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PRIMARY SUPERFICIAL BLADDER CANCER RISK GROUPS ACCORDING TO PROGRESSION, MORTALITY AND RECURRENCE

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ABSTRACT

Purpose: We identified risk groups in primary superficial bladder cancer according to progression, mortality and recurrence rates.

Materials and Methods: The prognostic factors of progression, mortality and recurrence were identified by multivariate analysis in a cohort of 1,529 patients with primary superficial bladder cancer. Risk groups were designed by combining the relative risk of these prognostic factors. We performed survival analysis of progression, tumor mortality and recurrence by risk group using the Kaplan-Meier method. Relative risk in each group was calculated by Cox regression. We present timetables of progression, mortality and recurrence by risk group.

Results: Risk groups were classified as low—grade 1 stage Ta disease and a single grade 1 stage T1 tumor, intermediate—multiple grade 1 stage T1 tumors, grade 2 stage Ta disease and a single grade 2 stage T1 tumor, and high—multiple grade 2 stage T1 tumors, grade 3 stages Ta and T1 disease, and any stage disease associated with carcinoma in situ. Survival analysis of progression, mortality and recurrence revealed a statistically significant difference among the 3 risk groups. The rates of recurrence, progression and mortality were 37%, 0% and 0% in the low, 45%, 1.8% and 0.73% in the intermediate, and 54%, 15% and 9.5% in the high risk group, respectively. The relative risks of recurrence, progression and mortality in the low versus the intermediate and high risk groups were 1.37, 2.84 and 1, and 1.87, 24.76 and 14.69, respectively.

Conclusions: Risk group classification based on prognostic factors defines progression, mortality and recurrence rates in primary superficial bladder cancer. It may be useful for designing treatment and followup strategies.

KEY WORDS: bladder, bladder neoplasms, risk, prognoses

Pathological evaluation is useful for determining factors that influence disease evolution, so that a prognosis may be established, and treatment and followup strategies designed. This information may be achieved by knowledge of the prognostic factors. A great deal has been published about prognostic factors in primary superficial bladder cancer.[1–15] However, few groups propose a risk group classification based on these prognostic factors.[2,16–18] Tumor evolution is different according to possible combinations of the main prognostic factors. For example, a poorer prognosis is expected for grade 3 than grade 1 disease and multiple than single tumors. Therefore, when primary superficial bladder cancer is classified according to a combination of prognostic factors, some risk groups may be identified. These groups would be useful for predicting possible tumor evolution, so that treatment and followup schedules may be designed.

Nevertheless, flaws have been described in several survival studies of superficial bladder cancer and other urological pathologies.[19,20] Some studies present values for disease-free survival without providing a definition of that parameter. Steineck et al noted this problem in 15 of 28 previously published studies (54%) of prostate cancer.[19] In addition, when a superficial bladder cancer study is performed, the main analyzed end points are recurrence and progression, while tumor mortality is usually ignored. Kalish et al believed that the reason for this neglect was that invasive disease develops in only a few patients.[20] Thus, to reveal a significant difference a greater number of patients and longer followup are needed to increase the power of the common statistical tests. On the other hand, there is the assumption that recurrence is associated with a great risk of invasive tumor, and so recurrence is usually the only studied end point. Kalish et al also proved that this theory was not true by showing that the risk of invasive disease is independent of previous recurrence.[20] For all of these reasons they argued that any superficial bladder cancer study should consider time to invasive disease as a major end point. Since few evaluations of superficial primary bladder cancer risk groups have been done and the majority focused on recurrence, we performed our study to establish primary superficial bladder cancer risk groups, focusing mainly on progression and tumor mortality. We also evaluated the usefulness of this classification for predicting tumor evolution.

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MATERIALS AND METHODS

We evaluated a cohort of 1,529 patients treated from November 1968 to December 1996 with transurethral resection and random bladder biopsy for primary superficial transitional cell carcinoma of the bladder. We previously reported patient characteristics, technique and followup.[15] Median followup was 40 months (range 3 to 315). Although the grading classification was recently changed,[21] we used the previous classification[22] because it represents a historical cohort. Multivariate analysis demonstrated that the main prognostic factors of recurrence were multiplicity (relative risk 2, 95% confidence interval [CI]1.6 to 2.4), tumor size greater than 3 cm. (relative risk 1.65, 95% CI 1.3 to 2), carcinoma in situ association (relative risk 1.65, 95% CI 1.2 to 2.2) and treatment with bacillus Calmette-Guerin (BCG) instillation (relative risk 0.39, 95% CI 0.27 to 0.56). The prognostic factors of

