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The value of tumor-associated tissue inflammatory reaction in primary superficial bladder cancer

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Summary. The data of 92 patients who entered the prospective study between 1980 and 1982 were evaluable. The prevalence of tumor-associated tissue inflammatory reaction according to the tumorparameters stage, grade, multiplicity, tumor-weight and concomittant urothelial changes in primary superficial transitional cell cancer was estimated. Using high power field on the microscope tumor-associated cells were classified as lymphocytes, plasma cells, mast cells and eosinophils by morphological criteria. Recurrence rate, tumor progression and survival rate were evaluated for the group with tumor-associated cell infiltration and compared with the data of the group without any tumor-associated inflammatory reaction. According to recurrence rate, progression rate and survival rate there was a tendency to better prognosis for tumors with associated inflammatory reaction but this could not be proven by statistical analyses.

Key words: Superficial bladder cancer – Tumor-associated tissue inflammatory reaction – Recurrence rate – Tumor progression – Survival rate

Superficial transitional cell cancer (STCC) of the bladder, classified as stages pTa to pT1, grade 1–3 by the recommendation of the International Union Against Cancer (UICC) and the histological typing of the World Health Organisation (WHO), has a tendency to recur in many patients even after complete transurethral resection (TUR) of the primary tumor [14, 15]. According to the tumor parameters the frequency of recurrences varies between 29%–70%, the tumor progression in stage or grade varies between 4%–31% and the 5 year survival rate varies between 64%–95% [6, 8]. Therefore it is important to get as much as possible information about the potential biological activity of the tumor at the time of initial diagnosis to select those patients at high risk.

The aim of this prospective study was to evaluate the frequency of a tumor-associated tissue inflammatory reaction (TATIR) in relation to the tumor parameters and to analyse the influence of TATIR on recurrence rate, tumor progression and survival.

Materials and methods

92 patients with primary STCC were admitted into the study between 1980 and 1982. The data of all patients were evaluable.

Before TUR a clinical examination, excretory urography (IVP), chest x-ray and complete laboratory diagnostic studies were performed. After bimanual examination during anesthesia TUR with separate resections of the tumor-base and the tumor-margin were performed after the visible tumor was removed. Cold cup biopsies of the bladder with a minimum of 6 biopsies in woman (trigone, right and left lateral bladder wall, posterior wall, dome and anterior wall) and 7 biopsies in men (including the prostatic urethra) were performed in each case. The histological confirmation of the diagnosis was performed according to the TNM-category of the UICC [14] and the grading (1–3) according to the classification of the WHO [15]. The histological slides were stained with hematoxylin and eosin and examined for the presence of a mononuclear cell infiltration in close association with the tumor. TATIR was deemed to be present when 10 areas exhibited more than 100 cells per high power field (HPF) used on the microscope. In the cases with TATIR a differentiation of cell types according to morphological criterias was performed. The following cells were differentiated and by counting the frequency of a cell type in 10 areas the relative percentage in each tumor was evaluated: lymphocytes, plasma cells, mast cells and eosinophils.

All patients received a topical adjuvant short-term chemotherapy after TUR with doxorubicin hydrochloride. 50 mg doxorubicin per 50 ml saline were instilled once weekly over a period of 6 weeks. After this regime no further adjuvant treatment was performed. Criteria for exclusion of the study were bacterial cystitis, chronic or recurrent urinary tract infections and previous pelvic radiation therapy.

All patients were followed by cystoscopy every 3 months for the first two years and every 6 months afterwards. Cytological examinations were not evaluated because they were not performed routinely in the first year of the study.

End point of study was tumor progression with invasion of the muscular coat (T2 or more), death or followup of 5 years.

