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Research Article

Prognostic Significance of Tumor Budding in Urothelial Carcinomas of the Bladder: Comparison of Two Different Tumor Budding Evaluation Methods

Mesanenin Ürotelyal Karsinomlarında Tümör Tomurcuklanmasının Prognostik Önemi: İki Farklı Tümör Tomurcuklanma Değerlendirme Yönteminin Karşılaştırılması

Irfan Ocal, Ismail Guzelis

Izmir Katip Celebi University, Ataturk Training and Research Hospital, Department of Pathology, Izmir, Turkey

Abstract

Aim: In our study, we aimed to reveal the effect of tumor budding(TB) on prognosis in urothelial carcinomas and to compare the most commonly used alternative method (AM) and the International Tumor Budding Consensus Conference (ITBCC) system. TB can be easily assessed on routine hematoxylin and eosin-stained slides. In studies, TB was found to be associated with prognostic parameters in many organs. TB assessment in many organ cancers is based on ITBCC or alternatively different values used by different authors.
Material and Method: Forty-eight urothelial cancers were obtained from 2010 to 2016 that was comprised of those having undergone surgical staging with a cystectomy or cystoprostatectomy and at least 5 years followed up. All hematoxylin and eosin-stained slides were re-evaluated for the status of TB according to ITBCC and AM.
Results: According to ITBCC TB was not correlated with pT, lymphovascular invasion, lymph node involvement (LNI), tumor stage and 5-year mortality (p=0.102, p=0.722, p=0.165, p=0.431, p=0.524). According to AM, TB was more frequent as pT advanced, and was marginally associated with LNI (p=0.027, p=0.058). There was no relationship between TB and overall survival (p=0.130).
Conclusion: We found the cut-off value in AM more useful than ITBCC recommendations. Although the association of TB with some of the prognostic parameters suggests that it may also be associated with prognosis, no relationship was found with overall survival. This may be related to the number of our cases.

Keywords: Tumor budding, bladder, urothelial carcinoma

Öz

Giriş: Çalışmamızda ürotelyal karsinomlarda tümör tomurcuklanmasının (TT) prognoza etkisini ortaya koymayı ve en sık kullanılan alternatif metod (AM) ile Uluslararası Tümör Tomurcuklanması Konsensus Konferans (ITBCC) sistemini karşılaştırmayı amaçladık.TT, rutin Hematoksilen&Eozin boyalı preparatlarda kolayca değerlendirilebilmektedir. Yapılan çalışmalarda TT'nin birçok organ kanserinde prognostik parametrelerle ilişkili olduğu bulunmuştur. TT değerlendirmesi, birçok organ kanserinde ITBCC'ye veya alternatif olarak farklı yazarlar tarafından kullanılan farklı değerlere dayanmaktadır.
Materyal ve Methot: Çalışmaya 2010'dan 2016'ya kadar, sistektomi veya sistoprostatektomi ile cerrahi evreleme yapılan ve en az 5 yıl takip edilen vakalardan oluşan kırk sekiz ürotelyal kanser dahil edildi. Tüm hematoksilen ve eozin boyalı preparatlar, ITBCC ve AM'ye göre TT durumu açısından yeniden değerlendirildi.
Bulgular: ITBCC'ye göre TT, pT, lenfovasküler invazyon, lenf nodu tutulumu(LNT), tümör evresi ve 5 yıllık mortalite ile korele değildi (p=0.102, p=0.722, p = 0.165, p=0.431, p=0.524). AM'ye göre, TT, pT ilerledikçe daha sıktı ve LNT ile marjinal olarak ilişkiliydi (p=0.027, p=0.058). TT ile genel sağkalım arasında ilişki yoktu (p=0.130).
Sonuç: Çalışmamızda AM'deki eşik değeri ITBCC önerisinden daha faydalı bulduk. TT'nin bazı prognostik parametrelerle ilişkisi prognozla da ilişkili olabileceğini düşündürse de, genel sağkalım ile bir ilişki bulunamadı. Bu durum vaka sayımızla ilgili olabilir.

Anahtar Kelimeler: Tümör tomurcuklanması, mesane, ürotelyal kanser

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Corresponding Author: Irfan Ocal, Izmir Katip Celebi University, Ataturk Training and Research Hospital, Department of Pathology, Izmir, Turkey, Turkey, **E-mail**: drirfanocal@hotmail.com

INTRODUCTION

Bladder cancer is the most common urinary tract cancer and the thirteenth most mortal of malignant neoplasms (1). Urothelial carcinoma is the most frequent cancer type of bladder and is characterized by a propensity of divergent differentiation. Stage, grade, angiolymphatic invasion, and presence of some histological variants such as poorly differentiated and small cell differentiation are important prognostic parameters (2). According to the International Tumor Budding Consensus Conference (ITBCC) tumor budding (TB) is an isolated single tumor cell or non-glandular small cancer cell cluster with less than 5 cells in front of the invasive margin (3). TB can be easily assessed on routine Hematoxylin&Eosin-stained slides. In studies, TB was found to be associated with prognostic parameters in colorectal, endometrial, laryngeal, and esophageal carcinomas (4-9). TB assessment in many organ cancers is based on ITBCC or alternatively different values used by different authors (3-9). ITBCC recommends the triple assessment system with 1-4 buds as Bd1, 5-9 buds as Bd2, 10 and above buds as Bd3. In the alternative method (AM) used in most of the studies that are not based on ITBCC, the presence of 5 buds or more is assessed as TB, and the presence of fewer than 5 buds as no TB (8-10). There is a limited number of studies that have been conducted on TB in bladder cancer (10-15). Therefore, there is no consensus on how to evaluate TB in urothelial carcinomas of the bladder, and the ITBCC system has never been studied in bladder cancer. In our study, we aimed to reveal the effect of TB on prognosis in urothelial carcinomas and to compare the most commonly used AM and ITBCC system.