progression were grade 3 disease (relative risk 19.9, 95% CI 2.6 to 150), multiplicity (relative risk 1.9, 95% CI 1.1 to 3.2), tumor size greater than 3 cm. (relative risk 1.7, 95% CI 1 to 3), carcinoma in situ association (relative risk 2.1, 95% CI 1.1 to 4) and treatment with BCG instillation (relative risk 0.3, 95% CI 0.1 to 0.7). Furthermore, the mortality prognostic factors were grade 3 disease (relative risk 14, 95% CI 1.8 to 109) and carcinoma in situ association (relative risk 3, 95% CI 1.4 to 6.6).

We previously reported that progression and mortality were the 2 main end points of our study, and grade was the main prognostic factor of progression and mortality.[15] When the risk groups were identified, a greater value was assigned to the variable grade. Consequently the other variables were stratified from the variable grade. When we defined the high risk group, the initial cases represented grade 3 disease because of worse evolution independent of its association with other prognostic factors, such as tumor size, multiplicity and carcinoma in situ association. On the other hand, when we analyzed grades 1 and 2 disease, we discovered worse evolution in cases with carcinoma in situ association.[15] Thus, any tumor associated with carcinoma in situ was included in the high risk group independent of grade. Furthermore, we identified different evolutions for grades 1 and 2 disease depending on multiplicity (single or multiple tumors) and stage Ta or T1. Therefore, the 9.3% progression and 4.5% mortality rates of multiple grade 2 stage T1 disease were not as high as those of grade 3 or carcinoma in situ associated tumors but they were too different from those of other tumors. For this reason we also included the former lesions in the high risk group. In addition, for grade 1 disease we successfully differentiated cases without progression and mortality by stage and multiplicity. These grade 1 stage Ta and single grade 1 stage T1 tumors were classified in the low risk group. Furthermore, we included the remaining multiple grade 1 stage T1, grade 2 stage Ta and single grade 2 stage T1 tumors in the intermediate risk group. Table 1 shows this classification with the incidence of each risk group.

We assessed the evolution of each group by survival analysis using the end points of progression, defined as a change to a higher tumor stage or T2 to T4, mortality and recurrence. We estimated the cumulative distribution of the disease-free interval in each risk group using the Kaplan-Meier method and calculated relative risk in each group by the Cox proportional hazards model using the stepwise forward selection procedure with 2-sided p values. Timetables of disease progression, mortality and recurrence by risk group are provided.

RESULTS

Survival analysis by the Kaplan-Meier method demonstrated a significant difference in the 3 groups for each end point of recurrence, progression and mortality (table 2 and figs. 1 to 3). In our cohort overall recurrence, progression and mortality were 48%, 7.5% and 4.57%, while in the low, intermediate and high risk groups the recurrence rate was 37%, 45% and 54%, respectively. Tumors in the low group did not progress or cause death. The rates of progression and mortality were lower in the intermediate than in the high group (1.8% and 0.73% versus 15% and 9.5%, respectively). On the other hand, when we calculated relative risk by the Cox regression method the risk of recurrence increased gradually in the 3 groups (1, 1.37 and 1.87, respectively, table 2). Furthermore, the risk of progression was almost 3-fold greater in the intermediate than in the low and almost 25-fold greater in the high than in the low group. The risk of mortality was similar in the low and intermediate groups but it increased to almost 15-fold greater in the high group.

We also constructed a timetable of the 3 end points by risk group based on the Kaplan-Meier survival analysis method (table 3). This information shows the percent of progression, mortality and recurrence in the 3 risk groups during the initial 5 years. For example, there was 25% recurrence in the initial 2 years in low risk and 1% mortality in high risk cases during year 1.