Table 1. Observed frequencies of TATIR depending on sex of patients with primary STCC (Comparisons of frequencies were based on Pearson Chi-square test or Yates corrected Chi-square test and showed p values greater than 0.05)

TATIR	Male		Female		Total		Ratio M:F
	No.	(%)	No.	(%)	No.	(%)	
Present	21	31.3	5	20.0	26	28.3	4:1
Absent	46	68.7	20	80.0	66	71.7	2:1
Totals	67	72.8	25	27.2	92		3:1

TATIR = Tumor-associated tissue inflammatory reaction; STCC = superficial transitional cell carcinoma

Table 2. Observed frequencies of TATIR depending on stage, grade, multiplicity, tumor-weight and concomittant dysplasia or TIS in patients with primary STCC of the bladder (Comparisons of frequencies were based on Pearson Chi-square test or Yates corrected Chi-square test and showed p values <0.05 for stage and grade and >0.1 for comparisons of the other parameters)

TATIR	Total %	Stage %		Grade %			Solitary %	Tumor-weight <5 g %	Concomittant D 1–3/TIS %
		pTa	pT1	1	2	3			
Present	28.2	19.2	39.0	20.0	25.7	61.5	29.7	26.0	26.0

TATIR = Tumor-associated tissue inflammatory reaction; STCC = superficial transitional cell carcinoma; TIS = carcinoma in situ; D 1–3 = Dysplasia grade 1–3

Statistical evaluation

The curves of survival and time to first recurrence were estimated by the Kaplan-Meier method [4]. The levels of significance were assessed by generaized Wilcoxon (Breslow) and Savage (Mantel-Cox) tests. For statistical analyses BMDP Statistical software, University of California was used. The recurrence rate is defined by the number of followup cystoscopy studies at which a recurrence was noted divided by the total numer of months of followup. The result then is multiplied by 100 to simplify the presentation [2]. Comparisons of individually calculated recurrence rate were based on Mann-Whitney U-test, a non parametric test for comparison of two groups. Comparisons of frequencies were based on Pearson Chi-square test or Yates corrected Chi-square test.

Results

The data of 92 patients were evaluable. The mean age was 68.3 years with a range of 29 to 86 years. 72.8% of the patients were men. (Table 1). All tumors were histological transitional cell carcinomas. 44.6% of the tumors invaded the lamina propria (pT1), 48.9% were well differentiated (grade 1) and 14.1% poorly differentiated (grade 3). 41.3% of the tumors were solitary and 50% had a tumor-weight less than 5 g. 25.0% of the bladder mapping specimens showed histological dysplasia grade 1–3 or carcinoma in situ (TIS). A TATIR was found in 23.1% of all cases.

According to the tumor-parameters the frequency of TATIR correlated with tumor invasion to the lamina propria (39.0% in pT1 tumors versus 19.6% in pTa tumors, $p>0.05$) and with the dedifferentiation of the tumor (20.0% in grade 1 tumors versus 61.5% in grade 3 tumors, $p>0.05$, Table 2). There was no significant difference in the frequency of TATIR depending on multiplicity, tumor-weight or concomittant dysplasia or TIS (Table 2).

Recurrences

The over-all percentage of recurrences was 33.7%. There was no significant difference between the patients with TATIR 23.1% recurrences) and patients without TATIR (37.9% recurrences, $p=0.26$). The recurrence rate was 0.82 in the group with TATIR and 1.46 in the group without TATIR. The time to first recurrence was shorter in the group with TATIR (mean 9.3 months) in comparison with the group without TATIR (mean 13.2 months). The mean recurrence free interval was 16.7 months in the group with TATIR and 19.7 months in the group without TATIR (Table 3).

In a separate analysis of the tumor-parameters as risk factors for tumor recurrence the most important factor was demonstrated as severe dysplasia or TIS in the bladder mapping ($p=0.001$). Poor differentiation and multiplicity were also factors with a significant high risk for recurrences ($p=0.01$). Tumor stage and TATIR showed no significant influence on the risk for recurrence (Table 4).

