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Prediction of Survival and Recurrence in Bladder Carcinoma

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Summary. We have followed a large population of patients receiving radiation treatment for bladder carcinoma with respect to survival and recurrence-free survival. Bivariate and multivariate life table analyses have been performed using a set of independent variables. The most important were T class, grade (G), urinary carcinoembryonic antigen (U-CEA) taken before treatment and cytological analysis 4 months after treatment. We compared the usual way of classifying a patient (T + G) with the combination of U-CEA and cytology since the latter two variables seemed to have great prognostic importance. The analyses show that T + G gives the best significance for survival ($p = 0.0003$) while U-CEA and cytology is better for recurrence-free survival ($\rho = 0.0002$). 0.0002).

Key words: Bladder carcinoma, Recurrence prediction, Urine cytology, Tumour grade, Urinary carcinoembryonic antigen, Classification, Survival prediction.

Introduction

One of the most commonly used factors for prognostic evaluation of urinary bladder cancer is the T classification [4, 8, 10,13]. In practice, then, it is the size of the tumour, combined with other factors, that determines which treatment the patient is going to get. We are also aware of the importance of the histological grade (G) [1, 9] and a G3 patient is treated more aggressively, often with preoperative irradiation followed by cystectomy. When the tumour is not too deeply infiltrating, the treatment gives a higher 5-year survival rate than surgery or radiotherapy alone [5, 10]. This contrasts with patients whose tumour is small and well (G1) or moderately well (G2) differentiated; they often receive surgical treatment only and still have a relatively high 5-year survival rate.

Although the conventional way of classifying a bladder tumour is by T and G, there is considerable uncertainty about the clinical outcome in groups T2 and T3 with G2 or G3, in which more aggressive treatment would be feasible. In recent years, cytology has proved to be a valuable tool in the diagnosis and follow-up of bladder carcinoma patients [6, 7]. Bladder cancers appear to contain CEA [16]. Also, measurements of urinary CEA (U-CEA) before and after treatment of the tumour have shown a relation to recurrence-free survival and crude survival [15, 17, 20].

Having followed a large population of patients with bladder carcinoma for a considerable period with these parameters, we have applied more sophisticated statistical methods [2, 11, 12] to evaluate which parameter or combination of parameters can best predict the prognosis for carcinoma of the bladder. No attempt has been made to evaluate different means of treatment in this study. The predictive values of the T, G, U-CEA and cytology parameters, as well as combinations of these variables, have been studied.

Materials and Methods

Patients

The study comprises 297 patients with a diagnosis of bladder carcinoma, treated at Radiumhemmet, Karolinska Hospital, and studied at different stages of their disease. As the patients were primarily admitted for radiotherapy, there is an over-representation of tumours of T3 and T4 as well as of grade 3. The types of treatment have been described previously [17] and are not evaluated here.

We have already published the results for control groups [17]: 50 healthy persons who were laboratory personnel and not age-matched. Another 75 patients had been symptom-free for over 2 years and were used as a control population, age-matched to the patients with active disease.

The primary diagnosis of bladder cancer, established in most cases at the Department of Urology, Karolinska Hospital, was based on intravenous pyelogram (IVP), cystoscopy with bimanual palpation under anaesthesia, histopathology of biopsies and exfoliative cytology. The tumours were classified according to the TNM-system [8] and graded (G) histologically in terms of deviation from the morphology of normal transitional epithelium [9].

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Table 1. Variables studied for their prognostic value in patients with bladder carcinoma

Groups compared	*n*	Difference between groups[a]	
		symptom-free survival, *p*	relative survival, *p*
T1 + T2 compared with T3 + T4	297	0.022	0.056
G1 + G2 compared with G3	297	*0.001*	*0.003*
Cytology[b] at 4 months	259[c]	*≪0.001*[c]	*≪0.001*
Cytology at 8 months	231	*≪0.001*	*≪0.001*
Cytology at 12 months	202	*≪0.001*	*≪0.001*
U-CEA before irradiation <30 compared to >30 ng/ml	297	*0.001*	*0.004*

[a] Log-rank test performed on survival curves. Significant differences favour the first-mentioned group
[b] After treatment, benign compared to malignant
[c] Shown in Fig. 1

Different types of radiation treatment were given: 255 patients received full-dose radiation (64–84 Gy/8 weeks, see Ref. 17) and 42 patients had 21 Gy/5 days for palliative purposes. All patients received sulphonamides or nitrofurantoin before and during radiotherapy, as prophylaxis for urinary tract infection. Follow-up controls included cystoscopy, IVP, cytology, serum electrolytes including creatinine and urinary samples. Cystoscopy was performed to judge local regression or progression. Regression of local disease was based upon cystoscopic disappearance of tumour. Local recurrence was evaluated by cystoscopy with biopsy. Death was registered as due to carcinoma of the bladder or other causes.