TABLE 1. *Risk group classification*

	% Frequency
Low risk:	11.5
Grade 1 stage Ta	
Grade 1 stage T1, single tumor	
Intermediate risk:	44.6
Grade 1 stage T1, multiple tumors	
Grade 2 stage Ta	
Grade 2 stage T1, single tumor	
High risk:	43.9
Grade 2 stage T1, multiple tumors	
Grade 3 stage Ta	
Grade 3 stage T1	
Ca in situ association	

DISCUSSION

Others previously identified risk groups in bladder cancer.[2, 10, 16–18] In 1987 Takashi et al performed multivariate analysis of survival in 264 cases of primary superficial bladder tumors.[10] They noted certain prognostic factors and relative risks, including stages T2 to T4 versus Ta to T1 disease (relative risk 4.6), tumor size greater versus less than 3 cm. (relative risk 3.1), irritative versus no irritative symptoms (relative risk 2.5), patient age older versus younger than 70 years (relative risk 2.7) and grade 3 versus 1 to 2 disease (relative risk 2.1). By combining these prognostic factors they identified 6 risk groups according to the number of any of the factors, including stages T2 to 3 disease, tumor size greater than 3 cm., irritative symptoms, patient age older than 70 years or grade 3 disease. Survival analysis demonstrated that these groups were statistically significant in that a greater number of factors correlated with worse evolution. However, some points should be considered. Invasive tumors were included in analysis, which may be why stage was the variable with a higher relative risk of 4.6. Other variables such as grade were not independently studied, for example grade 1 versus 2. Also, it was not specified whether the variable studied in survival analysis was recurrence, progression, mortality or another factor. Furthermore, when the groups were designed, the same value was assigned to each variable instead of a greater value to those with high relative risk, such as tumor stage (4.6) or size (3.1). If this fact had been considered, differences among risk groups may have been more evident. In addition, we think that a classification of 6 risk groups is excessive for providing easy management of these cases.

In 1989 Parmar et al reported on 305 patients in whom the only prognostic factors of recurrence were multiplicity and mainly positive 3-month cystoscopy.[2] Neither tumor grade, stage, size nor localization was a prognostic factor in their study. By combining these 2 prognostic factors they identified risk groups 1—a single tumor with negative 3-month cystoscopy, 2—multiple tumors or positive 3-month cystoscopy and 3—multiple tumors and positive 3-month cystoscopy. During the initial 2 years 74%, 44% and 21% of the patients were recurrence-free in groups 1 to 3, respectively. We think that this series is interesting because a simple classification was proposed that differentiates recurrence using only 3 risk groups. Furthermore, they introduced positive 3-month cystoscopy as a variable, which to our knowledge was not assessed by others. Nevertheless, although this classification discriminates recurrence well, it may be not successful for evaluating progression or mortality because other variables would be more important, such as tumor size, stage, carcinoma in situ association

TABLE 2. *Recurrence, progression and mortality by risk group*

Risk Group	Recurrence		Progression		Mortality	
	% Kaplan-Meier	Cox Regression	% Kaplan-Meier	Cox Regression	% Kaplan-Meier	Cox Regression
Low	37	1	0	1	0	1
Intermediate	45	1.37	1.8	2.84	0.73	1
High	54	1.87	15	24.76	9.5	14.69
Overall	48		7.5		4.57	

Log rank test $p < 0.05$.

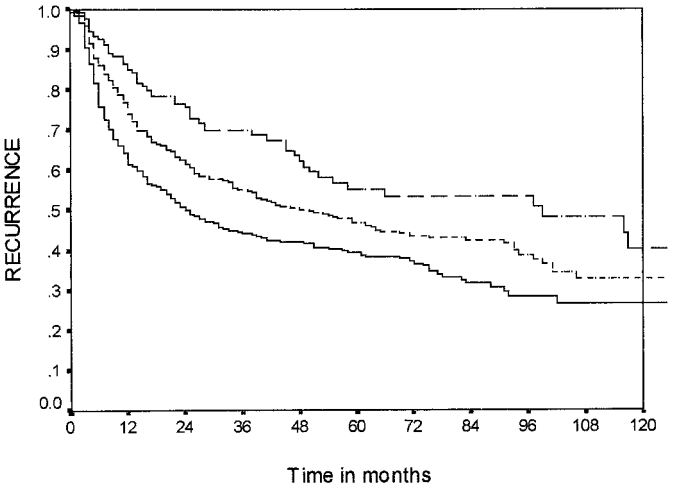

FIG. 1. Kaplan-Meier plot for recurrence comparing low, intermediate and high risk groups (log rank test significant at $p < 0.05$).