Table 3. Percentage of recurrences, recurrence rate (number of recurrences per 100 patients months), progression rate, mean time to first recurrence and mean recurrence free interval separated by present or absent TATIR (Comparisons of recurrence rates were based on Mann-Whitney U-test, a non parametric test for comparison of two groups and showed p values greater than 0.05. Comparisons of frequencies were based on Pearson Chi-square test or Yates corrected Chi-square test and showed p values greater than 0.05)

TATIR	Percentage of Recurrences	Recurrence Rate	Tumor-progression%	Mean Time to First Recurrence	Mean Recurrence Free Interval
Present	23.1	0.82	11.5	9.3	16.7
Absent	37.9	1.46	16.7	13.2	19.7
Total	33.7	1.28	15.2	11.6	19.2

TATIR = Tumor-associated tissue inflammatory reaction

Table 4. Recurrence and tumor progression depending on stage, grade, multiplicity, concomittant dysplasia or TIS and tumor-weight (Chi-square test = Pearson Chi-square or Yates corrected Chi-square test)

Tumorparameter	Recurrence %	Chi-square Test	Tumor-progression %	Chi-square Test
pTa	25.5		13.7	
pT1	43.9	n.s.	17.0	n.s.
Grade 1	17.8		8.9	
2	47.1		20.6	
3	53.8	$p<0.01$	23.1	n.s.
Solitary	19.1		6.4	
Multiple	48.9	$p<0.01$	24.4	$p<0.05$
Biopsies without Dysplasia/TIS	21.7		7.2	
- with D/TIS	69.5	$p<0.001$	39.1	$p<0.01$
Tumor-weight 5 g	32.6		21.7	
5 g	34.8	n.s.	8.7	$p<0.05$

TATIR = Tumor-associated tissue inflammatory reaction, TIS = carcinoma in situ; D = dysplasia grade 1-3, n.s. = not significant

Table 5. Mortality rate at 5 years depending on presence or absence of a TATIR in primary STCC of the bladder (Comparisons of frequencies were based on Pearson Chi-square test or Yates corrected Chi-square test and showed p values greater than 0.05)

TATIR	Dead over-all %	Dead of Disease %
Present	11.3	3.9
Absent	25.8	12.1
Total	21.7	9.8

TATIR = Tumorassociated tissue inflammatory reaction; STCC = Superficial transitional cell carcinoma

Tumor progression

The tumor progression rate was lower in the group with TATIR (11.5%) in comparison with the group without TATIR (16.5%) without statistical significance ($p>0.05$). A sparate analysis of the tumor-parameters as risk factors for tumor progression showed concomittant dysplasia or TIS as the most important factor ($p=0.01$). Multiple tumors and tumors with a weight less than 5 g showed also a significant high risk for tumor progression ($p<0.05$). Tumor stage, grade and TATIR showed no significant influence on the risk for tumor progression (Table 4).

Survival

The over-all mortality rate after 5 years was 21.7%. The tumor related mortality rate was 9.8%. There was a difference between the group with TATIR and the group without TATIR (Table 5). A tumor related death was noted in the group with TATIR in 3.9% and in 12.1% in the group without TATIR. The statistical analysis showed no significance ($p>0.05$).

According to the recurrence and progression rate a tumor related death was noted in 9.8% of the primary tumors, in 29% of the recurrent tumors and in 64% of recurrent tumors with progression in stage or grade.

Histology

Most of the cells in the mononuclear cell infiltration of tumor associated tissue were lymphocytes (Fig. 1 and 2). They were found in each tumor. The prevalence of plasma cells was 96%, of mast cells 73% and of eosinophils 62%.

The range of the frequency of cell types in one tumor was very variable (Table 6). Lymphocytes, plasma cells and eosinophils were found at less than 10% and 80%–90%. Only mast cells were noted in a frequency of less than 10 per cent in each case.

