Article is available online at http://www.webio.hu/por/2005/11/2/0087

ARTICLE

The Effect of Tumor Invasion Patterns on Pathologic Stage of Bladder Urothelial Carcinomas

Sema BIRCAN, Ozden CANDIR, Nilgun KAPUCUOGLU

Department of Pathology, Suleyman Demirel University School of Medicine, Isparta, Turkey

The aim of this study was to investigate tumor invasion pattern, its heterogeneity and association with histopathological features and stage in invasive urothelial carcinoma of the bladder. We studied 62 cases of invasive urothelial carcinoma of the bladder. World Health Organization (WHO) 1973, WHO/ISUP 1998 and WHO 1999 systems were used for tumor grading. Pathologic staging of each case was done according to 1997 TNM system. During evaluation of the slides three main tumor invasion patterns were detected: "nodular", "trabecular" and "infiltrative". In addition, homogeneity or heterogeneity of invasion patterns was also recorded for each case. Of sixty-two invasive cases, 17 (27%) had nodular, 36 (58%) trabecular, and 9 (15%) infiltrative invasion pattern. There was a statistically significant difference between invasion patterns in relation to pathologic stage (pT) (p=0.001), but not to grade. Of the 17 cases with nodular invasion pattern and 36 tumors with trabecular invasion pattern, 13 (77%) and 26 (72%) were pT1, respectively, whereas 8 of 9 infiltrative cases (89%) were advanced stage (pT2-3). According to heterogeneity, forty-two cases (68%) had homogeneous, while the remaining 20 (32%) had heterogeneous invasion pattern. Of the 42 homogeneous cases 34 (81%) were pT1, whereas 14 of 20 heterogeneous cases (70%) were advanced stage (p=0.000). The different invasion patterns seem to have a large impact on pathologic stage, especially the infiltrative pattern. In addition, invasion heterogeneity appears to be of value in determination of biologic aggressiveness in urothelial carcinoma. (Pathology Oncology Research Vol 11, No 2, 87–91)

Key words: urinary bladder, urothelial carcinoma, invasion pattern

Introduction

Stage is the most important prognostic parameter in urinary bladder urothelial carcinoma, and depends on the degree of invasion into the bladder wall.[1,2] Infiltrating urothelial carcinoma is a tumor that invades beyond the basement membrane.[2] Determination of the degree of invasion into the bladder wall may be difficult especially when the cancer is massive and destroying adjacent benign tissues,[3] as well as in the presence of secondary artifactual changes and poor orientation of the specimen.[1,2,4]

The criteria for urothelial carcinoma invasion are: isolated cells or small nests, irregular contours of cell nests, larger cells and cell nuclei, and marked cytoplasmic eosinophilia relative to surface epithelium.[2,5-7] Stromal desmoplasia and inflammatory stromal response may help to recognize invasion.[2,6] However, awareness of the histologic spectrum of lamina propria invasion enhances the pathologist's ability to recognize early invasion.[2,5] Tumors invading the lamina propria may be classified morphologically according to five patterns: carcinoma in situ with microinvasion, papillary urothelial carcinoma with microinvasion, invasion into the stalk, well-established invasion into underlying lamina propria, and endophytic or broad front growth pattern. An awareness of these patterns of lamina propria invasion permits the identification of invasion, even if it is focal.[2,5] Although no correlation has been reported between the invasion pattern and survival,[7] in some reports it has been noted that the invasion pattern is clinically important.[4,8] In general, a broad front invasion has a more favorable prognosis than tentacular invasion,[4,8,9] whereas an infiltrating growth pattern is associated with poorer prognosis,[10] and has a higher frequency of recurrence in contrast to other growth patterns.[11] According to the study of Jimenez

Received: Febr 22, 2005; *accepted:* March 10, 2005

Correspondence: Sema BIRCAN, MD, Suleyman Demirel Universitesi Tip Fakültesi, Patoloji Anabilim Dali, Isparta, Turkey;
E-mail: bircans2000@yahoo.com

© 2005 Arányi Lajos Foundation

et al.,[11] "infiltrative" pattern was associated with lower survival rate compared with tumors without an infiltrative pattern, but the difference was not statistically significant.

