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MULTIVARIATE ANALYSIS OF THE PROGNOSTIC FACTORS OF PRIMARY SUPERFICIAL BLADDER CANCER

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ABSTRACT

Purpose: We evaluate the prognostic factors of recurrence, progression and disease specific mortality in patients with primary superficial Ta and T1 transitional cell carcinoma of the bladder.

Materials and Methods: We studied a cohort of 1,529 patients with primary superficial transitional cell carcinoma of the bladder treated with transurethral resection and random bladder biopsies. Mean followup was 4.2 years. Statistical analysis was performed using the Kaplan-Meier method and multivariate analysis was done with the Cox proportional hazards model with stepwise forward selection. All p values were 2-sided, with odds ratios and 95% confidence intervals.

Results: Multiple tumors (odds ratio 2), tumor greater than 3 cm. (1.65) and carcinoma in situ (1.6) increased, whereas intravesical bacillus Calmette-Guerin (BCG) instillations (0.39) decreased the risk of recurrence. Grade 3 disease (odds ratio 19.9), multiple tumors (1.9), tumor greater than 3 cm. (1.7) and carcinoma in situ (2.1) increased, whereas BCG (0.3) decreased the risk of progression. Grade 3 disease (odds ratio 14) and carcinoma in situ (odds ratio 3) increased the risk of disease specific mortality.

Conclusions: Neither tumor stage nor dysplasia influenced tumor evolution. Multiple tumors, tumor greater than 3 cm. and intravesical BCG instillations were risk factors of recurrence and progression. Carcinoma in situ influenced recurrence, progression and disease specific mortality. Finally, the main predictor of progression and mortality was grade 3 disease.

KEY WORDS: bladder neoplasms, recurrence, disease progression, survival

Prognostic factors have been primarily evaluated in patients with superficial Ta and T1 transitional cell carcinoma of the bladder. Others have analyzed recurrence,[1–8] progression[9] or disease specific mortality,[10,11] or a combination of factors.[12–14] Sometimes it is difficult to discern whether the term survival refers to recurrence, progression or mortality.[10] Some have evaluated only primary,[2,3,8,10–13] whereas others have analyzed primary and recurrent tumors.[1,4–7,9,14] Some patients have received various types of intravesical instillations while others were given no additional treatment. The same variable has been studied differently, for instance grade 1 versus grade 2 or 3 disease.[1,3] Furthermore, the number of patients has varied from small series to large multicenter studies.[3,12–14] This disparity of characteristics and factors indicate that multivariate analysis is needed to determine the prognostic factors of transitional cell carcinoma of the bladder. Nevertheless, many published studies are based only on univariate analysis.[15–24] For these reasons we designed a study with a select cohort of patients who underwent complete transurethral resection and random bladder biopsies for primary superficial Ta or T1 transitional cell carcinoma of the bladder. Multivariate analysis was performed to determine the prognostic factors of recurrence, progression and disease specific mortality.

MATERIALS AND METHODS

Study patients. From November 1968 to December 1996, 5,095 patients underwent bladder tumor surgery. Of the 2,829 superficial tumors 2,324 (82%) were primary. In all patients transurethral resection was performed and 1,631 (70%) underwent a random bladder biopsy. The 42 cases with primary carcinoma in situ and 60 with no transitional cell carcinoma were excluded from study. Therefore, 1,529 patients treated with transurethral resection and random bladder biopsy for primary superficial Ta and T1 transitional cell carcinoma of the bladder were evaluated. Histopathology results were classified according to the TNM system.[5]

Technique and followup. At our institution all patients with a primary bladder tumor undergo cystoscopy followed by random bladder biopsy.[25] A cold flexible forceps is used to take biopsies of normal appearing mucosa of the trigone, retrotrigone, right and left lateral wall, dome and prostatic urethra in men. Tumor size is defined as the largest tumor measured with the resection loop that is 1 cm. long, and classified as less than 1.5, between 1.5 and 3, and larger than 3 cm., and papillomatosis is defined when the tumor covers more than 70% of the bladder surface. Complete transurethral resection of the tumor is performed and several deep muscular samples are taken using the resection instrument. Simple pathology reports performed by a uropathologist are used to obtain the cumulative data. The grade of nuclear atypia is used to distinguish carcinoma in situ and dysplasia. Carcinoma in situ appears similar to grade 3 disease but is a flat growth, whereas dysplasia is a flat lesion with less atypia.[26] These criteria have been recently validated.[27]