80.7% of the cell infiltrates showed a dominant lymphoid reaction with more than 50 per cent lymphocytes. In 2 tumors a predominance of plasma cells was found with 60 and 75% plasma cells. 3 cases showed a eosinophilia of 80%–95%. For a clinical evaluation of the influence of different cell types in the tumor associated

Table 6. Observed frequencies of cell types in the TATIR of 26 tumors with marked tissue cell infiltration

Frequency	Cell-Type			
	Lympho-cytes	Plasma Cells	Mast Cells	Eosino-philes
Present/all tumors	100%	96%	73%	62%
Range/tumor	< 10–95%	< 10–80%	< 10%	< 10–95%
Absent	–	4%	27%	38%

TATIR = Tumor-associated tissue inflammatory reaction

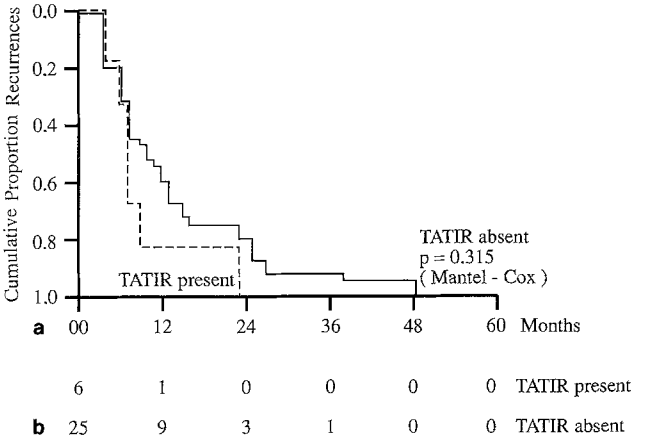

Fig. 1.a Number of patients at risk at the corresponding times. **b** Comparison of Kaplan-Meier curves for first recurrence depending on presence or absence of TATIR

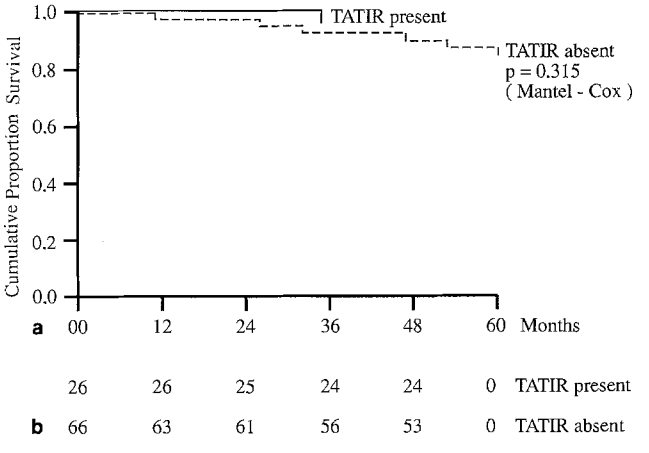

Fig. 2.a Number of patients at risk at the corresponding times. **b** Comparison of Kaplan-Meier curves for survival depending on presence or absence of TATIR

tissue the number was too small but it was noted that eosinophilia was seen in two cases with squamous metaplasia of the transitional cell tumor and none of these tumors had a recurrence.

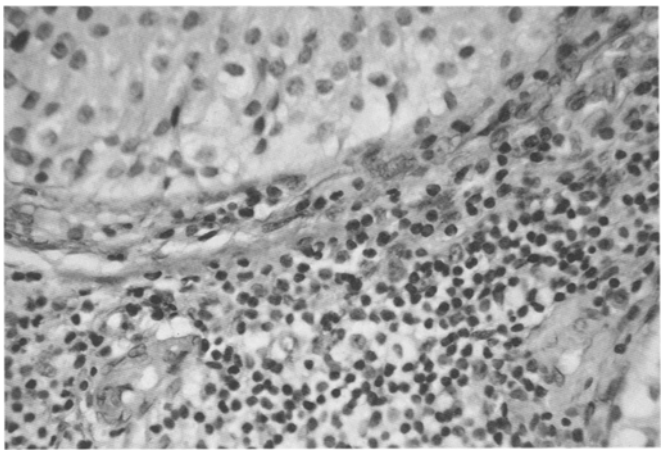

Fig. 3. Tumor-associated lymphoid tissue in a primary superficial transitional cell carcinoma of the bladder

