Prognostic role of the tumor-associated tissue inflammatory reaction in transitional bladder cell carcinoma

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Abstract. Many authors have indicated that the presence of an inflammatory response within the tumor may predict not only recurrence and progression but also survival in several tumors, including transitional cell carcinoma (TCC) of the urinary bladder. Several studies have been performed with a mean follow-up period that is often too limited for predicting patient outcome. The aim of the present study was to define the influence of inflammatory cell infiltrate on recurrence, progression and survival in TCC of the bladder over a long follow-up period. Between January and December 1995, 410 consecutive patients, who had undergone transurethral or open surgery for bladder tumors at the same urologic center, were selected for the study. All cases were reviewed to assess histotype, stage and grade of the tumor and presence or absence of tumor-associated inflammatory reaction. To better evaluate the prognostic role of each single factor in TCC, a follow-up of 10 years after surgery was performed. Pathologic evaluation showed superficial TCC in 312 patients, while 98 had an invasive bladder tumor. Three among 410 bladder tumors were squamous cell carcinomas. Out of 407 TCCs, 119 (29.23%) presented inflammation within the tumor or the lamina propria. At 10 years follow-up, a statistically significant association was shown between the presence of inflammation within the tumor or lamina propria and the number of recurrences ($p<0.0001$). Moreover, the absence of inflammatory infiltrate in the tumor established the relative risk of suffering more than one recurrence at 2.287 (95% CI 1.180-3.346). The Mann-Whitney test confirmed a statistically significant difference between superficial bladder tumors with inflammation and those without (26.3 vs 11.5 months, $p<0.001$). In terms of survival rate, a statistically significant difference was reported between carcinomas with and without inflammation ($p=0.0261$). On multivariate analysis, the presence of inflammation within the tumor was found to be an independent predictor of survival in patients with TCC of the bladder ($p=0.027$). Survival analysis by means of the Kaplan-Meier curves showed a statistically significant difference between patients with tumor-associated inflammatory reaction and those without ($p=0.0098$). These results confirm that the presence of inflammatory reaction has a good prognostic value in transitional bladder cell carcinoma. However, to better define its prognostic significance, the characterization of inflammatory cells in tumor-associated tissue reaction must be accomplished.

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Introduction

Transitional cell carcinoma (TCC) of the urinary bladder displays heterogeneous clinical behavior. Histologic grade and disease stage are well-defined prognostic indicators, but are not always useful in predicting outcome in individual cases (1,2). Tumor configuration, multiplicity, size, coexistent carcinoma *in situ* (CIS) and overexpression of genes and gene products may have prognostic significance in certain situations (3-10). In the attempt to better define the natural history of TCC, the significance of angiogenesis was also evaluated, but with no certain role in predicting patient outcome (11). Many authors have demonstrated a correlation between increased vascularization and poor clinical outcome (12). However, a positive correlation between inflammation in the tumor, angiogenic factors and good prognosis was described by Offersen *et al* (13). More recently, the presence of inflammatory response within the tumor has been shown to predict not only recurrence and progression, but also survival in patients with TCC (14-16). The fact that inflammation plays a primary role in host reaction to the tumor has also been widely emphasized in other neoplasms (17). Indeed, in a study published in 1936 by McCarty, the presence in colon cancer of intense inflammation, and lymphocytic infiltrate in particular, correlated with a good prognosis (18). In a more recent study carried out on 156 patients undergoing gastric resection for stomach cancer, Takeuchi proved that natural killer (NK) cell activity is an independent parameter of good prognosis (19). In TCC, the significance of inflammation has been analyzed in the literature with a mean follow-up period

