free survival curve observed in the second sample and the one expected from the Cox model for each stratum when using the log rank method

Stratum	Cumulative recurrence-free survival at 12 months: Observed	Predicted	χ^2	*P*
A	0.82	0.91	0.378	N.S.
B	0.42	0.43	0.098	N.S.
C	0.33	0.24	0.341	N.S.
D	0.10	0.10	0.345	N.S.

N.S., non-significant.

Table 8. Description of the proposed classification of patients of the second sample according to the previously published discriminant function [4]: *number of patients, (mean ± standard deviation of the discriminant function)*

Proposed classification	Classification of the discriminant function: Score ≤ 39 Good prognosis	Score > 39 Bad prognosis
Stratum A	$n = 27$ (31.4 ± 3.4)	$n = 0$
Stratum B	$n = 14$ (36.4 ± 3.4)	$n = 24$ (44 ± 5)
Stratum C	$n = 4$ (38.7 ± 0.5)	$n = 23$ (48.2 ± 6.6)
Stratum D	$n = 0$	$n = 30$ (51 ± 6.3)

Table 9. Distribution of the patients of the second sample according to the pTNM classification and the proposed classification in patients with bilharzial bladder cancer after radical cystecomy

Proposed classification	pTNM classification: Stratum I	Stratum II	Stratum III	Stratum IV	Total
Stratum A	0	2	21	4	27
Stratum B	0	1	28	9	38
Stratum C	0	0	18	9	27
Stratum D	0	0	22	8	30
Total	0	3	89	30	122

field of application, it should be of practical use for urological oncologists in countries where bladder cancer is mostly associated with schistosomiasis.

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