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ORIGINAL ARTICLE

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Patterns of invasion and histological growth as prognostic indicators in urothelial carcinoma of the upper urinary tract

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Abstract The biological significance of squamous and glandular differentiation and different patterns of invasion in upper urinary tract urothelial carcinoma is unclear. We reviewed 268 cases of consecutive upper urinary tract carcinomas with respect to the presence of squamous and/or glandular differentiation and different patterns of invasion (nodular, trabecular, and infiltrative) and correlated data with patient outcome. Squamous or glandular differentiation occurred in 47/268 (18%) tumors and its presence correlated with high tumor stage ($P<0.001$) and grade ($P<0.001$). Invasive patterns were nodular in 49/227 (22%), trabecular in 95/227 (42%), and infiltrative in 83/227 (37%) tumors. The nodular pattern prevailed in low stage ($P<0.001$) and low-grade ($P<0.001$) tumors, whereas the infiltrative pattern prevailed in high stage ($P<0.001$) and high-grade ($P<0.001$) tumors. Multivariate analysis proved that tumor stage ($P<0.001$) and the infiltrative pattern ($P<0.001$) are independent predictors of metastasis-free survival, whereas tumor grade and squamous and glandular differentiation lacked independent influence on patient outcome. In conclusion, the infiltrative pattern of invasion significantly correlated with advanced disease and poor patient outcome. In contrast, the presence of squamous and/or glandular invasion did not prove independent influence on patient outcome. The pattern of invasion should be commented upon separately in the pathology report.

Keywords Urothelial carcinoma · Squamous differentiation · Glandular differentiation · Pattern of invasion · Prognosis

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Introduction

Upper urinary tract urothelial carcinoma (UC) is relatively uncommon, accounting for approximately 5% of all epithelial tumors of the urinary tract with most tumors occurring in the bladder [10]. Standard treatment for localized upper tract UC is radical nephroureterectomy with bladder cuff resection [18]. Although numerous investigations showed that stage is the most important predictor of outcome [3, 5–8, 12–15, 19, 24, 31, 32, 34, 35], the clinicopathologic features predictive of metastatic disease are not well defined and the assessment of tumor grade shows considerable variation due to observer subjectivity [2, 44]. Thus, the identification of other prognostic variables that can easily be determined in routinely hematoxylin and eosin (H&E)-stained sections is required to select candidates for adjuvant therapy.

The majority of primary epithelial neoplasms of the urinary tract display conventional urothelial morphology but some tumors may additionally show aberrant differentiation thought to arise from metaplastic change [22, 39]. These areas are most frequently squamous or glandular in nature and their frequency was shown to increase with tumor grade and stage [1, 11, 42, 43, 45]. Thus, most urological oncologists share the view that mixed histology implies more aggressive disease, which may be less susceptible to radio- or chemotherapy [16, 25, 29]. However, there is only one study analyzing the prognostic impact of squamous and/or glandular differentiation in a series of 70 bladder carcinomas [30], whereas a systematical investigation analyzing the clinical significance of squamous and/or glandular differentiation in upper urinary tract cancer,

including both univariate and multivariate statistical analysis, is currently lacking.

Recently, Jiminez et al. [17] described three different patters of invasion (nodular, trabecular, and infiltrative) in a series of 93 muscle-invasive bladder cancers. According to their data, the infiltrative growth pattern may be associated with unfavorable patient outcome despite lack of significance in multivariate analysis. In a subsequent study by Krüger et al. [20] involving 153 muscle-invasive bladder cancers, the infiltrative pattern proved to be an independent predictor of poor disease-related survival. The authors concluded that the classification by Jiminez et al. [17] may serve as an additional tool to predict the prognosis of patients undergoing radical cystectomy for bladder cancer.

In the present study, we aimed to evaluate the potential prognostic significance of squamous and/or glandular differentiation in a large consecutive series of upper urinary tumors. Moreover, our study is the first to apply the classification introduced by Jiminez et al. [17] to this type of urothelial cancer and to assess its role in predicting metastasis-free survival. By performing a multivariate analysis, we analyzed the potential of the different histological variables to serve as independent predictors of patient outcome.