On the other hand, tumor heterogeneity is an important point, which may affect the outcome of the disease. Urothelial carcinoma of the bladder often contains different histologic grades within the same tumor, although the present grading systems does not take this into consideration, and the worst pathological grade is reported. However, according to Cheng[12] and Billis et al.,[13] grading that takes cancer heterogeneity into consideration allows stratification of patients into different prognostic groups, and seems to be of value in prediction of prognosis. On the other hand, pathologic staging also does not take tumor heterogeneity into consideration, and final stage is based on the deepest invasion. The influence of invasion pattern heterogeneity on stage is uncertain. In this study, we aimed to investigate the effect of different invasion patterns and the influence of invasion heterogeneity on histopathological features and pathologic stage in invasive urothelial carcinoma of the bladder. To our knowledge, there has not been such study in the literature.

Materials and methods

We studied 62 patients who underwent TUR and radical cystectomy. Histopathologically all cases were invasive urothelial carcinomas, randomly selected from routine archival material. All histologic slides obtained from neutral formalin-fixed, paraffin-embedded blocks were reviewed retrospectively. For tumor grading, we used three reported grading systems separately: WHO 1973,[14] WHO/ISUP 1998[6] and WHO 1999[15] systems. According to WHO 1973 grading system, carcinoma cases are subdivided into grade 1, 2 and 3. In the WHO/ISUP 1998 system, they are classified as papillary urothelial neoplasms of low malignant potential (PUNLMP), and low-grade (LG) and high-grade (HG) carcinomas. In WHO 1999 grading system HG carcinomas are subdivided into grades 2 and 3. Thus, LG and HG carcinomas of WHO/ISUP 1998 system correspond to LG-1, HG-2 and HG-3 carcinoma groups in WHO 1999 system, respectively. Staging of each case was done according to the 1997 TNM staging system:[16] T1 – the tumor invades subepithelial connective tissue; T2 – the tumor invades the muscularis propria; and T3 – the tumor invades perivesical tissue. During the process of reviewing of the slides, three main architectural patterns of tumor invasion were determined histologically according to Jimenez et al.[11] "Nodular" invasion pattern was composed of mostly well-formed, rounded nests of tumor cells. The tumor nests varied in diameter, but their roundness was maintained overall (*Figure 1*). "Trabecular" invasion pattern consisted of infiltrating broad trabeculae, which usually anastomosed with each other. The trabeculae were at least three cells thick (*Figure 2*). "Infiltrative" invasion pattern was composed of infiltrating narrow cords or single cells (*Figure 3*). A major invasion pattern was record-

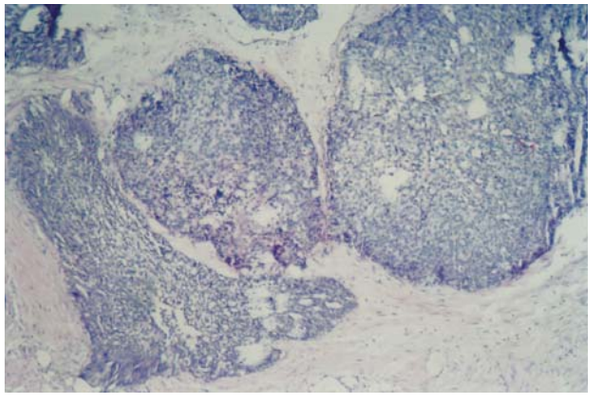

Figure 1. *"Nodular" invasion pattern, well-formed, rounded nests of tumor cells invading the stroma of the bladder wall (HE; x40).*

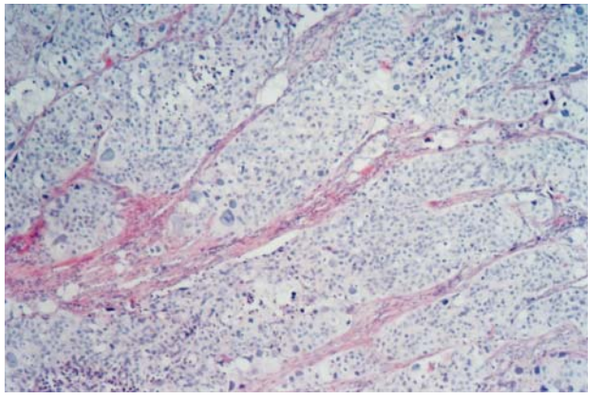

Figure 2. *"Trabecular" invasion pattern consisting of anastomosing broad, infiltrative trabeculae of tumor cells (HE; x40).*

