Survival of Patients with Bladder Cancer
—Analysis of Prognostic Factors—

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Summary: A recognition of prognostic factors in the treatment of patients with bladder cancer is important. Using a variety of clinical and histological parameters, we have performed monovariable and multivariable analyses on the survival rates of patients. Eighty three patients with bladder cancer who underwent total cystectomy were studied. Eleven factors were evaluated, i.e., age, sex, tumor form, number and size of the tumors, histological stage and grade, intramural infiltration pattern, presence of intramural lymphatic and venous invasion, and the use of adjuvant chemotherapy. Monovariable analysis of survival curves indicated that histological stage and grade, intramural lymphatic invasion, venous invasion, and infiltration pattern are important as prognostic factors. Multivariable analysis, which is more relevant than monovariable analysis, showed that histological stage, followed by age, histological grade, intramural lymphatic invasion and infiltration pattern, in order of decreasing value, were most important as prognostic factors.

Key words: bladder cancer—prognostic factors—multivariable analysis—monovariable analysis—total cystectomy

Introduction

Certain histological features of cancer of the urinary bladder are thought to be important factors in determining the prognosis of the disease. In particular, the histological stage (pT) is considered to be one of the most crucial prognostic factors (Jewett and Strong, 1946; Jewett et al. 1964; Marshall, 1952). The histological grade (G) (Broders, 1922; Marshall et al. 1956) and cancer infiltration into intramural vessels of the urinary bladder (Austen and Friedell, 1965; Bell et al. 1971) appear to be of similar importance. In general, prognoses are made by using the relative importance of clinical and histological factors involved in the prognosis of urinary bladder cancer patients and calculating the patients’ survival rate for each factor separately. However, cancer of the urinary bladder is clinically and histologically diverse, and the factors used in its prognosis can interact with one another. Thus simultaneous consideration of these factors is important for more accurate prognoses and a more precise definition of the relative importance of each factor. Multivariable analysis enables a comprehensive evaluation of the relative importance of multiple, mutually interacting factors and the results of their interactions. In this study, the relative importance of a variety of clinical and histological parameters as prognostic factors has been evaluated in 83 patients with urinary bladder cancer.

Subjects and Methods

This study includes 83 patients who,
during the last 10 years in our department, underwent total cystectomies with ileal conduits as urinary diversion following diagnosis of urinary bladder cancer. Sixty-two males and 21 females were involved. Seventy-six had transitional cell carcinomas, 6 had squamous cell carcinomas and one had an adenocarcinoma. A total of 11 clinical and histopathological factors was examined. Clinical factors were: age and sex of the patient, form, number and size of the lesions. The five histopathological factors were: histological stage and grade, intramural infiltration pattern (INF), presence of intramural lymphatic (ly) and venous (v) invasion. The final parameter was post-operative adjuvant chemotherapy (T) using e.g. doxorubicin (ADR), 5-fluorouracil (5-FU), mitomycin C (MMC) and tegafur. Clinically, lesions in bladder cancer patients were classified according to their morphological features: papillary pedicled, non-papillary pedicled, papillary sessile and non-papillary sessile; or according to their number: single or multiple. According to size, lesions were divided into categories of <1cm, 1-3cm, 3-5cm and >=5cm dia. Histological classifications used, such as stage and grade, are based on those of the International Union Against Cancer (UICC). Infiltration pattern was divided into three types, i.e. INFα, INFβ and INFγ. INFα has no intramural tumor dissemination. INFγ has prominent intramural tumor dissemination and INFβ has a moderate dissemination. Intramural lymphatic invasion is given as ly0, ly1 and ly2. There is no invasion of intramural lymph vessels in ly0. ly1 indicates that invasion of tumor cells has been observed in superficial lymph vessels. ly2 indicates tumor invasion of deep lymph vessels. In travenous tumor invasion is also divided into 2 types; v (+) includes tumor invasion in mural veins and v (−) indicates invasion has not been observed. The adjuvant chemotherapy factors was divided into 4 groups: T1 indicates use of MMC only; T2, MMC+5FU+cylocide; T3, ADR+tegafur and T4, no drugs. The patients’ 5-year survival rate for each factor was first calculated by the Kaplan-Meier method (Kaplan and Meier, 1958). The effect of each factor was assessed by examining the survival curves drawn for the different categories of the factor in a monovariable analysis using the generalized Wilcoxon test (Gehan, 1965). Subsequently, all 11 factors were assessed simultaneously by the Quantification II method (Hayashi 1950, 1952).

Results

Many of the patients studied died from carcinomas within 2 years of their cystectomies; the resulting 2-year survival rate was 75.6%. The survival rate showed only minor changes thereafter, having a value of 63.3% at 5 years (Fig. 1).