Materials and methods

Case selection

Two hundred sixty-eight consecutive upper urinary tract UCs (169 pelvic and 99 ureteral tumors) from 239 consecutive patients (108 women and 131 men) undergoing surgery between January 1984 and December 2004 were retrieved from the files of our institute. The mean and median ages of patients were 70 and 71 years (range 39–89), respectively. Seventeen out of 239 (7%) patients presented with local lymph node metastases at the time of their primary operation. All tumor specimens were examined by the same protocol including multiple sections obtained from the tumor itself, the kidney, and the pelvic wall adjacent to and distant from the tumor, along with the ureter and lymph nodes, if present.

For the correlation of histopathological data with metastasis-free survival, all noninvasive cancers (41 tumors from 33 patients) and all tumors from patients with multiple invasive cancers (37 tumors from 16 patients) were excluded resulting in a final sample of 190 UCs (134 pelvic and 56 ureteral tumors) from 190 patients (77 women and 113 men). Standard treatment included nephroureterectomy with bladder-cuff resection (n=130), alternatively, nephrectomy alone (n=40) or distal ureteral resection with reimplantation (n=20) were performed. Patients did not receive adjuvant therapy. Follow-up regimen included abdominal ultrasound and cystoscopy every 3 months for the first 3 years, every 6 months for the subsequent 2 years, and yearly thereafter and chest X-ray and computerized tomography every 6 months for the first 3 years and yearly thereafter. All procedures were in accord with the ethical standards established by our institution. Informed consent is not required for retrospective analyses dealing with archival material obtained during routine medical treatment.

Histopathology

H&E-stained slides from routinely formalin-fixed and paraffin-embedded material were systematically reevaluated by one pathologist (C. L.) who was blinded to regional lymph node status and the subsequent disease course. pT-stages were adjusted according to the International Union Against Cancer 2002 issue of the Tumor, Nodes, Metastasis system [41]. Grading was performed according to the recently published two-tiered WHO grading system following the WHO/International Society of Urological Pathology consensus classification [27]. During the process of reviewing the slides, special attention was drawn toward the presence of aberrant histological differentiation. According to the WHO criteria for the diagnosis of histological variants of urothelial cancer [27], squamous differentiation was defined as the presence of intercellular bridges or keratinization. Glandular differentiation was defined as the presence of true glandular spaces and gland-like lumina within tumor cell nests; special care was taken to differentiate these glandular structures from pseudoglandular spaces caused by drop-out of necrotic cells or artifact. A significant proportion of tumors displayed both squamous and glandular differentiation. In these cases both patterns were recorded. Three main architectural patterns of tumor invasion were recognized following the definition by Jiminez at al. [17]: The nodular pattern was composed of well-delineated round nests of tumor cells. These nests varied in diameter but a tendency of roundness was maintained throughout (Fig. 1a). Desmoplasia was usually not prominent and necrosis was not observed. The trabecular pattern consisted of infiltrating broad trabeculae that usually anastomosed with each other and were sometimes associated with extensive necrosis and a desmoplastic stroma (Fig. 1b). The trabeculae were at lest three cells thick. The infiltrative pattern showed infiltrating narrow cords or single tumor cells (Fig. 1c). Desmoplasia and necrosis were common. Cells were usually highly pleomorphic or small and undifferentiated. Tumor heterogeneity represents a well-known phenomenon in urothelial cancers and different subclones with different phenotypes are known to coexist within the same tumor, among which, those bearing the most aggressive biological potential eventually determine patient outcome [4]. Accordingly, in cases showing two or more patterns of invasion, only the most aggressive type of tumor growth (infiltrative > trabecular > nodular) was recorded.

