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Possibilities for an Extended Classification of Bladder Cancer

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Summary. Patients with bladder cancer were evaluated for T-class, histo-pathological grade and U-CEA (urinary carcinoembryonic antigen) before treatment and the cytological picture 4 months after treatment. Previous work has shown that these variables are not significantly intercorrelated. Scores were computed, consisting of the sums of these (dichotomized) variables. In a statistical analysis with the life-table technique, the scored variables have been log-rank tested for a prognostic trend. In 155 patients, p for symptom-free survival between subgroups with low and high scores was 0.0019 and for relative survival 0.0005. This implies that a combination of variables may have predictive value in bladder cancer.

Key words: Bladder cancer, Carcinoembryonic antigen.

Introduction

Progress in the treatment of bladder cancer has been disappointing [2]. Only 60% of patients with superficial tumors and 25% of those with invasive cancer are alive 5 years after diagnosis. More intensive or new treatments should thus be considered for patients with the poorest prognosis. This in turn implies a need for more accurate predictive methods.

The conventional classification of a bladder tumor includes size (T) and histopathological grade (G). These parameters do give prognostic guidance but uncertainty still prevails concerning the clinical outcome in groups T2 and T3 with grades 2 or 3 [13]. In recent years cytology has proved to be a valuable tool in the diagnosis and follow-up of bladder carcinoma patients [3]. Bladder cancers [15, 19] as well as urine [5, 7, 14] from these patients appear to contain CEA. Measurements of urinary CEA (U-CEA) before and after treatment of the tumor have shown a relation to recurrence-free survival and crude survival [16]. These findings suggested that a combination of all four variables would be advantageous in predicting the outcome of bladder cancer. A similar scoring approach has been used by Palmer et al. in the prediction of acute leukemia [11]. In the present paper we show that the four variables combined accurately predict the relative and symptom-free survival of bladder cancer patients.

Patients and Methods

The study comprises 155 patients with a diagnosis of bladder carcinoma, treated at Radiumhemmet, Karolinska Hospital, Sweden. This patient group as a whole has a poor prognosis, since radiotherapy is only given for invasive disease. The primary diagnosis was based on intravenous pyelogram (IVP), cystoscopy with bimanual palpation, histopathology of biopsies and exfoliative cytology. The tumors were classified according to the TNM-system [8] and graded histologically in terms of deviation from the morphology of normal transitional epithelium [9]. The treatments for the different subclasses were based on the combined TG assessment and was described previously [16].

Follow-up included cystoscopy, IVP, cytology, serum electrolytes including creatinine, and urine analysis. Cytological analyses of exfoliated cells were performed on bladder washings after treatment [3]. The 4-month cytology was used by us for the calculations below, the reason being that many samples were available and that in practice it will be desirable to evaluate prognosis and perhaps treatment effect as soon as possible after radiation. Experience has shown that in the majority of responders a malignant cytology becomes benign after radiotherapy. This has often occurred by the time of the first cystoscopic control, four months after radiotherapy [4].

Urine samples were taken aseptically for U-CEA, sediments, bacterial cultivation and urinary creatinine. 5–10 ml samples of morning urine were collected 0–1 month before therapy. Samples with bacterial infection were rejected [16]. The radioimmunoassay (RIA) for urinary CEA included extraction with perchloric acid, and determination by a solid phase, double antibody assay (18). Mean U-CEA for 253 samples from healthy persons was 14.8 ± 12.9 ng/ml.

Table 1. Testing for prognostic trend in bladder cancer with a score comprising 4 explanatory variables

Sub-groups	Score[a]	*n*	Symptom-free survival O/E	Relative Survival O/E
A	0–1	30	0.65	0.39
B	2	62	0.95	0.97
C	3	41	1.13	1.37
D	4	22	1.82	1.67
			p (for trend) = 0.0019	*p* (for trend) = 0.0005

[a] The variables were given the following values. T: 0 = T1 + T2, 1 = T3 + T4; G: 0 = G1 + G2, 1 = G3; U-CEA: 0 = < 30 ng/ml 1 = > 30 ng/ml; Cytology 4 months after treatment: 0 = benign, 1 = malignant. The score is the sum of values for T + G + U-CEA + cytology