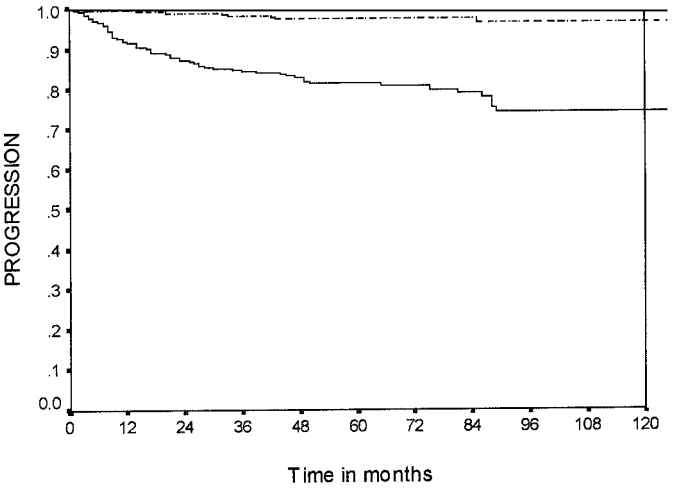

FIG. 2. Kaplan-Meier plot for progression comparing low, intermediate and high risk groups (log rank test significant at $p < 0.05$).

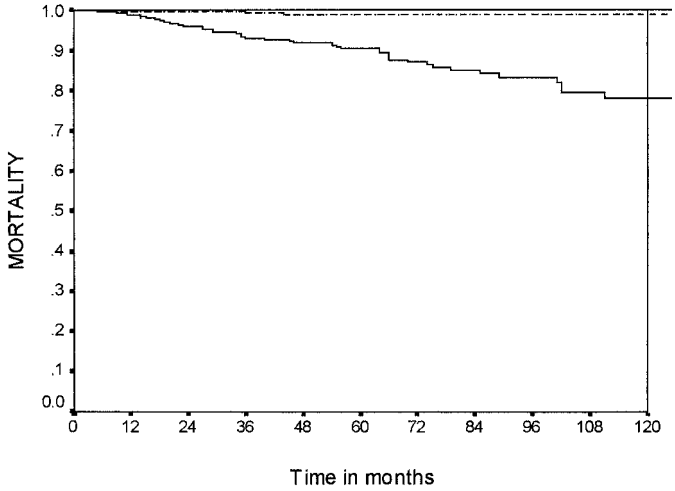

FIG. 3. Kaplan-Meier plot for tumor mortality comparing low, intermediate and high risk groups (log rank test significant at $p < 0.05$).

and particularly grade. However, Parmar et al did not evaluate the 2 end points of progression and mortality.

The classification of Parmar et al was followed by others, such as that of Arrizabalaga Moreno et al.[16] In their study survival analysis of recurrence by the Kaplan-Meier model was also statistically significant among the 3 risk groups. Furthermore, a nonrisk progression and mortality subgroup was defined as a single grade 1 stage Ta tumor less than 1 cm. with negative cytology and no carcinoma in situ association.

In 1995 Kurth et al assessed factors affecting recurrence, progression and death from malignant disease in patients with a total of 576 superficial bladder tumors who received intravesical chemotherapy.[17] Multivariate analysis showed that the most powerful predictors of these 3 end points were the previous recurrence rate, tumor size, tumor grade and positive 3-month cystoscopy. As in our study,[15] T stage was not a prognostic factor. Nevertheless, they also considered the yearly recurrence rate as a variable, defined as the number of followup cystoscopies at which recurrence was visualized divided by the total number of followup months. By combining the variables grade, tumor size and recurrence rate 3 group risks were established. The odds ratio of invasion and death for every combination of factors was determined by the Cox model. The survival study of invasion and death according to the 3 risk groups by Kaplan-Meier analysis was also significant. Unfortunately although Kurth et al provided a good model of risk groups, they did not perform survival analysis of recurrence according to these 3 groups. Thus, the usefulness of this classification for predicting recurrence was not determined.

Fradet also classified superficial bladder tumor cases into risk groups.[18] In a study of 382 primary superficial bladder tumors he observed that the main recurrence prognostic factors were tumor multiplicity, size, stage and grade. He defined adverse disease characteristics as multiple grade 2 or 3 stage T1 tumors greater than 3 cm. According to the number of adverse tumor characteristics he designated the risk groups as low—0, intermediate—1 or 2 and high—3 or 4 characteristics. During year 1 this classification indicated that recurrence and progression were 21% and 0%, 36% and 1%, and 66% and 9% in the low, intermediate and high risk groups, respectively. In our opinion this classification is not only simple, but also detects recurrence and progression. However, its capacity to discriminate would have increased if the value of each adverse tumor characteristic had been assigned as a function of its risk of recurrence or progression. In this model the same value was assigned to each adverse tumor characteristic.