Statistical analyses

Associations between patterns of invasion or histological differentiation and tumor stage as well as tumor grade were

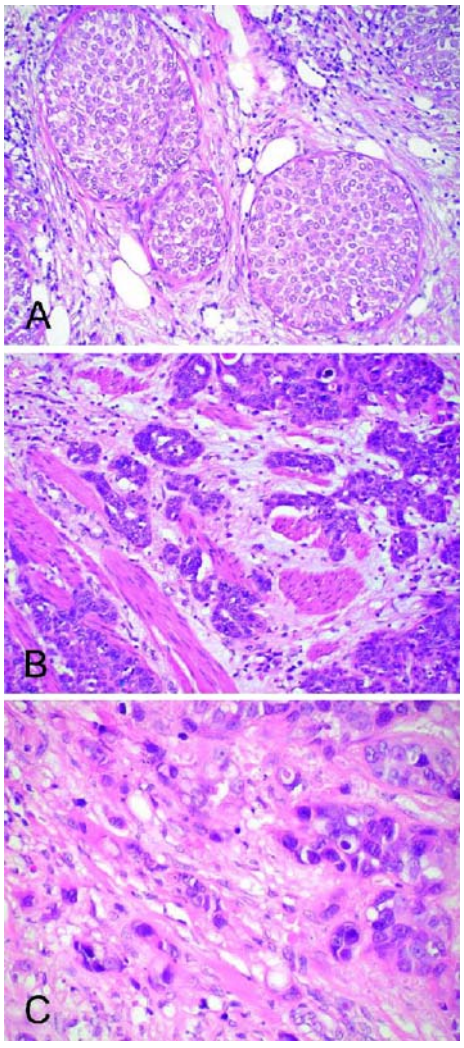

Fig. 1 Urothelial carcinoma of the upper urinary tract with nodular (**a** H&E), trabecular (**b** H&E), and infiltrative (**c** H&E) pattern of invasion according to the definition by Jiminez et al. [17]

analyzed using the Fisher's exact test. Patient outcome was investigated using the Kaplan–Meier method and compared by the log-rank test. Disease progression was defined as the occurrence of nodal and/or distant metastases. Metastasis-free survival was calculated from definitive treatment of upper tract disease (e.g., nephroureterectomy) to the occurrence of metastatic disease or the last follow-up in patients with no evidence of disease progression. For multivariate testing, a Cox's proportional hazards regression model was performed. All reported *P* values were two-sided with significance at $P<0.05$.

Results

Overall, stage pTa was present in 41 (15%), pT1 in 102 (38%), pT2 in 37 (14%), pT3 in 80 (30%), and pT4 in eight (3%) cases. One hundred forty-one (53%) tumors were of low tumor grade and 127 (47%) were of high tumor grade. Pelvic and ureteral tumors showed a comparable distribution regarding the different categories. High tumor grade was associated with high tumor stage [53/139 (38%) pT1/pT2 vs 74/88 (84%) pT3/pT4, $P<0.001$]; no high-grade tumors were detected among noninvasive cancers.

Squamous differentiation occurred in 47/268 (18%) tumors. The majority of them showed small interspersed islands of squamous epithelium with mild to moderate atypia in otherwise typical urothelial carcinoma (Fig. 2a). In some cases, however, poorly differentiated tumor cells showing squamous differentiation (with or without keratinization) gradually merged with the surrounding urothelial tumor cells, ultimately representing the predominant histological growth pattern (Fig. 2b). Squamous differentiation prevailed in high stage [15/180 (8%) pTa-pT2 vs 32/88 (36%) pT3/pT4, $P<0.001$] and high grade [8/141 (6%) low grade vs 39/127 (31%) high grade, $P<0.001$] cancers (Table 1).