Of the patients 32% received intravesical instillations. Since 1989 every patient diagnosed with grade 3 disease and/or carcinoma in situ has been treated with bacillus Calmette-Guerin (BCG) instillations. BCG for other situations and other intravesical instillations (mainly mitomycin C, thiotepa and doxorubicin) were given according to urologist criteria. Thus, BCG instillations were given in 15% of cases, including 1% grade 1, 4.5% grade 2, and 43% grade 3 disease, 52% carcinoma in situ and 21% dysplasia. Further-

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more, 6% of patients received mitomycin C, 5.5% thiotepa, 3.5% doxorubicin and 2% other instillations. Cystoscopy and cytology were performed 4 months after therapy and, if no recurrence was found, alternate followup with ultrasonography and cytology versus cystoscopy and cytology was done every 4 months for 2 years and every 6 months thereafter. Excretory urography was performed at bladder tumor diagnosis to rule out a synchronous upper urinary tract tumor, and repeated every 2 years during followup. Mean followup was 4.2 years.

Statistical methods. The end points of the study were recurrence, progression defined as a shift to stage T2, T3 or T4 disease and disease specific survival. Therefore, a longitudinal, retrospective, observational and analytical study was performed. Prognostic factors were disease grade and tumor stage, carcinoma in situ in any random bladder biopsy sample, multiple tumors (single versus 2 or more), tumor size (smaller or greater than 3 cm.), dysplasia in any random bladder biopsy sample and intravesical instillations. Instillations were classified as no treatment, BCG or other. Estimation of the cumulative distribution of the disease-free interval in separate groups was calculated according to the Kaplan-Meier method. Multivariate analysis of the data was performed with the Cox proportional hazards model with stepwise forward selection. All p values were 2-sided, with odds ratios and 95% confidence intervals.

RESULTS

Patients (table 1). Of the patients 89% were men with a median age of 64 years (57 in 25th percentile and 71 in 75th percentile). Disease was grade 1 in 12%, 2 in 62% and 3 in 26% of the cases, and tumor stage was Ta in 36% and T1 in 64% (table 2). Carcinoma in situ was found in 19% of cases and was multifocal in 57%, and dysplasia was noted in 26.5%. Number of tumors was unknown in 36 cases (2.5%) and multiple tumors were found in 35%. Tumor size was not specified in 447 cases (29%) and was greater than 3 cm. in 21.5%. Of the patients 32% received intravesical instillations, of which 47% were BCG.

TABLE 1. *Patient characteristics*

	No. Pts. (%)
Total	1,529 (100)
Primary tumor	1,529 (100)
Men	1,357 (89)
Women	172 (11)
Grade:	
1	185 (12)
2	942 (62)
3	400 (26)
T category:	
Ta	546 (36)
T1	981 (64)
Associated Ca in situ:	
Yes	284 (19)
No	1,245 (81)
No. tumors:	
Unknown	36 (2.5)
	1,493 (97.5)
1	976 (65)
2	186 (12.5)
3	81 (5.5)
More than 3	250 (17)
Size of tumor (cm.):	
Less than 1.5	488 (45)
1.5–3	360 (33)
More than 3	200 (18.5)
Papillomatosis	34 (3)
Intravesical instillations:	
Unknown	37 (2.5)
None	1,003 (65.5)
	489 (32)
BCG	229 (47)
Mitomycin C	91 (19)
Thiotepa	83 (17)
Doxorubicin	56 (11.5)
Other	25 (5.5)

TABLE 2. *Relationship of grade of disease to T stage*

	No. Ta Stage (%)	No. T1 Stage (%)	Total No. (%)
Grade 1	158 (10)	27 (2)	185 (12)
Grade 2	325 (21)	617 (40)	942 (62)
Grade 3	63 (4)	337 (22)	400 (26)
Totals	546 (36)	981 (64)	1,527 (100)

Recurrence. Kaplan-Meier analysis revealed that recurrence was statistically significant for multiple tumors, tumor size, disease grade and intravesical instillations (fig. 1). No statistical differences were found for tumor stage and carcinoma in situ. However, multivariate analysis revealed that multiple tumors, tumor size, carcinoma in situ and intravesical instillations were prognostic factors of recurrence (table 3). Grade and tumor stage were not predictors of recurrence. Recurrence risk was twice as high for multiple tumors, and 1.6 times higher for tumors greater than 3 cm. or carcinoma in situ compared to those smaller than 3 cm. or no such association. Intravesical instillations were a protective factor of recurrence since the risk was lower than 1. Thus, the risk of recurrence was 0.39 times lower for patients treated with BCG, whereas other instillations did not modify this risk significantly.