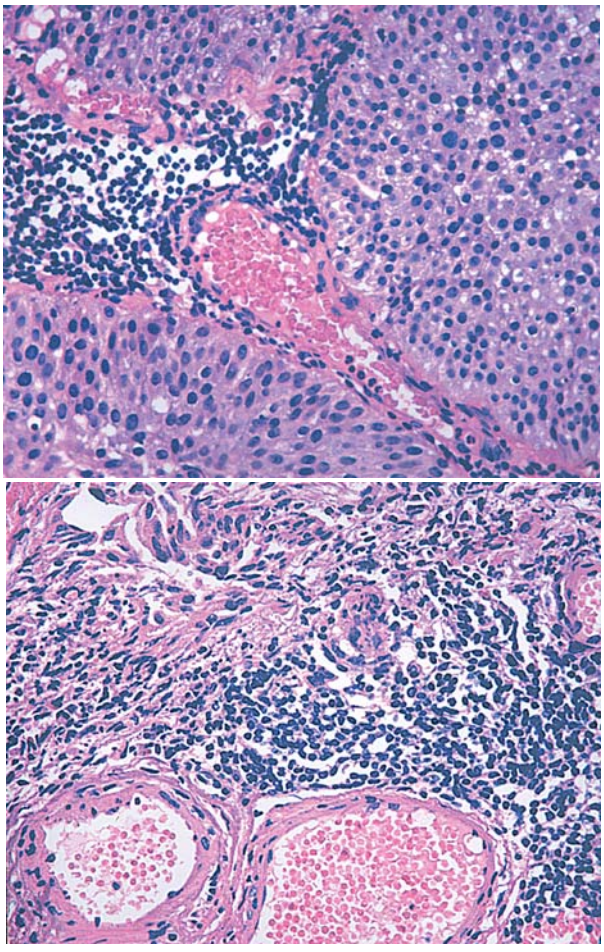

Figure 1. (A) Prominent lymphoid infiltrate is seen around the vessels and near the surface of a non-invasive TCC. (B) Intense inflammatory reaction is evident in the lamina propria around invasive islets of tumor tissue.

that is often too limited for the prediction of patient outcome. The aim of this study was to ascertain the influence of inflammatory cell infiltrate on recurrence, progression and survival in TCC of the bladder over a long follow-up period.

Materials and methods

Study design. To evaluate the prognostic significance of tumor-associated tissue inflammatory reaction in transitional bladder cell carcinoma, 410 consecutive patients, who had undergone surgical treatment [transurethral resection (TUR) or open surgery] for bladder carcinoma at the Urologic Unit of the University of Florence between January and December 1995, were selected for the study.

Inclusion criteria. All patients who reported cystoscopically demonstrated bladder tumors and who gave their informed consent to comply with the follow-up schedule were selected for the study.

Exclusion criteria. All patients with a history of TCC of the upper urinary tract, those who had undergone surgery for benign prostatic obstruction at the same time as surgical treatment for TCC, and those with a history of prostate or other urologic cancers were excluded.

Table I. Pathologic data of 410 bladder tumors.

	TNM stage	Grade			Total
		G1	G2	G3	
TCC	pTa	155	88	14	257
	pT1	1	19	30	50
	pT2	0	2	43	45
	pT3	0	3	32	35
	pT4	0	0	15	15
Total		156	112	134	402
SCC	pTis				5
	pT3				3
Total					410

Distribution of 410 bladder tumors according to stage and grade. TCC, transitional cell carcinoma; SCC, squamous cell carcinoma.

Histopathology. All cases were reviewed on the basis of the available slides in order to evaluate histotype, stage and grade of the tumor, presence or absence of tumor-associated inflammatory reaction and characteristics of lymphocytic infiltrate. Specimens were pathologically staged according to the TNM classification of the International Union Against Cancer (UICC) (20) and the grade was assessed following the World Health Organization (WHO) scale (21). The presence or absence of mononuclear infiltrates within the tumor was evaluated in all cases. Tumor-associated inflammatory reaction was considered to be present when a gathering of >20 lymphocytes, at times mixed with plasma cells and polymorphonuclear leukocytes, was observed in at least one low-power (x40) field per section (Fig. 1).

Patient follow-up. Each patient was followed up in relation to the clinicopathologic characteristics of the tumor, in accordance with the European Association of Urology Guidelines of Bladder Cancer (22). Mean follow-up was 90 months (ranging from 84 to 96 months). On consideration of data from the literature, it was thought appropriate to carry out a long-term follow-up, so as to better determine the prognostic factors of recurrence, progression and disease-specific mortality (23). Recurrence was determined on the basis of papillary formations protruding into the bladder lumen and detected on cystoscopy, or the presence of neoplastic tissue diagnosed after vesical biopsy. Progression was defined as an increase in tumor stage or grade.