Collection and Evaluation of Cytological and U-CEA Samples

Cytological analysis of exfoliated cells was performed on bladder washings [3, 7]. Samples were taken before treatment and at follow-up 4, 8 and 12 months after the end of treatment. As often as possible the malignant cells in the samples were graded according to WHO [9].

Urine samples were taken aseptically for U-CEA sediments, bacterial culture and urinary creatinine. 5–10 ml samples of morning urine and serum were collected from patients 0–1 months before therapy. Quantitative cultures, detecting 10^3 bacteria per ml, were made. All urines from patients with bacterial infection were excluded [17, 20].

Radioimmunoassay for U-CEA

The radioimmunoassay (RIA) for CEA has been described earlier [19]. The urine and serum samples were extracted by perchloric acid, centrifuged and dialysed prior to assay. The sensitivity of the assay is around 0.3 ng CEA/ml. The intraassay variation for U-CEA is less than 8%; for interassay the coefficient of variation is around 20%. Mean U-CEA for 253 samples from healthy persons was 11.2 ng/ml.

Statistical Methods

As the U-CEA values were not normally distributed, mean values of the continuous variable were calculated from the natural logarithms (ln) of the CEA values. The two-tailed 95% confidence interval of the mean ln value was determined. Geometric means and interval limits were then obtained from the antilogarithms. Differences of means were calculated according to Student's *t*-test. When U-CEA was categorised to a discrete variable, logarithms were not used.

U-CEA was analysed in relation to relative survival or symptom-free survival in the sense of survival without local recurrence or metastases. The patients were divided into subgroups by the background variables (T class, grade, U-CEA, cytology). Survival rates were calculated by the life table method. The differences in survival over time and in symptom-free survival between the subgroups were studied using the log-rank test as described by Peto and co-workers [12]. The patients dying from bladder carcinoma or from other causes are considered lost to follow-up. The log-rank test thus takes censored data into account.

A regression model which also takes censored data into account [2] was used for the multivariate analysis of those variables that were in any way significantly different in the log-rank tests. The *p*-values of the $\hat{\beta}$: s refer to the estimated partial regression coefficients, that is the regression of, for instance, survival on an independent variable when the other independent variables considered are already in the equation. Briefly, the regression method is a follows: At any time, *t*, after diagnosis, a certain number of patients may die. The hazard function at time *t* is defined as the chance of dying on day *t* among patients living on day *t*. An undefined hazard function $\lambda_0(t)$ is taken to represent a standard hazard function, and the assumption of the Cox regression model is that the hazard function $\lambda(t)$ corresponding to a set $(Z_1, Z_2, \ldots, Z_p)$ of values of the prognostic variables is then just a multiple of the standard hazard function. This multiple is $e^a = Z_1\beta_1 + Z_2\beta_2 + \ldots + Z_p\beta_p$ and so the form of the Cox regression model is $\lambda(t) = e^a\lambda_0(t)$.

Results

Life Table Analysis

Each available variable was tested separately for recurrence-free survival and survival (Table 1, Fig. 1). All of them seem to have a good prognostic value. Previous calculations have shown that U-CEA <30, 30–50 and >50 ng/ml are levels useful in the clinic [17, 20].

Cytology undertaken before treatment showed malignancy in 91% of the cases. The distribution of the cytological samples obtained after radiation treatment is shown in Table 2. A majority of the patients had received full-dose treatment, but cytological data were also obtained on 42

Table 2. The cytological picture at various times after radiation treatment of bladder carcinoma

	Cytology after treatment, no. of samples					
	4 months	%	8 months	%	12 months	%
Benign	147	57	128	55	111	55
Malignant, all degrees of differentiation	112	43	103	45	91	45
Evaluable samples, total	259		231		202	