Progression. Kaplan-Meier analysis and multivariate Cox analysis demonstrated that multiple tumors, disease grade, tumor size and carcinoma in situ were significant prognosticators of progression (fig. 2 and table 3). Intravesical BCG instillation was only significant in the Cox analysis. Thus, patients with multiple tumors, tumors greater than 3 cm. or carcinoma in situ had a progression risk nearly twice that of those with a single tumor, tumor smaller than 3 cm. or no such association. Grade 3 disease was the most important prognostic factor because the risk of progression was nearly 20 times higher than that for grade 1 disease. Although grade 2 disease had an odds ratio of 3, it was not significant. BCG instillations decreased 0.3 times whereas other instillations did not modify the progression risk.

Disease specific survival. Kaplan-Meier univariate analysis and Cox multivariate analysis showed that mortality prognostic factors were disease grade, carcinoma in situ and intravesical instillations (fig. 3 and table 3). Grade 3 disease was again the main factor and, thus, the mortality risk was 14 times higher for grade 3 than for grade 1 disease, and it was not significant for grade 2. Moreover, patients with carcinoma in situ had a mortality risk 3 times higher than those without carcinoma in situ. BCG intravesical instillations decreased the mortality risk 0.44 times. However, this finding was not significant since the 95% confidence interval included the value 1.

DISCUSSION

Analyses of prognostic factors of transitional cell carcinoma of the bladder related to recurrence are sometimes difficult to compare. Reports usually include different parameters and groups of patients, and some have analyzed only primary while others have evaluated primary and recurrent tumors. In most the followup is unknown or a mean of 3.5 years.[3, 12, 13] To date multivariate analysis has been performed in few studies (table 4).

Loening et al found that the only significant prognostic factor of recurrence was tumor stage,[5] and Narayana et al reported that the risk of recurrence was higher for recurrent than primary tumors.[6] Furthermore, tumor stage was whereas multiple tumors were not a recurrence prognostic factor. Dalesio et al reported that prognostic factors of recurrence were multiple tumors, tumor size and the recurrence rate.[1] Parmar et al noted that multiple tumors and positive