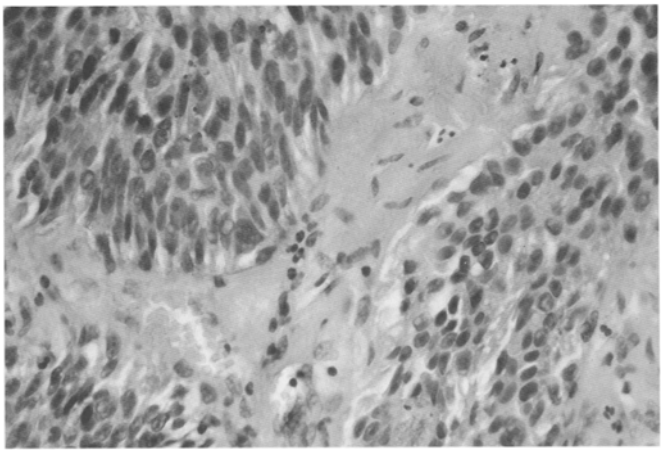

Fig. 4. Primary superficial transitional cell carcinoma of the bladder without tumor-associated tissue inflammatory reaction

Discussion

A tumor-associated lymphoid reaction was described 1970 by Sarma [9]. In a study of 230 patients with superficial and invasive bladder cancer he found in 73% adventious lymphoid tissue ranging from odd collections of cells to well-defined follicles crowding the microscopic field. With moderate and marked reactions, the tumors were less frequently high grade, infiltrated only occasionally and generally gave a good prognosis. In our study the frequency of TATIR increases with tumorinfiltration and poor differentation contrary to the results of Sarma. We also noticed a tendency for better prognosis in tumor with TATIR in comparison to tumors without TATIR but in this study we could not prove this effect by statistical methods. In a retrospective analysis of 428 patients with primary STCC the prognostic factor of TATIR relating to percentage of recurrences were proven to be significantly better ($p < 0.01$, unpublished data). Stöber confirmed the better prognosis in tumors with TATIR in a study of 50 patients with superficial and invasive tumors [12]. He

found a marked tumor-associated cell infiltration in 34% of the patients. In these cases the disease free interval was longer and the progression rate lower as in patients without a TATIR. Based on the results of our study we confirm the tendency of a lower progression rate in tumors with TATIR but we did not see any effect on the disease free interval. In an earlier study on patients with superficial and invasive tumors of the bladder we found an increase on the frequency of TATIR with the tumorinvasion (36% in pT1 tumors versus 43% in pT3 tumors) [3]. An increase with invasion was confirmed by Lowe for the eosinophilia [5]. In tumors where tumor-associated tissue eosinophilia (TATE) was found there was a greater likelihood that deep invasion has occurred with cavolvement of the muscularis. He also demonstrated the better prognosis in tumors with TATE with regard to survival. This seems to be the most important factor of a TATIR or TATE. Lowe found in his study of 1,305 cases 2.76 % TATE. In our group 3/92 (3.2%) had a massive eosinophilia. Regardless of the small number it was noted that 2 of the 3 patients with TATE had a transitional cell carcinoma with squamous metaplasia. In a study of Tiltman a rate of 7.1% heavy eosinophilia in bladder cancer was found [13]. Thus it appears that the finding of eosinophilia in bladder carcinoma is commoner in tumors with squamous diffrentiation and in invasive tumors [5]. The problem in the evaluation of TATIR is, that most of the patients with a STCC are at an age where non specific cystitis with generalized inflammatory reaction can be found in 60%–70% of the men and in 70%–80% of the women [10, 11]. A differentiation between TATIR and nonspecific inflammatory reaction can be made by comparing the biopsies from bladder mapping with the tumor-associated tissue. A local cell infiltration, especially a eosinophilia is possible but very unlikely in primary and superficial carcinomas [1].

The evidence is that a TATIR or TATE indicate better prognosis in comparison to a comparable tumor without a TATIR. Further studies are necessary to prove this tendency.

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