

# The effect of squamous and/or glandular differentiation on recurrence, progression and survival in urothelial carcinoma of bladder

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## Abstract

**Introduction** The effects of squamous and/or glandular differentiation in urothelial carcinoma of bladder on recurrence, progression and survival rate were evaluated in this study.

**Patients and methods** Between 1998 and 2003, a total of 223 patients who had been treated with transurethral resection for bladder cancers were evaluated. The patients were divided into two groups as; Group I: tumor patients with squamous and/or glandular differentiation, Group II: patients without these findings.

**Results** Histologically 189 (84.7%) were conventional urothelial carcinoma and 34 (15.2%) were tumors with squamous and/or glandular differentiation. The mean age of the

patients was  $64.4 \pm 12.7$  (range 36–81) years. Survival rates within a period of  $46.23 \pm 14.8$  (12–67) months were 76.47% for Group I and 89.94% for Group II ( $P = 0.027$ ). The stage distribution as pTa, pT1, and  $\geq$ pT2 was 2 (5.9%), 18 (52.9%), and 14 (41.2%) in Group I and 101 (53.4%), 51 (27%) and 37 (19.6%) in group II, respectively ( $P = 0.001$ ). There was a statistically significant tendency towards higher stage at presentation in Group I and the grade distribution was significantly higher in Group I than Group II ( $P < 0.001$ ).

**Conclusion** High recurrence rates and poor prognosis of these patients should be kept in mind in the follow-up period. In this respect, these patients should be followed up closely.

**Keywords** Bladder · Carcinoma · Squamous · Glandular · Prognosis

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## Introduction

The incidence of bladder cancer in the United States has been steadily increasing during the past years and now stands at 63,210 new cases with more than 13,180 deaths annually [1]. The most common histologic type of bladder cancers is urothelial carcinoma, accounting for 90% and 95% of bladder cancers. Urinary bladder carcinomas may sometimes have diverse histologic

features, which differ from the conventional urothelial carcinoma (UC) of the bladder and they account for approximately 15% of all urothelial cancers [2]. These divergent tumors are divided into four major categories as: variant forms of UC, squamous cell carcinoma, adenocarcinoma, and undifferentiated carcinoma. In the first category, the most common divergent tumor group is the carcinomas with squamous and/or glandular differentiation [3]. Although these variants often receive limited considerations when bladder cancer is discussed, they often pose difficult diagnostic problems and their correct interpretation frequently has important clinical implications [4, 5]. Moreover, it is a controversial issue that urothelial carcinoma of bladder with squamous and/or glandular differentiation behaves more aggressively than usual transitional cell urothelial carcinomas.

In this study, we evaluated the effects of squamous and/or glandular differentiation on recurrence, progression, and survival of bladder tumor patients.

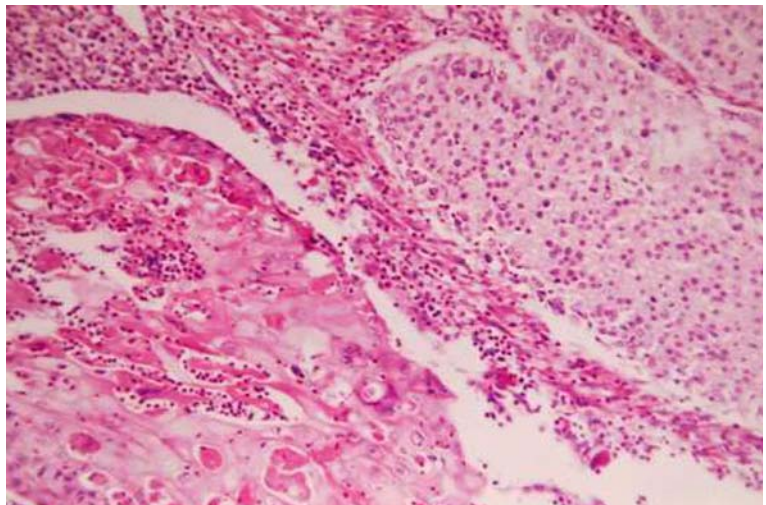
### Patients and methods

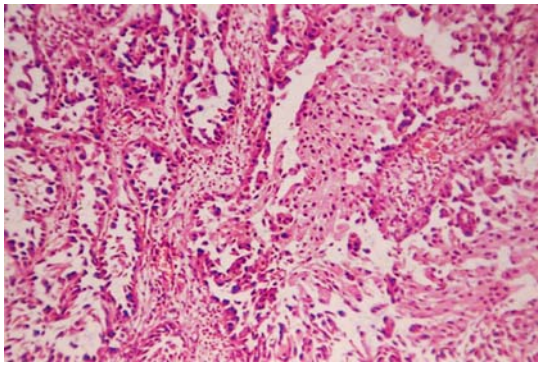
Between February 1998 and January 2003, 223 patients with primary UC of the bladder who underwent transurethral resection were enrolled into this study. All patients were evaluated with