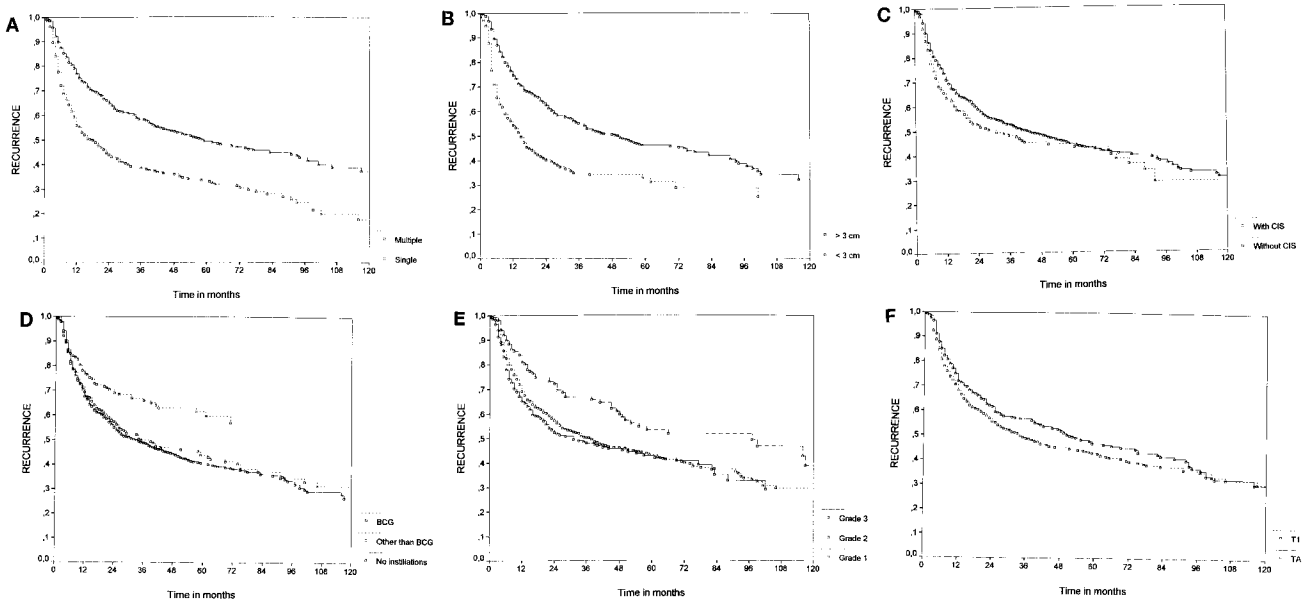

FIG. 1. Kaplan-Meier plot for recurrence comparing multiple and single tumors (log rank test, significant, p = 0.00001), tumors greater than and less than 3 cm. (significant, p = 0.00001), patients with and without carcinoma in situ (*CIS*) (not significant, p = 0.12), no, BCG and other instillations (significant, p = 0.0002), grades 1, 2 and 3 disease (significant, p = 0.005), and Ta and T1 tumors (not significant, p = 0.09).

TABLE 3. *Multivariate analysis of recurrence, progression and disease specific survival*

Prognostic Factor	Odds Ratio	95% CI
Recurrence		
Multiplicity:		
Single	1	
Multiple	2	1.6–2.4
Tumor size:		
Less than 3 cm	1	
Greater than 3 cm	1.65	1.3–2
Associated Ca in situ:		
No	1	
Yes	1.6	1.2–2.2
Intravesical instillations:		
None	1	
Other	0.76	0.6–1
BCG	0.39	0.27–0.56
Progression		
Multiplicity:		
Single	1	
Multiple	1.9	1.1–3.2
Grade:		
1	1	
2	3	0.4–22.8
3	19.9	2.6–150
Tumor size:		
Less than 3 cm.	1	
Greater than 3 cm.	1.7	1–3
Ca in situ association:		
No	1	
Yes	2.1	1.1–4
Intravesical instillations:		
None	1	
Other	1.3	0.7–2.5
BCG	0.3	0.1–0.7
Disease specific survival		
Grade:		
1	1	
2	1.7	0.2–13.9
3	14	1.8–109
Associated Ca in situ:		
No	1	
Yes	3	1.4–6.6

3-month cystoscopy were prognostic factors of recurrence.[2] They designed 3 risk groups by combining these 2 factors. In 1992 Witjes et al analyzed 1,026 cases of primary bladder tumors.[3] Prognostic factors of recurrence were tumor stage, intravesical instillations and number of bladder areas affected. A year later the same authors published a series of 1,674 primary bladder tumors.[12] Although the patients were from their previous cohort, multiple tumors were also a recurrence prognostic factor. Based on these data 3 risk groups were established. Surprisingly, a study performed later with the same cohort showed that tumor stage and disease grade were recurrence prognostic factors.[13] This contradiction might be attributed to the fact that tumors were analyzed without separating grade from stage. As in the aforementioned studies, intravesical instillations were but carcinoma in situ was not a prognostic factor. A study of 469 primary and recurrent bladder tumors was designed by Witjes et al to determine the influence of pathological evaluation.[4] Multiple tumors and tumor location were the only significant prognostic factors.[4,7] On the other hand, meta-analysis of 2,535 primary and recurrent tumors revealed that adjuvant intravesical instillations decreased the risk of recurrence.[14] Recently Shinka et al reported on primary tumors treated with BCG instillations.[8] Curiously, the only recurrence factors were tumor stage, female gender and tumor size (higher recurrence in smaller tumors). This controversial finding was interpreted as the bigger the tumor, the higher the antigen production, and so the tumor specific immune response increased.

Our recurrence prognostic factors were multiple tumors, tumor size, carcinoma in situ and intravesical instillations (table 3). Like the majority, in our study disease grade was not a prognostic factor of recurrence. However, in 1 study grade was a recurrence prognostic factor only in 215 primary but not recurrent tumors.[6] Grade as a prognosticator of recurrence in another study may have been due to the fact that it was not analyzed alone but together with tumor stage.[4] In our study tumor stage also was not prognostic of recurrence. On the other hand, there is consensus that intravesical instillations decrease significantly the recurrence risk.[3,12–14] Nevertheless, unlike others, we differentiated BCG and other types of instillations, and the latter did not while the former did decrease the recurrence risk. We also proved a higher recurrence risk for multiple tumors.[1,2,7,12,13] Paradoxically, some have reported contradictory results with patients from the same cohort.[3,12] The significance of tumor size is contro-