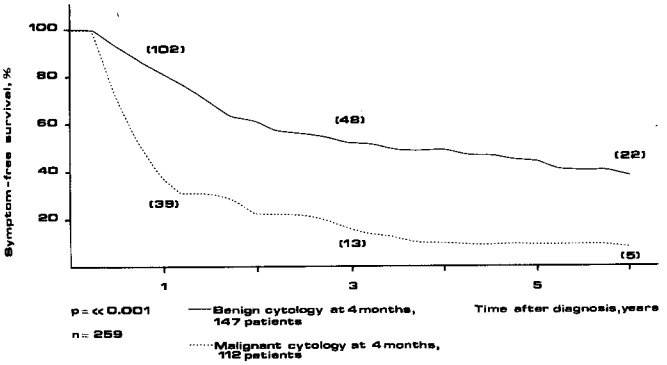

Fig. 1. Symptom-free survival (log-rank test) of patients with bladder carcinoma and benign (——) or malignant (– – –) cytology 4 months after radiation treatment. Number of patients given in brackets

Table 3. Repeated cytological evaluation after radiation treatment of bladder carcinoma

Cytological evaluation	Cytology post irradiation, no. of samples		
	4 months	8 months	12 months
Benign cytology	147		
remaining bening		98	72
altered to malignant		22	20
missing		27	6
Malignant cytology	112		
remaining malignant		72	51
altered to benign		18	6
missing		22	15
Total no. of evaluable samples from the same patients	259	170	123

patients receiving palliative radiation treatment. The frequency of benign cytologies at follow-up is similar at 4, 8 and 12 months, but the number of evaluable cases was highest at 4 months. It should be noted that cytology after, say, 12 months may comprise fewer patients with an initially malignant cytology because some may have died in the preceding period.

A separate study of the outcome of repeated cytology was made in the cases which provided cytological samples for at least a year (Table 3).

To understand the meaning of cytological findings at cytoscopy controls after radiotherapy, one must consider the following possibilities:

1. The tumour is radioresistant and still present unchanged after therapy. In most of these cases the cytology is malignant.

2. The tumour is greatly diminished in size and only a necrotic rest is left: cytology might still be malignant at the four month control but will be benign at follow-up together with complete disappearance of the tumour.

3. The tumour is radiosensitive and has completely disappeared at the first cytoscopic control at 4 months. Cytology may then be benign or malignant and the possible prognostic significance of these findings has been discussed earlier [6, 7].

From the very highly significant differences in Table 1 it can be said that a malignant cytology also means that the tumour is usually going to be macroscopically recurrent. Figure 1 illustrates the symptom-free survival of patients with benign and malignant cytology 4 months post-treatment. Unless otherwise mentioned, the 4-month cytology was used by us for the calculations below, the reasons being that (a) more samples were available, and (b) in practice, it will be desirable to evaluate prognosis and perhaps treatment effect as soon as possible after radiation.

Table 4 shows the survival of patients with benign or malignant cytology related to level of U-CEA, T class and grades. Log-rank tests were also made with those patients who had all cytologies benign compared to those with malignant cytology at any time. The difference in survival was highly significant ($p = 6.5 \times 10^{-6}$, not shown in tables). These results show that U-CEA before treatment and cytology after treatment at least partly measure different things (no high intercorrelation) and thus may complement each other as predictors. One example (from Table 4) is shown in Fig. 2. With an U-CEA >30 ng/ml before treatment, patients who do not have malignant cells in the urine at follow-up have a better prognosis than those who also have malignant cytology. The presumption that U-CEA and cytology have different qualities seems to be confirmed also by the fact that patients with e.g. a benign cytology at 4, 7 or 12 months after treatment might have had a low or high U-CEA before treatment.

Table 4. Survival of patients with bladder carcinoma and benign cytology or malignant cytology

Benign cytology compared with malignant cytology[a]	n	Difference between groups: symptom-free survival, p	relative survival, p
U-CEA <30 ng/ml	79	0.029	0.169
U-CEA >30 ng/ml	59	*≪0.001*[b]	*0.005*
T1 + T2	91	*≪0.001*	*0.003*
T3 + T4	110	*≪0.001*	*0.000*
G1 + G2	42	*0.017*	*0.036*
G3	172	*≪0.001*	*≪0.001*

[a] Log-rank test performed on survival curves. Significant differences favour the group with benign cytology. The benign (or malignant) cytology could occur at any of 4, 8 or 12 months after treatment