physical examination, urinary ultrasonography (USG) or intravenous urography (IVU), computerized tomography (CT) and also with cystoscopy if indicated. Clinical and pathological staging was done according to TNM classification (1997) and histological staging was done according to the classification of WHO (1973) [6, 7]. Although there were other aberrant differentiations of urothelial carcinomas such as, sarcomatoid, trophoblastic, or pseudosarcomatous stromal differentiation, only urothelial carcinomas which show squamous and/or glandular differentiation were included into the study. Patients were divided into two groups. Group I consisted of the tumor patients with squamous and/or glandular differentiation and Group II is composed of patients without these findings. In histologic sections squamous differentiation was defined by the presence of intercellular bridges or keratinization (Fig. 1) and the presence of true glandular spaces within the tumor microscopically pointed out glandular differentiation (Fig. 2). The data of two groups concerning recurrence, progression, and survival were compared statistically.

Chi-square test and independent sample *t* test were used for statistical analysis. Results were presented as mean  $\pm$  SD for quantitative variables and number of patients (%) for qualitative variables. For all tests,  $P < 0.05$  was considered to indicate statistically significant difference (Table 1).

**Fig. 1** Urothelial carcinoma with squamous differentiation (H & E, 125)





**Fig. 2** Urothelial carcinoma with glandular differentiation (H & E, 125)

## Results

A total of 223 patients with a mean age of  $64.45 \pm 12.7$  (36–81) years were followed up with a mean period of  $46.23 \pm 14.8$  (range 12–67) months. Histopathological examination of transurethraally resected tumor material of all patients showed squamous and/or glandular differentiation in 34 (15.25%) of them (Group I), and 189 (84.75%) were pure UC (Group II). The stage distribution of tumors as pTa (noninvasive papillary carcinoma), pT1 (tumor invading subepithelial connective tissue), and  $\geq$ pT2 (invasive carcinoma) according to group I and group II were 2 (5.9%), 18 (52.9%), and 14 (41.2%) and 101 (53.4%), 51 (27%), 37 (19.6%), respectively ( $P = 0.001$ ). These two groups were compared

with respect to recurrence, progression, survival, stage and grade distribution of tumor at presentation. The recurrences and progression rates were 70% and 35% in Group I, and 42.02% and 9.21% in Group II. As tumor recurrence and progression rates were concerned there was a statistical difference between the groups ( $P = 0.022$  and  $P = 0.013$ ). Correlation of the age and sex with tumor stage were not statistically significant ( $P > 0.05$ ). The mean survival rates in Group I and Group II were 76.47% (26/34) and 89.94% (170/189), respectively ( $P < 0.027$ ). Except two patients with grade 2 tumor (5.88%), all patients in Group I had grade 3 (94.11%) tumors. In Group II, frequency distribution of grade were as follows: 30 (15.9%) grade 1, 102 (53.9%) grade 2, and 57 (30.2%) grade 3 tumors ( $P = 0.001$ ).

## Discussion

Bladder cancer is the seventh most common cancer worldwide, with an estimated 260,000 new cases occurring each year in men and 76,000 in women [8]. The most common type of bladder cancer is urothelial carcinoma, derived from uroepithelium, which constitutes more than 90% of bladder cancer cases. Urothelial carcinoma has a propensity for divergent with the most common being squamous followed by glandular [9]. Squamous differentiation, which is defined by the