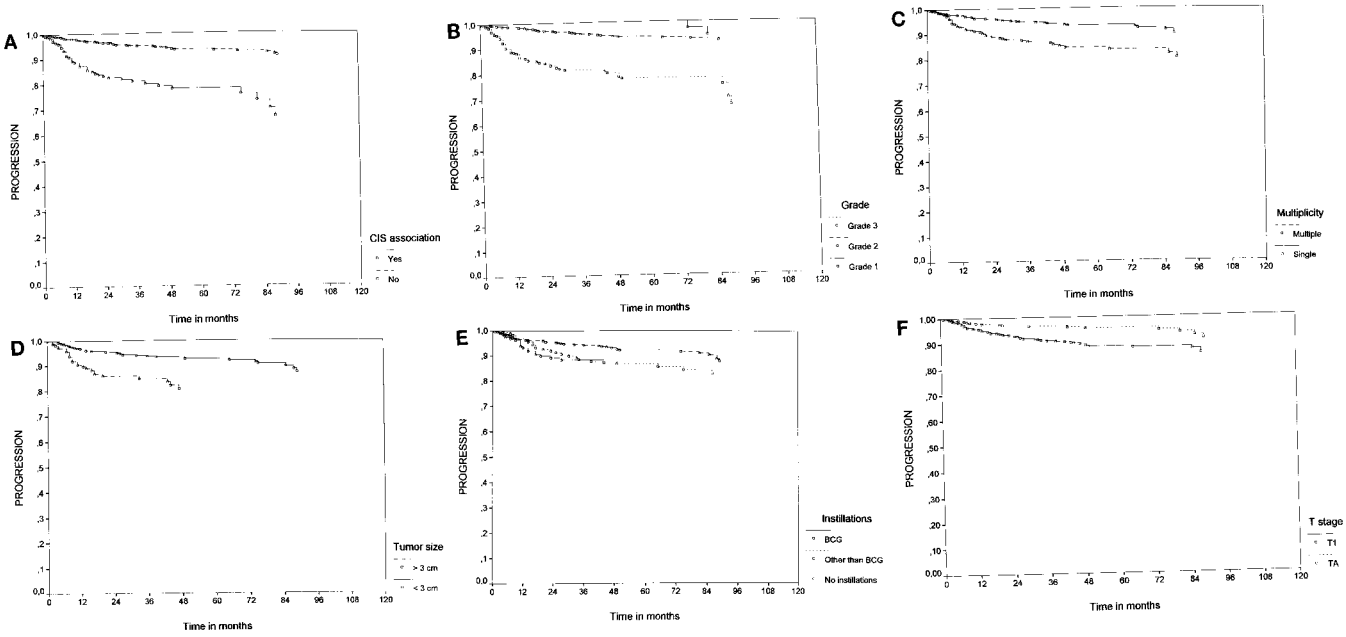

FIG. 2. Kaplan-Meier plot for progression comparing patients with or without carcinoma in situ (*CIS*) (log rank test, significant, $p = 0.00001$), grades 1, 2 and 3 disease (significant, $p = 0.00001$), multiple and single tumors (significant, $p = 0.0001$), tumors greater than and less than 3 cm. (significant, $p = 0.002$), no, BCG and other instillations (not significant, $p = 0.11$), and Ta and T1 tumors (significant, $p = 0.002$).