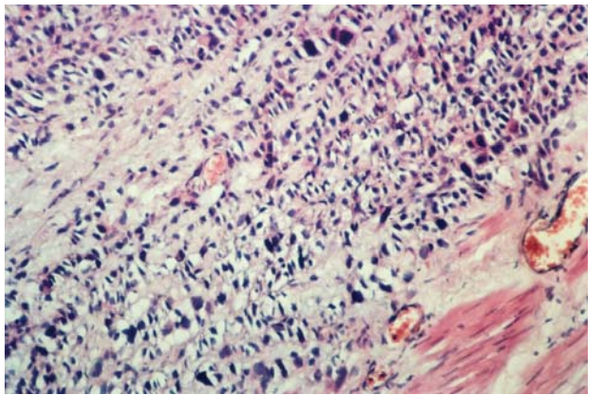

Figure 3. *"Infiltrative" invasion pattern, pleomorphic single cells or narrow cords invading the bladder wall (HE; x100)*

Table 1. **The association between pathologic stage and invasion patterns**

	Pathologic stage					
	pT1		*pT2-3*			
Invasion	*n*	*(%)*	*n*	*(%)*		
Nodular	13	(77)	4	(23)	n=17	p=0.001
Trabecular	26	(72)	10	(28)	n=36	
Infiltrative	1	(11)	8	(89)	n=9	
Homogeneous	34	(81)	8	(19)	n=42	p=0.000
Heterogeneous	6	(30)	14	(70)	n=20	

ed for each case that displayed more than one pattern; in addition, homogeneity and heterogeneity of invasion patterns were also recorded. Data were analyzed with Pearson's chi-square and Fisher's exact tests; values of $p<0.05$ were considered significant.

Results

Sixty-two urothelial carcinomas were distributed as 32 (52%) grade 2 and 30 (48%) grade 3; 9 (15%) LG and 53 (85%) HG; and 9 (15%) LG-1, 23 (37%) HG-2 and 30 (48%) HG-3 carcinomas according to WHO 1973, WHO/ISUP 1998 and WHO 1999 grading systems, respectively. Forty cases (65%) invaded lamina propria (pT1), and 22 cases (35%) were pathologic stage 2 and 3. Of these 62 invasive cases, 17 tumors (27%) had a nodular infiltration pattern, 36 (58%) had a trabecular pattern and 9 (15%) had an infiltrative pattern. Statistical analyses showed that there was a significant difference between invasion patterns in relation to pathologic stage (pT) (p=0.001), but there was no such association between invasion patterns and grades according to any of the grading systems (p>0.05) (*Table 1, 2*). Of the 17 tumors with nodular invasion pattern and 36 tumors with trabecular invasion pattern, 13 (77%) and 26 (72%) were pT1, respectively, whereas 8 of 9 (89%) infiltrative cases were advanced stage (pT2-3). Considering homogeneity, 42 cases (68%) had homogenous and 20 (32%) had heterogeneous invasion pattern. There was a statistically significant association between pathologic stage and heterogeneity/homogeneity. Of the 42 homogeneous cases, 34 (81%) were pT1, whereas 14 (70%) of 20 heterogeneous cases were advanced stage (p=0.000).

Discussion

Histopathologic features of urothelial carcinoma of the bladder have prognostic significance. Recognition of invasion and of its level of penetration into the bladder wall forms the basis of pathologic staging and patients' therapy.[1,2,5] Staging depends on the pathologic examination, the presence or absence of invasion to lamina propria and muscle wall, and extravesical extension. However, determination of the degree of invasion into the bladder wall may be difficult when the cancer is massive and destroying adjacent benign tissue, and because of artifactual changes or poor orientation of TUR specimens.[1-4]

Foci of invasion are often single and solid, but may be mixed with other growth patterns such as endophytic or broad front growth.[2,4,5,9] Single cells or irregular nests within the stroma, and sometimes tentacular or finger-like extensions can be seen at the base of the papillary tumor.[2] Commonly, there are nests and small clusters of cells that irregularly infiltrate the bladder wall and elicit a stromal fibrous response. Conversely, there may be solid diffuse growth with little intervening stroma.[4] The pattern of growth has clinical importance; broad front invasion is associated with a more favorable prognosis than tentacular invasion,[4,8,9] whereas an infiltrative pattern of growth is associated with poorer prognosis.[10] The study of Jimenez et al.[11] displayed that any degree of "infiltrative" pattern had a higher frequency of recurrence in contrast to nodular or trabecular patterns. The presence of any infiltrative pattern in the tumor was associated with a median survival of 29 months, compared with 85 months in tumors without an infiltrative pattern (p=0.006). However, Mazzucchelli et