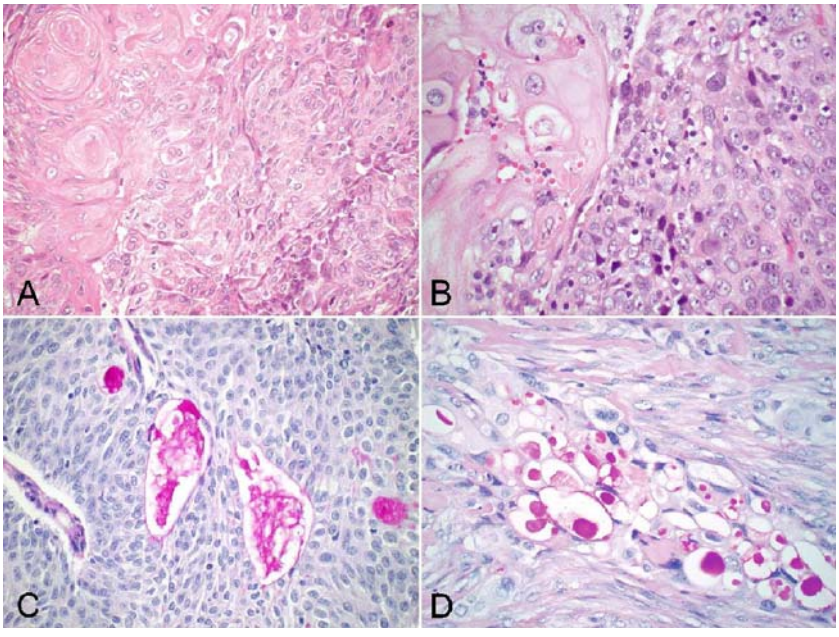

Fig. 2 Urothelial carcinoma of the upper urinary tract with squamous (**a**–**b** H&E) and glandular differentiation (**c**–**d** PAS) as demonstrated in low-grade (**a** and **c**) and high-grade (**b** and **d**) tumors

Table 1 Squamous differentiation in upper urinary tract urothelial carcinomas related to tumor stage (pT1a–pT4) and tumor grade [low grade (LG) and high grade (HG)]

	All tumors		Pelvic tumors		Ureteral tumors	
	Samples	%	Samples	%	Samples	%
pTa	1/41	2	1/19	5	0/22	0
pT1	8/102	8	6/60	10	2/24	5
pT2	6/37	16	3/20	15	3/17	18
pT3	29/80	36	21/62	34	8/18	44
pT4	3/8	38	3/8	38	–	–
LG	8/141	6	4/48	5	4/57	7
HG	39/127	31	30/85	35	9/42	21
Total	47/268	18	34/169	20	13/99	13

Glandular structures were observed in 47/268 (18%) tumors. The amount of glandular differentiation was variable with the majority of cases showing only focal glands bordered by a single layer of cuboidal or columnar cells or gland-like lumina scattered among nests of otherwise typical urothelial carcinoma (Fig. 2c). In some cases, however, the glandular differentiation represented the predominating histological growth pattern (Fig. 2d). Glandular differentiation prevailed in high stage [22/180 (12%) pTa-pT2 vs 25/88 (28%) pT3/pT4, P=0.002] and high grade [17/141 (12%) low grade vs 30/127 (24%) high grade, P=0.02] cancers (Table 2). Occasionally, the glands underwent cystic dilatation, resulting in a microcystic appearance. One case displayed a colloid-mucinous pattern characterized by nests of cells "floating" in extracellular mucin. It is interesting to note that the glandular growth pattern was associated with the presence of squamous differentiation. Thus, 20/47 (43%) tumors with glandular lumina simultaneously showed foci of squamous differentiation compared with 27/221 (12%) tumors without glandular differentiation (P<0.001).

According to Jiminez et al. [17], patterns of invasion were nodular in 49/227 (22%), trabecular in 95/227 (42%), and infiltrative in 83/227 (37%) tumors. The nodular pattern prevailed in low stage [45/139 (32%) pT1/pT2 vs 4/88 (5%) pT3/pT4, P<0.001] and low grade [44/100 (44%) low grade vs 5/127 (4%) high grade, P<0.001] cancers, whereas the infiltrative pattern prevailed in high stage [20/139 (14%) pT1/pT2 vs 63/88 (72%) pT3/pT4, P<0.001] and high grade [0/100 (0%) low grade vs 83/127 (65%) high grade, P<0.001] cancers (Table 3).

Follow-up data were available from 186/190 (98%) patients. After a mean and median follow-up of 46 and 31 months, respectively, progressive disease was observed in 74/186 (40%) patients including 60 patients who died from cancer and 14 patients who are currently alive with metastatic disease. Mean time to progression was 19 months (median 8.3, range 0–110). Twenty-five patients died from causes not related to cancer. Actuarial overall and metastasis-free survival rates were 63 and 56% at 5 years and 52 and 45% at 10 years.