[b] Shown in Fig. 2

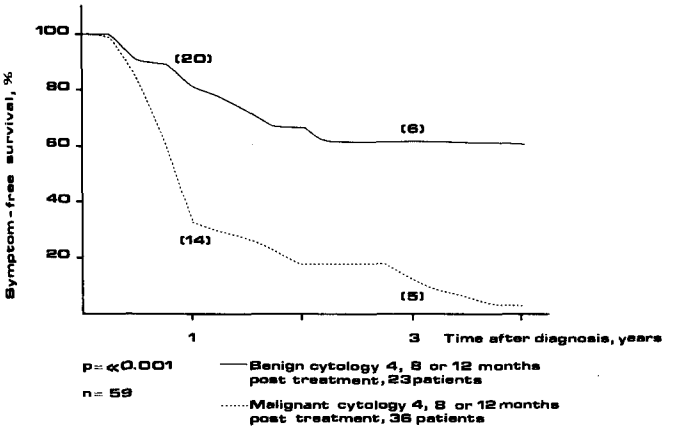

Fig. 2. Symptom-free survival (log-rank test) of patients with bladder carcinoma, U-CEA >30 ng/ml, and benign (——) or malignant (– – –) cytology at 4, 8 or 12 months after radiation treatment. Number of patients given in brackets

Table 5. Cox analysis of factors measured in 297 patients with bladder carcinoma

	Symptom-free survival		Relative survival	
	p	$\hat{\beta}$[a]	p	$\hat{\beta}$
U-CEA	<0.001	0.32	0.002	0.30
Sex	0.670	0.08	0.574	0.12
T	<0.001	0.31	≪0.001	0.59
G	0.589	0.10	0.420	0.22

[a] One needs to know the coding of the discrete variables used in the Cox regression analysis in order to compare the partial $\hat{\beta}$:s. Coding details can be obtained from the autors

Table 6. Cox analysis of the combination T + G compared to U-CEA before treatment and cytology at 4 months after treatment in patients with bladder carcinoma

	Difference between groups: symptom-free survival		relative survival	
	p	$\hat{\beta}$[a]	p	$\hat{\beta}$
U-CEA + cytology at 4 months post treatment	0.0002	0.36	0.002	0.36
T + G	0.005	0.23	0.0003	0.45

[a] Discrete values used for the independent variables: 0–5

Multivariate Analysis

The factor and combination of factors giving the best prognostic information for recurrence-free survival or relative survival were sought. Cox multivariate regression analysis was used with the factors mentioned above. From Table 5 it will be seen that the T classification and U-CEA (both evaluated before treatment) are good indicators of prognosis, as previously reported with other types of analyses. Grade here appears to give less information about the prognosis. The importance of cytology at different time points was sought on two more tests with a few variables. Cytology at 4 months in these tests was a good predictor (p = 0.003, not shown in tables).

We compared the usual way of classifying a patient (T + G) with the combination of U-CEA and cytology at 4 months, since the latter two variables seemed to have large prognostic importance. Table 6 shows that T + G gives the best significance for survival, while U-CEA + cytology is superior here for recurrence-free survival.

Discussion

Cytology in bladder washings was evaluated after full-dose radiation. Since the number of samples available for analysis was greatest 4 months after treatment, we chose the evaluation at that time. However, highly significant predictive values were also obtained with cytology after 8 and 12 months. Probably, the 12-month follow-up cytological evaluation would be the most reliable, since benign cytology may change into malignant but the reverse seldom occurs, unless further treatment is given. The fact that pretreatment non-malignant cytology can be obtained in around 9% of the cases has been pointed out in previous papers [7] and might be explained by the fact that highly malignant grade 3 tumours, which are overrepresented in the present study, are often necrotic and shed strongly degenerated non-diagnostic cells together with inflammatory cells.

Raised U-CEA before treatment has been shown to be a sign of bad prognosis. Also, U-CEA rises in recurrence of bladder carcinoma [17, 20]. Raised U-CEA influenced by bacterial infection, which in any case was below 10% in this material [17], was avoided by not using these values. Although cigarette smoking has been mentioned as one suspected aetiological factor of bladder carcinomas, increased U-CEA levels were not seen in otherwise healthy smokers (unpublished findings).

Several variables have been useful in characterising the biological and clinical properties of carcinoma of the bladder. Tumour size, histological grading, the DNA [14] and chromosome pattern all are morphological criteria. Markers of urothelial tumour activity are, among others, release of carcinoembryonic antigen into the urine, deletion of endogenous blood group antigens and characterisation of the host's lymphocyte population [18]. In the present paper, we have attempted to combine the morphological and functional characteristics previously studied by us into a more detailed statistical analysis of a large number of patients. We found, by the Cox multivariate analysis, that T + G has a high predictive value for survival. High U-CEA before treatment and malignant cytology after treatment predict the recurrence of localized disease. The combination of these two factors here turned out to be even better than T + G. At urological and oncological centres where the facilities are available, a very high degree of prognostic accuracy can be obtained by combining all four of these parameters.

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