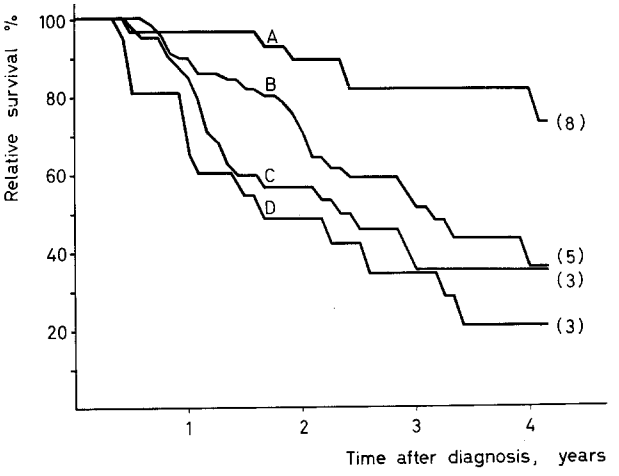

Fig. 1. Survival curves for subgroups of 155 patients with scores according to Table 1. *p* for the trend = 0.0005. Number of surviving patients is given in parentheses. These patients are still at risk to develop disease.

Subgroups and Statistical Methods

The patients were divided into subgroups on the basis of the background variables: T-category, grade, U-CEA before treatment and cytology 4 months after treatment. Each variable was dichotomized (transformed to a dummy variable; Table 1). The dummy variables were then summed forming a score for each patient. Survival rates were calculated by the life-table method. The differences between subgroups in survival over time and in symptom-free survival were assessed by means of log-rank test for trend, as described by Peto and coworkers [12]. If a group of patients is divided into more than two subgroups with respect to an explanatory variable, these subgroups may have a natural order (low, medium, high etc.) and can be numbered 1, 2, 3, ... in a nonarbitrary way. It is then possible to test whether that explanatory variable shows a statistically significant tendency for a prognostic trend. In the same way a score consisting of more than one explanatory variable can be used.

O denotes the observed number of events (deaths or recurrences), *E* the expected number of events for each time period. Death was registered as being due to bladder cancer or to other causes. The patients dying from other causes than bladder carcinoma are considered as lost to follow-up.

Results

Log-rank tests were performed to evaluate survival and symptom-free survival for each of the four variables T, G and U-CEA before treatment and cytology 4 months after treatment of bladder cancer. High predictive values were obtained for all four (not shown). Each patient was given values 0 or 1 for his variables as specified in the note to Table 1. The values were summarized to a score. A life-table analysis was then performed, using the scores to form subgroups and testing for trend in the prognosis of survival and disease-free survival. The underlying data are given in Table 1. Figure 1 shows that the patient's scores are very strongly related to their prognosis. The median survival time for subgroup A patients was 70 months, for groups B, C and D 38, 28 and 21 months respectively.

Discussion

Several properties have proved useful for characterizing the biological behaviour of carcinomas of the bladder. Histological grading and cytology are morphological criteria, as is the chromosome pattern [1]. Immunologic changes which have been described are deletion of blood group antigens from tumor cells and synthesis of CEA, increasing Ig content in the urine, and the activation of certain host lymphocytes [17]. Still another parameter, the DNA content of the tumor cell nuclei [6], adds significantly to the evaluation of the prognosis.

T, G and U-CEA have all been shown to add prognostic information [16] and cytology confers predictive value when controlling for CEA [10]. We have previously compared the usual way of classifying a patient's tumor (T + G) with evaluation of U-CEA and cytology, since the latter two variables seemed to have considerable prognostic importance [10]. A multivariate analysis of data from 425 patients showed that T + G best explained the variation in survival, while U-CEA + cytology was better for recurrence-free survival. The combination of all four variables has now been evaluated in 155 patients. It appears to give prognostic information superior to any of these factors alone. At urological and oncological centres where the facilities are available, such scoring should be useful for evaluating patients with bladder cancer.

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