The development of distant metastases was associated with the presence of squamous and/or glandular differentiation. Thus, 25/43 (58%) UCs with squamous differentiation developed disease progression compared with 49/143 (34%) UCs without squamous differentiation (P=0.001; Fig. 3). Actuarial 5-year metastasis-free survival rates for patients with UCs with and without squamous differentiation were 33 and 63%, respectively. Similarly, 19/36 (53%) UCs with glandular differentiation developed disease progression, compared with 55/150 (37%) UCs without glandular differentiation (P=0.04; Fig. 4). Actuarial 5-year metastasis-free survival rates for patients with UCs with and without glandular differentiation were 45

Table 2 Glandular differentiation in upper urinary tract urothelial carcinomas related to tumor stage (pT1a–pT4) and tumor grade [low grade (LG) and high grade (HG)]

	All tumors		Pelvic tumors		Ureteral tumors	
	Samples	%	Samples	%	Samples	%
pTa	6/41	15	3/19	16	3/22	14
pT1	10/102	10	5/60	8	5/42	12
pT2	6/37	16	5/20	25	1/17	6
pT3	23/80	29	19/62	31	4/18	22
pT4	2/8	25	2/8	25	–	–
LG	17/141	12	12/84	14	5/57	9
HG	30/127	24	22/85	26	8/42	19
Total	47/268	18	34/169	20	13/99	13

Table 3 Patterns of invasion in upper urinary tract urothelial carcinomas related to tumor stage (pT1–pT4), tumor grade [low grade (LG) and high grade (HG), and tumor location (pelvic and ureteral)]

	Nodular		Trabecular		Infiltrative	
	Samples	%	Samples	%	Samples	%
pT1 (*n*=102)	39	38	52	51	11	11
pT2 (*n*=37)	6	16	22	59	9	24
pT3 (*n*=80)	4	5	20	25	56	70
pT4 (*n*=8)	–	–	1	13	7	88
LG (*n*=100)	44	44	56	56	–	–
HG (*n*=127)	5	4	39	31	83	65
Pelvic (*n*=150)	34	23	61	41	55	37
Ureteral (*n*=77)	15	19	34	44	28	36
Total (*n*=227)	49	22	95	42	83	37

and 59%, respectively. In addition, disease progression was associated with the pattern of invasion. Thus, only 3/41 (7%) UCs with a nodular pattern developed disease progression compared with 18/78 (23%) UCs with a trabecular pattern and 53/67 (79%) UCs with an infiltrative pattern (P<0.002; Fig. 5). Actuarial 5-year metastasis-free survival rates for UCs with nodular, trabecular, and infiltrative pattern of invasion were 94, 74, and 12%, respectively (Table 4). No significant prognostic influence was observed for tumor location, patient age, and gender.

In a Cox's proportional hazards regression model including age, gender, tumor stage, grade, and location (pelvis vs ureter), squamous and glandular differentiation, as well as the different patterns of invasion, pT-stage >1 [P<0.001, risk ratio (RR)=4.02, 95% confidence interval (CI)=1.82–8.84] and the infiltrative pattern of invasion (P<0.001, RR=3.88, 95% CI=1.87–8.05) proved to be independent predictors of metastatic disease. Patients with UCs showing a nodular pattern of invasion were less likely to develop disease progression but this difference was not statistically significant (P=0.16, RR=0.39, 95% CI=0.11–1.43). Tumor grade and location and presence of squamous and/or glandular differentiation lacked independent influence on patient outcome.