Table 2. **The association between invasion patterns and grades**

		Nodular		*Trabecular*		*Infiltrative*			
		n=17	*(%)*	*n=36*	*(%)*	*n=9*	*(%)*	*n=62*	*(%)*
WHO 73	Grade 2	12	(71)	18	(50)	2	(22)	32	(52)
	Grade 3	5	(29)	18	(50)	7	(78)	30	(48) p=0.061
WHO 98	LG	5	(29)	3	(8)	1	(11)	9	(15)
	HG	12	(71)	33	(92)	8	(89)	53	(85) p>0.05
WHO 99	LG-1	5	(29)	3	(8)	1	(11)	9	(15)
	HG-2	7	(41)	15	(42)	1	(11)	23	(37)
	HG-3	5	(30)	18	(50)	7	(78)	30	(48) p=0.077

al.[7] analyzed 70 patients with invasive carcinoma, and found that neither the grade, growth pattern (infiltrating versus expanding) or vascular invasion had any consistent effect on survival, and the depth of invasion was an independent prognostic factor. The growth pattern was called "expanding" when the invasive margin was pressing on adjacent tissue but the tumor had a circumscribed border, and "infiltrating" when the tumor had invaded smooth muscle and perivesical tissue and had poorly circumscribed border. However, they did not found correlation between this variable and clinical outcome. On the other hand, in tissues removed transurethrally even in radical cystectomy specimens, assessment of the growth pattern was difficult because both patterns were frequently seen in different areas of the same tumor. In our study on 62 invasive urothelial carcinomas we found an association of invasion patterns with pathologic stage, but not with grade. Tumors with infiltrative pattern had more advanced stage (pT2-3) than those with nodular and trabecular invasion patterns. These findings suggest that the influence of infiltrative invasion pattern on pathologic stage is more important in comparison to nodular or trabecular patterns. Not only the depth of invasion into the bladder wall but also invasion patterns seem to have an effect on tumor stage.

Urothelial carcinomas of the bladder are often heterogeneous tumors and contain different histologic grades within the same tumor. Cheng et al.[12] and Billis et al.[13] found different primary and secondary grades in 32% of 52 patients and 28% of 81 patients, respectively. According to these studies, approximately one-third of patients with pTa urothelial carcinoma had cancer containing more than one histologic grade. They suggested that the grading of urothelial carcinoma that takes cancer heterogeneity into consideration allows precise stratification of patients into different prognostic groups. On the other hand, the influence of invasion pattern heterogeneity on stage is uncertain, and final stage is based on the deepest invasion. Pathologic staging system does not take invasion heterogeneity of bladder carcinomas into consideration. In this study, we found that there was a difference between homogeneous and heterogeneous invasion patterns. In contrast to homogeneous cases, those with heterogeneous invasion pattern were advanced stage diseases. According to this finding, more than one invasion pattern in the same tumor may show the possibility of advanced stage disease or the biologic aggressiveness of the tumor.

The presence or absence of invasion of the muscularis propria is the most crucial information for making therapeutic decisions. In assessing invasion it is important to recognize whether smooth muscle bundles represent muscularis mucosae or muscularis propria. Therefore, all of the material of TUR specimens received should be processed for histological examination.[1,6] Clinicians have divided urothelial carcinomas into superficial and invasive categories for a long time. Because of misinterpreted use of these terms, and a higher recurrence and metastatic potential of pT1 tumors, the TNM staging system is recommended.[1,5] Several studies have investigated the issue of substaging pT1 urothelial carcinomas,[9,17-19] most of them using the muscularis mucosa as an anatomic landmark to assess the depth of invasion in pT1 tumors. Cheng et al[17,18] proposed a novel approach of substaging based on the micrometric measurement of invasion. A 1.5 mm depth of invasion in TUR specimens predicted cancer progression and advanced stage of disease. In another study, the same authors[3] found that tumors with a depth of invasion greater than 4 mm in the TUR specimens were likely to have extravesical extension, and more aggressive treatment should be considered in these cases.