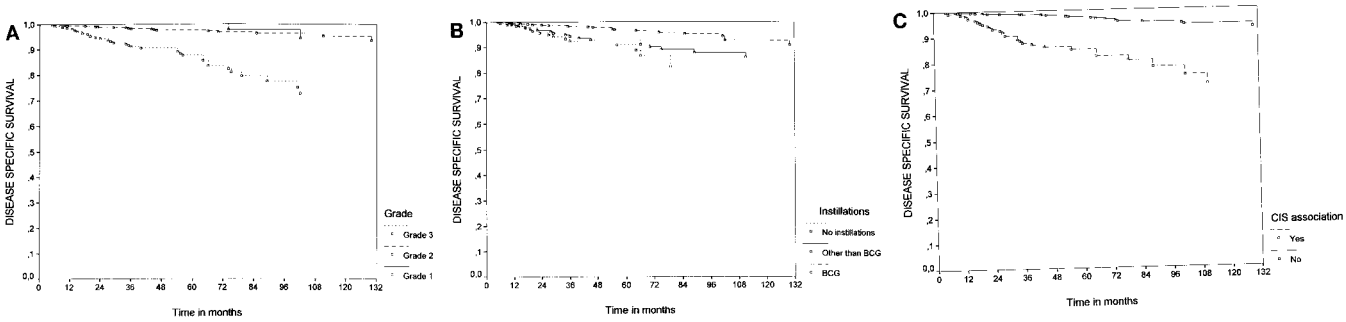

FIG. 3. Kaplan-Meier plot for disease specific survival comparing grades 1, 2 and 3 disease (log rank test, significant, $p = 0.00001$), no, BCG and other instillations (significant, $p = 0.0004$), and patients with and without carcinoma in situ (*CIS*) (significant, $p = 0.00001$).

versial because it was not a prognostic factor in some studies[2,4,5,7] although significant in ours and others.[1,6,8]

A new finding in our study was that carcinoma in situ increased the risk of recurrence. The role of carcinoma in situ in the evolution of transitional cell carcinoma of the bladder has not been studied by many authors. The studies based on a large number of patients from the same cohort concluded that it was not a recurrence prognostic factor.[3,12,13] However, although in those studies tumors were primary as in ours, there are several noteworthy differences. For example, 4 samples were taken in the random bladder biopsy whereas we took 6, and biopsy was performed in only 673 of 1,674 patients (40%)[12] and 701 (42%),[13] whereas we included only those with random biopsy. There was a 21% to 22% incidence of abnormal random bladder biopsy findings in the aforementioned studies but patients with carcinoma in situ and dysplasia were analyzed together. In our study dysplasia and carcinoma in situ were independently analyzed revealing a 19% incidence of the latter. Furthermore, in 1 study disease grade 1 versus 2 or 3 was analyzed,[3] and in another tumors were analyzed by grade and stage, and then compared to G1Ta tumors.[13] In our study disease grade and tumor stage were independently analyzed and no reference tumor was predetermined. Finally, Witjes et al concluded that carcinoma in situ and random bladder biopsy had no prognostic value in recurrence.[3] Furthermore, they criticized previous studies that claimed a higher risk of recurrence related to an abnormal random bladder biopsy finding.[16,18–20] They argued that these studies had few patients with short followup and that the variable of an abnormal random bladder biopsy finding was not adjusted to others by multivariate analysis. None of these considerations applies to our study as there were 1,529 patients with 4.2 years of followup, and multivariate analysis was performed.

Progression and mortality have been studied by even fewer authors. Herr et al found that tumor stage was the only prognostic factor of progression at diagnosis of the initial tumor and at the 3 and 6-month evaluations.[9] Positive cytology was a prognostic factor at 3 and 6 months. Groups of progression risk were classified by tumor stage and cytology. Kiemeney et al reported that progression prognostic factors were disease grade, tumor stage, multiple tumors and abnormality in random bladder biopsy (carcinoma in situ or dysplasia).[12,13] Like Pawinski et al,[14] they reported that intravesical instillations did not influence tumor progression. In our study prognostic factors of progression were tumor size (which to our knowledge has not been evaluated by others), multiple tumors, carcinoma in situ, intravesical BCG instillations and, most important, grade 3 disease (table 3). The fact that disease grade, carcinoma in situ and multiple tu-

TABLE 4. *Multivariate analyses of major prognostic factors of recurrence progression and disease specific survival*