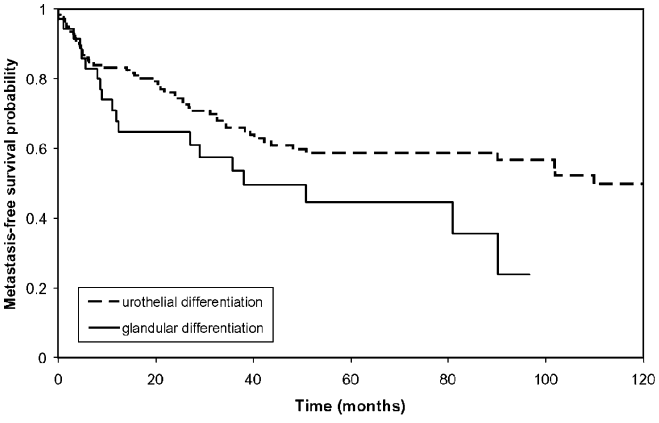

Fig. 4 Metastasis-free survival (months) in patients with upper urinary tract urothelial cell carcinomas related to the presence of glandular differentiation (P=0.04, log-rank test)

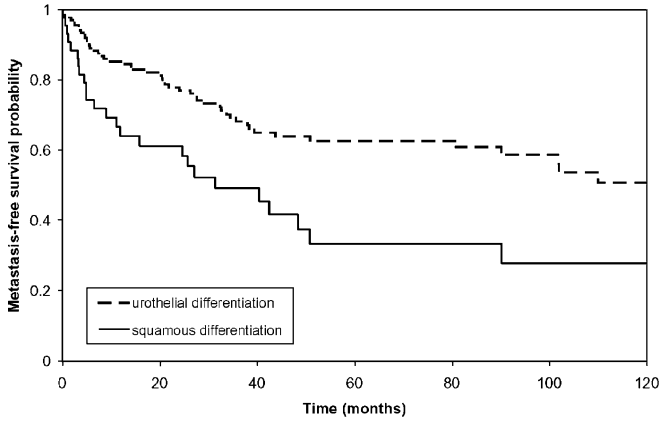

Fig. 3 Metastasis-free survival (months) in patients with upper urinary tract urothelial cell carcinomas related to the presence of squamous differentiation (P=0.001, log-rank test)

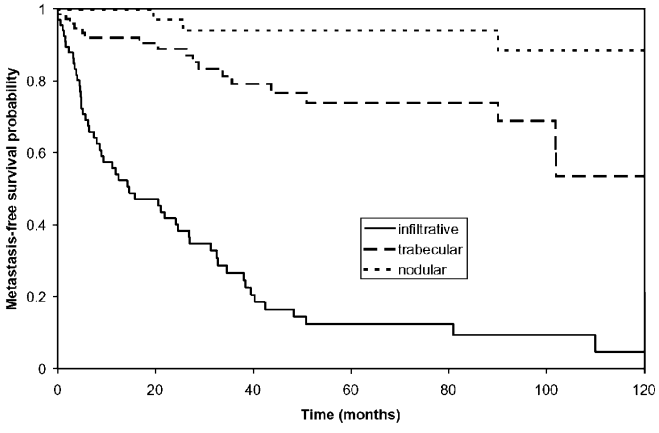

Fig. 5 Metastasis-free survival (months) in patients with upper urinary tract urothelial cell carcinomas related to different patterns of invasion (P<0.001, log-rank test)

Table 4 Disease progression in upper urinary tract urothelial carcinomas related patterns of invasion (nodular, trabecular, and infiltrative) and histological differentiation (pure urothelial, squamous, and glandular)

	All tumors		Pelvic tumors		Ureteral tumors	
	Samples	%	Samples	%	Samples	%
Overall disease progression	74/186	40	57/131	44	17/55	31
Nodular pattern	3/41	7	2/30	7	1/11	9
Trabecular pattern	18/78	23	15/54	28	3/24	13
Infiltrative pattern	53/67	79	40/47	85	13/20	65
Urothelial differentiation	41/126	33	30/87	34	11/39	28
Squamous differentiation	25/43	58	21/32	66	4/11	36
Glandular differentiation	19/36	53	16/28	57	3/8	38

The follow-up data available are from 186 patients

Discussion

According to literature, metastatic disease occurs in 19–54% of upper tract urothelial cancers and a significant proportion of patients eventually die due to tumor dissemination [6, 8, 13–15, 31, 32, 34, 35, 37]. Thus, the identification of independent prognostic factors is an essential step for the evaluation of affected patients not only to predict disease evolution, thus aiding surveillance strategies, but also to identify subgroups that might benefit from adjuvant cancer therapy.