We also identified risk groups based on prognostic factors determined by previous multivariate analysis.[15] It is difficult to construct a risk group classification that includes every

TABLE 3. *Kaplan-Meier timetable of recurrence, progression and mortality by risk group*

Time	% Recurrence			% Progression		% Mortality	
	Low	Intermediate	High	Intermediate	High	Intermediate	High
3 Mos.	2	4	9.4	0.2	1.3	0	0
6 Mos.	7	14	24	0.4	3.3	0.2	0.4
9 Mos.	12	19.6	32	0.4	7	0.2	0.6
1 Yr.	15	26	39	0.4	8	0.4	1
1.5 Yrs.	22	34	44	0.9	11	0.4	2.5
2 Yrs.	25	39	50	1.2	13	0.4	4
3 Yrs.	30	45	56	1.8	16	0.7	7
4 Yrs.	38	50	58	2.6	17	1	8
5 Yrs.	45	53	61	2.6	19	1	10

possible evolution of all hypothetical combinations of types of tumor. Nevertheless, we believe that an almost ideal classification must consider certain points. The classification should be based on a combination of previously established prognostic factors. The same value should not be assigned to every prognostic factor, but based on the relative risk determined by previous multivariate analysis. The classification should indicate the various evolutions associated with recurrence, progression and tumor mortality because knowledge of these 3 events is necessary to provide patients with an adequate prognosis and treatment.[20] However, because of the difficulty of this goal, it may be possible that the classification would correctly define recurrence but not progression. The number of risk groups should be a balance between a minimum that guarantees representation of every possible evolution and a maximum that is not excessive but enough to plan easily followup and treatment strategies.

Our main intention was to construct a classification with a reasonable number of risk groups that would together determine progression, mortality and recurrence. We think that these aims were achieved because this classification correctly differentiates the 3 events using only 3 risk groups, making it possible to design simple schedules of treatment and followup. On the other hand, a low risk group was defined with a 37% rate of recurrence but no progression or mortality. For this reason exhaustive followup is not required in this group. The high risk group represents an evolution that is different from that of the other 2 groups because its 15% progression and 9.5% mortality rates are also different. Thus, more aggressive adjuvant therapy and closer followup would be indicated in the high risk group. Another contribution of this study is the availability of a timetable of the 3 events (table 3). This table indicates tumor evolution in each group, which aids in making treatment and followup decisions. For example, the timetable shows that in the intermediate risk group only 1.2% of the patients have disease progression during the initial 2 years and none dies during the initial 3 months.

Nevertheless, this classification has certain weak points, as do others. Although the difference in recurrence is statistically significant among the 3 groups, it is not as dramatic as that of progression and mortality in the low, intermediate and high risk groups (37%, 45% and 54% versus 0%, 1.8% and 15%, and 0%, 0.73% and 9.5%, respectively, table 2). For this reason while risks of progression and mortality are 25 and 15-fold greater in the high than in the low risk group, respectively, the risk of recurrence is only 2-fold greater (table 2). Consequently the groups identified by Parmar et al[2] and Fradet[18] provide better differentiation of the recurrence risk than our classification. On the other hand, we analyzed the overall cohort of 1,529 patients to create risk groups independent of whether adjuvant therapy was administered. Because BCG treatment was mainly given in grade 3 or carcinoma in situ association cases, a selection bias may be present because all cases were included in analysis. Thus, a high rate of recurrence and progression may have been expected in the high risk group due to the beneficial effect of BCG therapy on recurrence and progression. However, this fact does not invalidate our results. If only patients without adjuvant therapy were included in analysis, the difference among groups would again have been significant but with a greater relative risk. In addition, it may be assumed that risk is higher than what we present in our study.

CONCLUSIONS

Our classification considers the relative risk of each prognostic factor and depends on only 3 risk groups. In addition, this classification achieves good differentiation of recurrence, and particularly good differentiation of progression and mortality. These variables are not only less studied, but also the main variables that determine the prognosis and management of a primary superficial bladder tumor.

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