References	Study Type	Tumor Status	No. Pts.	Grade	T Stage	Associated Ca in Situ	Multiple Tumors	Tumor Size	Intravesical Instillations
Recurrence:									
Loening et al[5]	Retrospective	Primary, recurrent	178	No	Yes	—	No	No	—
Narayana et al[6]	Prospective	Primary, recurrent	468	Yes, no	Yes, yes	—	No, no	Yes, no	—
Dalesio et al[1]	Prospective	Primary, recurrent	308	No	—	—	Yes	Yes	—
Parmar et al[2]	Prospective	Primary	305	No	No	—	Yes	No	—
Witjes et al[3]	Prospective	Primary	1,026	No	Yes	No	No	—	Yes
Kiemeney et al[12]	Prospective	Primary	1,674	No	Yes	No	Yes	—	Yes
Kiemeney et al[13]	Prospective	Primary	1,674	Yes	Yes	No	—	—	Yes
Witjes et al[4]	Prospective	Primary, recurrent	469	No	No	—	Yes	No	—
Mulders et al[7]	Prospective	Primary, recurrent	371	No	No	—	Yes	No	—
Pawinsky et al[14]	Meta-analysis	Primary, recurrent	2,535	—	—	—	—	—	Yes
Shinka et al[8]	Prospective	Primary	141	No	Yes	No	No	Yes	—
Present study	Retrospective	Primary	1,529	No	No	Yes	Yes	Yes	Yes
Progression:									
Herr et al[9]		Primary, recurrent	221	—	Yes	—	—	—	—
Kiemeney et al[12]	Prospective	Primary	1,674	Yes	Yes	Yes	Yes	—	No
Kiemeney et al[13]	Prospective	Primary	1,674	Yes	Yes	Yes	—	—	No
Pawinski et al[14]	Meta-analysis	Primary, recurrent	2,535	—	—	—	—	—	No
Present study	Retrospective	Primary	1,529	Yes	No	Yes	Yes	Yes	Yes
Disease specific survival:									
Takashi et al[10]	Retrospective	Primary	264	Yes	Yes	—	—	Yes	—
Flamm and Havelec[11]	Retrospective	Primary	345	Yes	No	Yes	No	—	No
Pawinski et al[14]	Meta-analysis	Primary, recurrent	2,535	—	—	—	—	—	No
Present study	Retrospective	Primary	1,529	Yes	No	Yes	No	No	No

mors were prognostic factors of progression is in agreement with findings of others. Furthermore, grade 3 disease was the main progression factor. Unlike other studies, tumor stage was not a progression prognostic factor in our study. Finally, intravesical BCG instillations seemed to modify favorably tumor progression in our study but not in others. This discrepancy might be attributed to the fact that progression was considered as a shift to stage T2, T3 or T4. Unlike other studies, neither node invasion nor metastasis was considered in our definition of tumor progression. Thus, it may be assumed that BCG instillations improve local control of disease rather than node and metastasis dissemination.

Takashi et al reported that prognostic factors of mortality were grade and stage of disease, and tumor size.[10] However, patients with infiltrative bladder tumor were included in their study, only 55% were treated with transurethral resection and only 245 were diagnosed with transitional cell carcinoma. Thus, their results are not comparable with others. Flamm and Havelec showed that survival prognostic factors were grade 3 disease, absence of inflammatory tissue associated with tumor and carcinoma in situ in the tumor margin.[11] Finally, a meta-analysis performed by Pawinski et al proved that the use of intravesical instillations did not influence mortality.[14] Nevertheless, our study has demonstrated that the only mortality prognostic factors are grade of disease (particularly grade 3) and carcinoma in situ (table 3). Although BCG instillations seemed to reduce the risk of mortality 0.44 times, this finding was not significant. As far as disease grade and carcinoma in situ are concerned, our results agree with those of Flamm and Havelec.[11] It has also been shown that the real prognostic factor is grade 3 disease because its mortality risk is 14 times higher than that of grade 1. On the other hand, although Flamm and Havelec found that carcinoma in situ was a poor prognostic factor, they analyzed carcinoma in situ in the tumor margin while we analyzed samples of normal appearing mucosa taken by random bladder biopsy. Nevertheless, our results agree with those of Flamm and Havelec,[11] and Pawinsky et al,[14] although there are some differences. Flamm and Havelec did not distinguish BCG and other types of instillations. Furthermore, patients treated with BCG were not studied in the meta-analysis of Pawinsky et al. However, we differentiated 3 groups of no, BCG and other intravesical instillations. All of these studies concluded that intravesical instillations do not modify the mortality risk.

CONCLUSIONS

After primary superficial transitional cell carcinoma of the bladder has been treated with transurethral resection and random bladder biopsy, it can be assumed that evolution will not depend on tumor stage or dysplasia but other factors. Thus, patients with multiple tumors or tumor greater than 3 cm. will have a greater risk, whereas those treated with intravesical BCG instillations will have a decreased risk of recurrence and progression. On the other hand, carcinoma in situ has been shown to influence recurrence, progression and mortality. Finally, the main predictor of progression and mortality was grade 3 disease. Future studies that combine these factors to create risk groups can be useful in the design of therapeutic and followup strategies of primary superficial transitional cell carcinoma of the bladder.

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