Primary squamous cell carcinoma and adenocarcinoma of the renal pelvis and ureter, defined as tumors showing pure squamous or pure glandular phenotype, are highly uncommon, representing less than 1% of all primary tumors of the upper urinary tract [36]. Their pathogenesis was related to urothelial metaplasia due to long-standing chronic irritation and/or inflammation leading to dysplasia (intraepithelial neoplasia) and ultimately to squamous cell carcinoma or adenocarcinoma [28]. Thus, medical history of affected patients commonly discloses information regarding chronic pyelonephritis and/or nephrolithiasis. Patients often present at an advanced stage of the disease and the outcome is generally poor [23, 33, 38, 40].

In contrast, aberrant squamous and/or glandular differentiation in otherwise typical urothelial cancers is by far more common, occurring in 7–60% of bladder [1, 9, 22, 26, 29, 30, 42, 45] and 10–15% of upper urinary tract UCs [7, 11]. In our series, squamous or glandular differentiation occurred in 74/268 (28%) upper urinary tract tumors, its presence being significantly correlated with high tumor stage and grade. Both squamous and glandular differentiation indicated poor prognosis in univariate analysis. However, multivariate analysis revealed that neither squamous nor glandular differentiation possessed independent influence on patient outcome. Our data are in line with a previous study investigating bladder cancer by Mazzucchelli et al. [30] who reported a significant correlation between squamous differentiation and prognosis in univariate analysis (P=0.05), but not in multivariate analysis.

The high frequency of squamous and/or glandular differentiation in otherwise typical urothelial cancers is not easy to understand because the urinary tract is normally exclusively lined by urothelial cells. To bring light in this topic, Kunze and Francksen [21, 22] systematically investigated carcinoma tissues from human and rat urinary bladder. The authors were able to show that the underlying histogenetic principle is based on the pluripotent metaplastic potential of normal and neoplastic urothelium to undergo several pathways of cellular and architectural differentiation. By demonstrating a direct conversion of typical urothelial carcinoma cells into squamous and/or glandular cells, they concluded that squamous and glandular differentiation develop by a metaplastic process within preexisting conventional UC. This process occurs during tumor progression and dedifferentiation, most probably owing to the embryologic origin of the urinary tract from pluripotent tissues of the cloacal endoderm and the mesodermal Wolffian ducts.

The infiltrative pattern according to Jiminez et al. [17] was significantly associated with the development of metastatic disease and proved to be a new independent prognostic marker that can be determined in routinely H&E-stained sections and is thus easily applicable worldwide. The original analysis by Jiminez et al. [17] and a subsequent study by Krüger et al. [20], which were both restricted to bladder tumors, revealed comparable results. The infiltrative pattern serves as an independent histological prognosticator with a relative risk comparable to that of tumor stage, emphasizing the necessity for pathologists to comment specifically on its presence (or absence).

Tumor heterogeneity represents a well-known phenomenon in urothelial cancers and a significant proportion of tumors in our study and in the previous reports on bladder cancer displayed two or more patterns of invasion. For this reason, a major and a minor pattern was recorded for each patient in both previous reports [17, 20]. However, because both previous studies clearly showed that the presence alone of a minor infiltrative component had the same impact on patient outcome as the presence of a major infiltrative component, we recorded only the most aggressive type of tumor invasion (infiltrative > trabecular > nodular) to improve practicability of the system in daily routine work. In contrast to Krüger et al. [20] who suggested an abbreviated two-tiered classification of invasion

(infiltrative vs noninfiltrative), we retained the original three-tiered system because analogous to the negative prognostic effect of the infiltrative pattern, the nodular pattern indicated a tendency toward a more favorable outcome.

In summary, tumor stage and the infiltrative pattern of invasion significantly correlated with advanced disease and enhanced local and distant metastatic spread, clearly indicating that the pattern of invasion is a reliable prognostic factor for patients with upper urinary tract cancer. In contrast, the presence of squamous and/or glandular invasion did not prove independent influence on patient outcome. The pattern of invasion should be commented upon separately in the pathology report.

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