Fig. 1. A survival curve, calculated by the Kaplan-Meier method, of all patients with bladder cancer who underwent total cystectomies (n=83).
Fig. 2. Monovariable analysis of survival curves using a variety of histopathological and clinical factors: a, histological stage, b, histological grade, c, lymphatic invasion, d, venous invasion, e, type of infiltration, f, adjuvant chemotherapy. For a given parameter, patients were subdivided into groups on the basis of various grades of the parameter as described in “Subjects and Methods”.
1. Monovariable analysis of various clinical and histopathological factors

Age: The 5-year survival rate was 62.5% for subjects younger than 49, 72.6% for subjects 50-69 and 71.1% for subjects older than 70. However, the differences among the 3 age groups were not statistically significant.

Sex: The 5-year survival rate was 68.9% for male patients and 49.7% for female patients; the differences, however, were not statistically significant.

Form of lesion: The 5-year survival rate was 80% for papillary pedicled tumors, 0% for non-papillary pedicled tumors, 68.7% for papillary non-pedicled tumors, 53.3% for non-papillary non-pedicled tumors. These differences were not statistically significant.

Number of lesions per patient: The 5-year survival rate was 57.8% for single lesions and 65.8% for multiple lesions; the differences, however, were not statistically significant.

Size of tumor: The 5-year survival rate was 73.5% for tumors 1-3 cm dia., 51.3% for tumors 3-5 cm dia. and 67.6% for tumors 5 cm or larger. These differences were not statistically significant.

pT: The 5-year survival rate for pT1 was 95.5%, 80.8% for pT2, 80% for pT3a, 24.2% for pT3b and 24.6% for pT4. Prognoses for patients with pT4 lesions were significantly worse than for those with pT1 (p<0.01), pT2 (p<0.01), and pT3a (p<0.05) (Fig. 2a).

G: With regard to the different degrees of atypism, the 5-year survival rate was 100% for G1, 89.9% for G2 and 30.6% for G3. The prognosis for G3 patients was significantly worse than for G2 patients (p<0.05) (Fig. 2b).

ly: The 5-year survival rate was 95.2% for ly0, 74.4% for ly1 and 0% for ly2. Survival curves indicated significantly worse prognoses for ly2 than for ly0 (p<0.01) and ly1 (p<0.05) (Fig. 2c).

v: The 5-year survival rate was 81.5% for v (-) and 36.8% for v (+). Survival curves showed significant differences between v (+) and v (-) (p<0.01) (Fig. 2d).

INF: Results for tumor infiltration patterns showed the 5-year survival rate was 100% for INFα, 70.2% for INFβ and 34.5% for INFγ. The prognosis of INFγ was significantly worse than for INFβ (p<0.01) and INFα (p<0.01) (Fig. 2e).

Chemotherapy: Fig. 2f shows survival curves for different surgical adjuvant chemotherapy. The 5-year survival rate for T1 was 62.5%, 60.6% for T2, 72.6% for T3 and 71.1% for T4. However, these differences were not statistically significant.

2. Multivariable analysis of prognostic factors

The patients were divided into two groups those who died from the cancer and those who were alive 2 years after surgery. The relative importance of each of the various factors studied was assessed by the Quantification II method. All 11 factors were used as predictor variables in 38 patients in whom data for all these factors were available. From

![Fig. 3. Accumulated discrimination graph constructed by the Quantification II method as described in "Subjects and Methods".](image-url)
partial correlation coefficients and the multiple correlation coefficient matrix, the factor with the greatest effect on a prognosis was found to be pT (0.6692), followed by age (0.5393), G (0.5298), ly (0.5266) and INF (0.5250). The correlation ratio was 0.8849, F-value was 8.5349 and p-value was 0.000, indicating a marked significance. A prognosis could be made in about 90% of the patients by drawing an accumulated discrimination graph based on this table (Fig. 3).

Discussion

There has been only a small number of studies in which the prognostic factors of cancer of the urinary bladder have been examined by multivariable analysis. Using Cox's proportional hazards model, Narayana et al. (1983) have reported that pT, G and size of the cancer are prognostic factors in patients treated for the first time; age and pT are important factors in recurrent cancer cases. A study by Nilsson et al. (1982) using a similar model has suggested that the pT is the most important factor among sex, pT, G and urinary carcino-embryonic antigen. In the present study, monovariable analysis of the survival curves of the urinary bladder cancer patients has shown that the histopathological factors pT, G, ly, v and INF pattern all are important as prognostic factors. In contrast, age, sex, tumor form, number and size of the tumors and the use of adjuvant chemotherapy appeared to have had no prognostic value. Multivariable analysis of the parameters studied indicated that pT, age, G, ly and INF were prognostically very important in order of decreasing importance. These results indicate that when simultaneous involvement with other factors is taken into consideration, pT, which is commonly regarded as an important prognostic factor, is in fact the most important one. Although we have demonstrated that the histological stage of the lesion is the most important factor in the evaluation of patients with bladder cancer and in the selection of their treatment, the clinical staging using a variety of diagnostic methods is often inconsistent with histopathological staging. Further efforts to improve the accuracy of clinical staging appear to be necessary. In this study, the majority of the clinical parameters was not of prognostic importance. Ideally, however, it should be possible to make accurate prognoses preoperatively on the basis of only clinical factors. We intend to explore this possibility in our future studies.

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References


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