Statistical analysis. Pearson's coefficient was adopted to evaluate the correlation between the different parameters in both superficial and invasive bladder cancer patients, and Fisher's exact test was used to assess statistical significance with $p<0.05$ accepted as significant. The Mann-Whitney test was also performed to compare different parameter mean values. The ANOVA test was used for univariate analysis

and the log-rank test (Mantel Cox) for multivariate analysis. Kaplan-Meier survival curves were also used to estimate survival. All statistical analyses were performed using SPSS 11.5 for Windows (SPSS, Inc. Chicago, Illinois).

Results

Patients' clinicopathologic characteristics. Of the 410 patients recruited for the study, 306 were male (74.6%) and 104 were female (25.3%). Patient age ranged from 32 to 93 (mean, 68.89 years). At least one recurrence was experienced by 83 of the 410 patients (20.4%), whilst the remaining 327 (79.6%) were diagnosed for the first time with bladder cancer. Ten of the patients with recurrence presented disease progression from pTa to pT1 (8.3%) and 22 patients had progression from superficial to invasive disease (26.5%). A TUR of the tumor was performed on 316 patients (77.03%) and radical cystectomy with urinary diversion on 94 (22.97%). Pathologic examination gave the following results: out of the 410 tumors analyzed, 407 were TCCs (99.26%) and 3 were squamous cell carcinomas (0.74%). Histologic data are detailed in Table I. In one case, CIS was associated with pT1G3. Pathologic assessment of lyxmph node status gave 6 Nx (3 pT1, 3 pT4a), 36 N0 (1 pTa, 7 pT1, 11 pT2, 15 pT3, 2 pT4), 7 N1 (1 pT2, 5 pT3, 1 pT4) and 7 N2 (3 pT2, 3 pT3, 1 pT4). Among the patients undergoing TUR, 201 received adjuvant treatment for 6 weeks with weekly bacillus Calmette-Guerin (BCG) instillations (63.6%) at an average interval of 21 days after the operation. Adjuvant treatment with different chemotherapeutic agents was administered to 86 patients (27.5%) but 29 patients were not given any adjuvant intravesical therapy (8.8%).

Tumor-associated tissue inflammatory reaction analysis. Inflammation within the tumor or the lamina propria was found in 119 of the 407 patients with TCC (29.23%). Of these, 99 had superficial lesions (83.19%) and 20 had invasive lesions (16.81%). Among the invasive tumors, one of the patients with positive lymph nodes exhibited pronounced inflammatory infiltrate in the tumor and lamina propria, whereas only one of the three squamous cell carcinomas presented inflammation within the tumor (Table II). Intense inflammatory reaction was present in superficial and invasive tumors, 31.13% and 21.73% respect-ively. Even though inflammation occurred more frequently in superficial tumors, no statistically significant difference was noted (p=0.0904).

Statistical analysis on superficial bladder cancers

Recurrence. Overall, 174 of the 318 superficial tumors presented only one recurrence (54.71%), whilst 144 patients presented two or more recurrences (45.29%). Among the 99 superficial tumors with inflammation, 73 (73.73%) had one recurrence, while the other 26 (26.27%) had two or more. Among the 219 patients with superficial tumors and no inflammatory reaction, 101 experienced one recurrence (46.11%), whilst 118 had two or more (53.89%). A statistically significant relationship was shown between the presence of inflammation within the tumor or lamina propria and the number of recurrences (p<0.0001). Indeed, the absence of inflammatory infiltrate in the tumor established the relative risk of suffering more than one recurrence at 2.234 (95% CI 1.574 - 3.430).

Table II. Bladder tumor distribution according to the presence of inflammatory infiltrate.

			Inflammation		Total
			Absent	Present	
TNM stage	TCC	pTa	168	89	257
		pT1	40	10	50
		pT2	34	11	45
		pT3	28	7	35
		pT4	13	2	15
		pTis	5	0	5
	SCC	pT3	2	1	3
	Total		290	120	410
Grade	TCC	G1	116	40	156
		G2	61	51	112
		G3	106	28	134
	Total		283	119	402

Presence of inflammatory infiltrate in all bladder carcinomas according to stage and in TCC of the urinary bladder according to grade. TCC, transitional cell carcinoma; SCC, squamous cell carcinoma.