In conclusion, according to the results of the current study there is a relationship between pathologic stage and invasion pattern and its heterogeneity. In urothelial carcinomas of the bladder, the different invasion patterns seem to have a large impact on pathologic stage, especially the infiltrative pattern. Not only the depth of invasion but also the invasion pattern seems to have an effect on the stage of the tumor. In addition, invasion heterogeneity appears to be of value in determining biologic aggressiveness in urothelial carcinomas. The pathology reports should include both the subtype of invasion pattern and its heterogeneity or homogeneity.

References

1. *Lapham RL, Grignon D, Ro JY:* Pathologic prognostic parameters in bladder urothelial biopsy transurethral resection, and cystectomy specimens. Semin Diagn Pathol 14: 109-122, 1997
2. *Lopez-Beltran A, Cheng L:* Stage pT1 bladder carcinoma: diagnostic criteria, pitfalls and prognostic significance. Pathology 35: 484-491, 2003
3. *Cheng L, Weaver AL, Bostwick DG:* Predicting extravesical extension of bladder carcinoma: A novel method based on micrometer measurement of the depth of invasion in transurethral resection specimens. Urology 55: 668-672, 2000
4. *Bostwick DG, Mikuz G:* Urothelial papillary (exophytic) neoplasms. Virchows Arch 441: 109-116, 2002
5. *Amin MB, Gomez JA, Young RH:* Urothelial transitional cell carcinoma with endophytic growth patterns: A discussion of patterns of invasion and problems associated with assessment of invasion in 18 cases. Am J Surg Pathol 21: 1057-1068, 1997
6. *Epstein JI, Amin MB, Reuter VR, et al:* The Bladder Consensus Conference Committee. The World Health Organization/International Society of Urological Pathology Consensus Classification of Urothelial (Transitional Cell) Neoplasms of the Urinary Bladder. Am J Surg Pathol 22: 1435-1448, 1998
7. *Mazzucchelli L, Bacchi M, Studer UE, et al:* Invasion depth is the most important prognostic factor for transitional cell carcinoma in a prospective trial of radical cystectomy and adjuvant chemotherapy. Int J Cancer 57: 15-20, 1994
8. *Farrow GM, Utz DC:* Observations on microinvasive transitional cell carcinoma of the urinary bladder. Clin Oncol 1: 609-615, 1982

9. *Bostwick DG, Ramnani D, Cheng L:* Diagnosis and grading of bladder cancer and associated lesions. Urol Clin North Am 26: 493-507, 1999
10. *Mostofi FK:* Pathology and spread of carcinoma of the urinary bladder. In: Cancer of the Genitourinary Tract. (Eds: Johnson DE, Samuels ML), Raven, New York, 1979, pp 303-308
11. *Jimenez RE, Gheiler E, Oskanian P, et al:* Grading the invasive component of urothelial carcinoma of the bladder and its relationship with progression-free survival. Am J Surg Pathol 24: 980-987, 2000
12. *Cheng L, Neumann RM, Nehra A, et al:* Cancer heterogeneity and its biologic implications in the grading of urothelial carcinoma. Cancer 88: 1663-1670, 2000
13. *Billis A, Carvalho RB, Mattos AC, et al:* Tumor grade heterogeneity in urothelial bladder carcinoma: Proposal of a system using combined numbers. Scand J Urol Nephrol 35: 275-279, 2001
14. *Mostofi FK, Sobin LH, Torloni H:* Histological typing of urinary bladder tumours. International Histological Classification of Tumours, No. 10. Geneva, Switzerland, World Health Organization, 1973
15. *Busch C, Algaba F:* The WHO/ISUP 1998 and WHO 1999 systems for malignancy grading of bladder cancer. Scientific foundation and translation to one another and previous systems. Virchows Arch 441: 105-108, 2002
16. *Sobin LH, Wittekind C:* International Union Against Cancer (UICC). TNM Classification of Malignant Tumours. 5th ed. New York: Wiley-Liss, 1997, pp187-190
17. *Cheng L, Neumann RM, Weaver AL, et al:* Predicting cancer progression in patients with stage T1 bladder carcinoma. J Clin Oncol 17: 3182-3187, 1999
18. *Cheng L, Weaver AL, Neumann RM, et al:* Substaging of T1 bladder carcinoma based on the depth of invasion as measured by micrometer: A new proposal. Cancer 86: 1035-1043, 1999
19. *Smits G, Schaafsma E, Kiemeney L, et al:* Microstaging of pT1 transitional cell carcinoma of the bladder: Identification of subgroups with distinct risks of progression. Urology 52: 1009-1014, 1998