**Table 1** Clinical and pathological features of the patients

	Group I n (%)	Group II n (%)	P
Age (year)	66.29 (54–81)	62.38 (36–71)	0.241
<i>Sex distribution</i>			
Male	20 (58.8)	103 (54.5)	0.769
Female	14 (41.2)	86 (45.5)	
<i>Pathologic distribution</i>			
pTa	2 (5.9)	101 (53.4)	0.001
pT1	18 (52.9)	51 (27)	
pT2	14 (41.2)	37 (19.6)	
<i>Histologic features</i>			
Grade I	0	30 (15.9)	0.001
Grade II	2 (5.88)	102 (53.9)	
Grade III	32 (94.11)	57 (30.2)	
Recurrence	14 (70)	65 (42.02)	0.022
Progression	7 (35)	14 (9.21)	0.013
Survival rates	26 (76.47)	170 (89.94)	0.027

presence of intercellular bridges or keratinization, occurs in up to 10–20% of urothelial carcinomas of the bladder and in 44% of tumors of the renal pelvis, and glandular differentiation is less common than squamous differentiation [10]. Glandular differentiation is defined as the presence of true glandular spaces within the tumor. These may be tubular or enteric glands with mucin secretion. In our study, squamous and/or glandular differentiation ratio was 15.25% and 27 (79.41%) of them were squamous, and 7 (20.59%) were glandular differentiation. The glands with squamous or glandular differentiation are variable in appearance, occasionally being small and tubular. Squamous differentiation may show basaloid or clear cell features. Cytokeratin 14 and L1 antigen have been reported as immunohistochemical markers of squamous differentiation [8]. The clinical significance of squamous differentiation remains uncertain, but seems to be an unfavorable prognostic feature in such patients undergoing radical cystectomy, possibly, because of its association with high grade tumors [8]. Glandular and squamous differentiation is usually found in moderate to high grade tumors often with deeply invasive behavior [11]. In this study, 94.11% (32/34) of the patients in Group I with squamous and/or glandular differentiation had high grade and 94.11% (32/34) were infiltrative tumors (pT1 and  $\geq$ pT2). Glandular and/or squamous differentiation is rarely present in well-differentiated noninvasive papillary tumors; and had been found to be in 2% of the cases in one study [12, 13]. In our study this ratio was 2 (5.88%).

Following the recommendation of the WHO and other authorities, squamous and glandular differentiating tumors are placed in the general category of urothelial carcinoma (UC), and the diagnosis of squamous carcinoma or adenocarcinoma are reserved for neoplasms composed purely of those types of cells [14]. According to Frazier et al. [15] squamous and/or glandular differentiation was an unfavorable feature in patients undergoing radical cystectomy. Previous reports have suggested that these variants may be more resistant to chemotherapy and radiation therapy than pure UC, but further studies are needed to confirm these results [9, 16].

Squamous and glandular differentiation in urothelial carcinomas has been thought to have little clinical significance generally [17]. Squamous and glandular differentiation were predictive of a poor response to radiation therapy and possibly also systemic chemotherapy. In the article by Logothesis et al. [18] the presence of glandular differentiation was associated with poorer response to systemic chemotherapy. In a recent report by Genega et al. [19] from the Memorial Sloan-Kettering Center with a total 224 cystectomies, 161 (72%) patients had conventional urothelial carcinoma and 63 (28%) had urothelial carcinoma with aberrant differentiation and the latter included squamous, glandular, and small/neuroendocrine differentiation. In this study, a trend toward higher final pathologic stage in urothelial carcinoma with aberrant differentiation compared to conventional urothelial carcinoma had been mentioned, however the analysis of disease specific survival rate had showed no significant difference between the two groups. In this study we found the different results that the survival rates between the groups had significant correlation. Billis et al. [20] found significant relationship between tumor stage and differentiation in a group of UC patients with squamous and/or glandular differentiation, compared to a group with pure urothelial carcinoma. In their study, tumors of all patients with glandular and/or squamous differentiation were infiltrative (pT1 and pT2) and none were superficial (pTa) tumors. In this study, among 223 transurethral tumor resection materials, histopathologic examination showed 84.75% (189/223) pure urothelial carcinoma and 34% (15.25) showed aberrant differentiation which were squamous and/or glandular differentiation. Great majority of the cases (94.11%) in the group with squamous or/and glandular differentiation at presentation were invasive (pT1 and  $\geq$ pT2). There was statistically significant difference in the comparison of stage distribution between the tumor group with differentiation and the other group with a preponderance to higher stage in the first group ( $P = 0.001$ ). This finding highly suggests that squamous and/or glandular phenotype in urothelial carcinoma is a marker of invasiveness and consequently of a more aggressive behavior.

## Conclusions

As a conclusion, we can make a suggestion that, histologically squamous and/or glandular differentiated type of urothelial carcinoma of the bladder behaves more aggressively than conventional urothelial carcinoma and consequently may lead to more invasive and higher grade tumor detection at presentation.

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