Disease-free interval. Correlating the presence of tumor-associated inflammatory reaction with the interval free from disease, the average time before the first recurrence of all superficial tumors was 18.9 months. Superficial bladder tumors with inflammation had an average time lapse of 26.3 months before the first recurrence. Carcinomas without inflammation had a mean interval of time to the first recurrence of 11.5 months. The Mann-Whitney test confirmed that this difference was statistically significant (p<0.0001).

Progression. Of the 318 superficial tumors, 8 pTa (5 G3 and 3 G2) progressed to pT1G3, whereas 12 pT1 and 1 pTa (10 pT1G3, 2 pT1G2, 1 pTaG2) progressed to invasive carcinomas. No correlation was found between the presence of inflammatory reaction within the tumor and stage or grade progression.

Survival rate. With regard to the superficial lesions, 18 patients died from tumors (5.66%), 66 died from causes unrelated to the tumor and 234 are currently alive with no evidence of disease. Of the 18 patients who died from tumors (10 pT1G3, 1 pT1G1, and 7 pTaG3) (mean survival 43.3 months), only two presented areas of inflammation associated with the tumor (2 pT1G3). These two patients survived for 67 and 61 months (mean survival, 64 months). The Mann-Whitney test for comparing

Table III. Multivariate analysis of factors affecting survival in 407 TCCs.

Categories (variables)	No. of patients (%)	No. of survivals (%)	Multivariate analysis p
Presentation			0.329
First occurrence	323 (79.36)	211 (65.32)	
Recurrence	84 (20.64)	53 (63.09)	
Number of lesions			0.810
Single	377 (92.62)	246 (65.25)	
Multiple	30 (7.38)	18 (60.00)	
Stage			<0.001
pTis	5 (1.22)	3 (60.00)	
pTa	257 (63.14)	187 (72.76)	
pT1	50 (12.28)	38 (76.00)	
pT2	45 (11.05)	33 (73.33)	
pT3	35 (8.59)	3 (8.05)	
pT4	15 (3.72)	0 (-)	
Grade[a]			<0.001
G1	156 (38.80)	115 (73.71)	
G2	112 (27.86)	86 (76.78)	
G3	134 (33.34)	60 (44.77)	
Associated CIS	1	-	N.E.
Inflammation			0.027
With inflammation	119 (29.23)	87 (73.10)	
Without inflammation	288 (70.77)	177 (61.45)	
Adjuvant therapy after TUR[b]			0.038
Administered	287 (90.82)	197 (68.64)	
Not administered	29 (9.18)	19 (65.51)	
Number of recurrences			0.390
1	173 (54.74)	157 (90.75)	
≥2	143 (45.26)	87 (60.83)	

Multivariate analysis of overall patient survival in 407 patients with TCC of the urinary bladder. [a]Grade: pTis excluded. [b]Adjuvant therapy: only in patients undergoing transurethral resection; 201 BCG, 86 chemotherapeutic drugs. N.E., cannot be evaluated.

mean values showed a statistically significant difference between these two populations (p=0.0261).

Statistical analysis on invasive bladder cancers

Survival rate. Concerning the 92 patients with invasive carcinoma, 48 (50.5%) died from disease progression, 11 died from causes unrelated to the disease and 36 (37.8%) were still alive and on follow-up. Of the last group, 14 patients showed disease progression and were subjected to treatment other than surgical. Of the 20 patients with inflamed invasive carcinoma, 9 were alive and disease-free, 9 died from the disease and 2 died from other causes. Among the cases with no sign of inflammation, 27 patients were alive with no evidence of disease, 39 died from cancer and 9 from other causes. No statistically significant correlation was noted between survival and the presence of inflammation in invasive carcinomas.

Multivariate analysis using the ANOVA model selected stage and grade as independent determinants of prognosis (stage p<0.001, grade p<0.001). Furthermore, the presence of inflammation within the tumor proved to be an independent predictor of survival in patients with TCC of the bladder (p=0.027) (Table III). Survival analysis by means of the Kaplan-Meier curves showed a statistically significant difference between patients with tumor-associated inflammatory reaction and those without (p=0.0098) (Fig. 2).

Discussion

Recent data have indicated that inflammation is a critical component of tumor development and progression (24). A fundamental stage in progression towards widespread disease is the potential of neoplastic cells to divert host immune

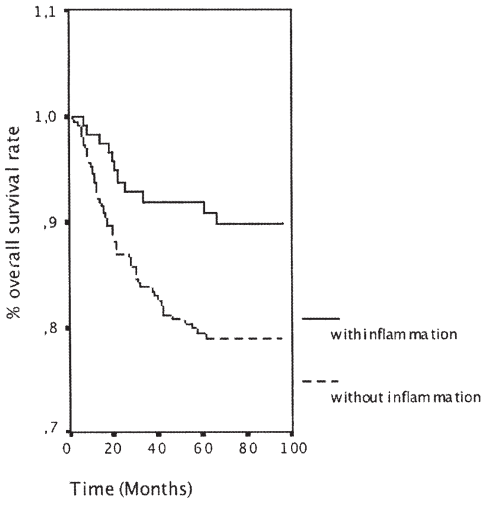

Figure 2. Kaplan-Meier curves illustrating the association between inflammatory reaction within the tumor and overall patient survival. Only patients with TCC were analyzed (p=0.0098; HR, 2.287; 95% C.I, 1.180-3.346).

response (25). Indirect proof of the interaction between the tumor and the immune system is the frequent finding within the tumor of diverse leukocyte populations, including lymphocytes and macrophages. The presence of inflammatory infiltrate is thought to indicate an active host response against cancer cells, as has also been seen in TCC of the bladder. In a retrospective analysis on 428 patients, Flamm focused on the correlation between the presence of inflammatory reaction associated with TCC and the lower incidence of disease-specific deaths (26). Similarly, it was demonstrated by other authors that the presence of inflammatory infiltrate within the tumor correlates with fewer recurrences and cancer-related deaths (27,28). Further indirect proof that host immune response can favorably modify the course of TCC comes from the efficacy of intravesical treatment with BCG, which actively recruits T lymphocytes (29).

Our study highlighted that the presence of tumor-associated tissue inflammatory reaction significantly correlated with a smaller number of recurrences in superficial bladder carcinoma ($p<0.0001$) and a prolonged disease-free interval ($p<0.0001$). The fact that no relationship could be found between the presence of inflammatory reaction and progression in superficial tumors was, in all likelihood, due to the paucity of data. Survival analysis, performed using Kaplan-Meier curves, also showed a statistically significant difference between tumors with and without inflammation (p=0.0098) (Fig. 2). On multivariate analysis, tumor-associated tissue inflammatory reaction proved to be an independent prognostic variable (p=0.027), together with other well-known indicators of clinical outcome (stage $p<0.001$ and grade $p<0.001$). In a previous study, we reported a strong correlation between peritumoral neoangiogenesis and improved survival in superficial TCC[30], demonstrating that this correlation may be due to the angiogenic stimulation of a local inflammatory reaction generated by the host against superficial bladder cancer, as suggested by Offersen *et al* (13). Moreover, we found that inflammatory reaction occurred more frequently in superficial rather than invasive carcinomas, giving rise to the hypothesis of a substantial deficiency in the host immune response against invasive tumors (30). As many studies have shown, this could depend on several factors inherent in both the tumor and the host. Tumor cells may produce various cytokines such as TGF-α and IL-10, secrete autocrine growth factors such as IL-6, TNF and IL-10, and alter the CD3-ζ chain expression. In addition, alterations in the host's recruitment of macrophages and antigen presenting cells, together with the expansion of the T suppressor lymphocyte population, can be observed. In a study performed on 146 patients subjected to gastric resection for carcinoma, Ishigami demonstrated that it is the whole lymphocytic population that has an impact on prognosis and not just single subpopulations such as NK cells (31). Our study did not take into account the different cell populations in tumor-associated tissue inflammatory reaction, though the characterization of inflammatory cells in TCC may help in better perceiving the functional relationship between inflammation and cancer. To improve our understanding of the biologic behavior of bladder TCC, a more thorough analysis of host immune reaction would be helpful for a tailored therapeutic strategy which would modify the disease course and reap benefits in terms of survival and quality of life.

Our findings revealed the significant prognostic role of inflammatory reaction in TCC of the urinary bladder and demonstrated that active host immune response against the tumor is a valuable indicator of clinical outcome. In order to better elucidate the mechanisms linking inflammation with a good prognosis in TCC, the characterization of inflammatory cells in tumor-associated tissue reaction must be accomplished.

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