MATERIAL AND METHOD

A retrospective review of all cases of bladder urothelial carcinoma diagnosed at the Izmir Kâtip Celebi University Ataturk Training and Research Hospital from January 2010 through January 2016 was carried out. The patients included in the study were comprised of those having undergone surgical staging with a cystectomy or cystoprostatectomy and at least 5 years followed up.

Parameters such as patient demographics, tumor grade, histological type, lymph node status, and follow-up data were gathered from our medical records. Tumors were classified according to histological typing and surgical staging described in the WHO 2016 classification system (2).

Overall survival data were gathered from The Death Notification Service. All patients were followed up, and the median follow-up period was 14 months. The study approval was obtained from the institutional review board at Izmir Kâtip Celebi University medical faculty (2021-GOKAE-0116).

Histopathological Analysis

All available hematoxylin and eosin (H&E) stained sections of tumoral tissue (median 14 slides) were collected from the archive. All slides were re-examined by an expert pathologist (I.O.) and a pathology resident (I. G.), who were blind to the clinical outcomes, in an attempt to evaluate tumor budding. Cases called TB by two observers were considered TB positive.

Tumor budding was defined as an isolated single cancer cell or small cell clusters composed of <5 tumor cells found in the invasive margin. To assess TB in surgical resection specimens, 10 fields in the invasive margins had been scanned and tumor buds had been counted in the selected hotspot area (20xobjective, Olympus BX-50) (Figure 1). According to ITBCC, TB positive cases were grouped as 0-4 buds low budding (Bd 1), 5-9 buds medium budding (Bd 2), and 10 or more buds high budding (Bd 3) (3). According to AM, the presence of 5 buds or more was evaluated as TB, while the presence of fewer than 5 buds was evaluated as as no TB.

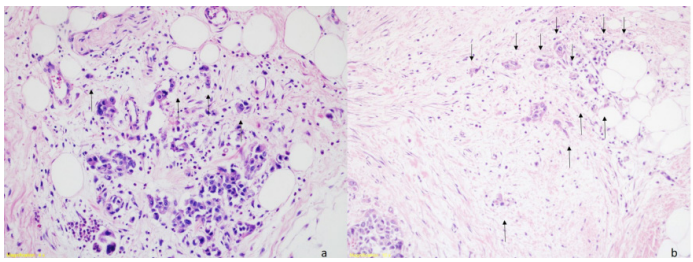

Figure 1. Example of tumor budding that is defined as single tumor cells or tumor cell clusters at up to four cells (a-b, on 20x magnification)

Statistical analysis

Statistical analysis was conducted by Jamovi (version 1.2). The comparison of the groups and the relationship between tumor budding and the other parameters were investigated using non-parametric tests, such as the Kruskal-Wallis test, Pearson's Chi-square test, and Mann–Whitney U test. Survival analyses were calculated using the Kaplan–Meier method. The Log-rank test was used for univariate analysis, while Cox proportional hazard regression (HR) models were performed for multivariate analysis. The probability level of 0.05 or less was chosen to represent statistical significance.

RESULTS

Patients features

A total of 48 patients with invasive urothelial carcinoma were included in the study. The clinicopathological characteristics of the patients are shown in table 1. The median age was found to be 61. Five cases with nested pattern, two cases with squamous differentiation, and one case with sarcomatoid differentiation were seen.

Based on WHO 2016 grading system, all tumors were histologically graded as high grade. Seven patients (15%) were present with pT1, 12 (25%) with pT2, 22 (46%) with pT3, and 7 (15%) with pT4 according to WHO TNM classification of carcinomas of the urinary bladder. Lymph

node involvement (LNI) was present in 13 patients (27%), while 5 cases with N1, 5 cases with N2, and 3 cases with N3. Five patients were stage I (10%), 11 patients were stage II (23%), 30 patients were stage III (62%), and 2 patients were stage IV (4.2%).

pT stage and TNM staging was associated with overall survival (OS) (p=0.00027, p<0.001). LVI was not associated with OS (p=0.24). A total of 40 patients (83.33%) died during follow-up, 39 of them within the first 5 years after surgery. LNI was found to worsen overall survival (OS) (p=0.026).

Table 1. Clinicopathologic caracteristics of the patients

Feature (N=48)	Frequency N(%) or mean (SD)
Operation Age (mean (SD)	63(8.01)
Sex	
Male	47(97.9%)
Female	1(2.1%)
pT	
1	7(14.6 %)
2	12(25%)
3	22(45.8%)
4	7(14.6 %)
Lymph node involvement	
Absent	35(72.9%)
Present	13(27.1%)
pN	
0	35(72.9 %)
1	5(10.4%)
2	5(10.4%)
3	3(6.3%)
Stage	
I	5(10.4%)
II	11(22.9%)
III	30(62.5%)
IV	2(4.2%)
TB according to ITBCC	
Low	29(60.4%)
Mild	5(10.4%)
High	14(29.2%)
TB according to AM	
Absent	29(60.4%)
Present	19(39.6%)
Lymphovascular invasion	
Absent	35(72.9%)
Present	13(27.1%)
N is the number of non-missing value	

Tumor Budding based on the International Tumor Budding Consensus Conference

The relationship between TB and clinicopathological features is shown in table 2.

TB was not correlated with pT, LVI, LNI, tumor stage and 5-year mortality (p=0.102, p=0.722, p=0.165, p=0.431, p=0.524).

Table 2. Clinicopathological features associated with Tumor Budding Based on the International Tumor Budding Consensus Conference

	N	Bd1	Bd2	Bd3	Test Statistic
	48	**29**	**5**	**14**	
pT	**48**				**P=0.102**
1		24.1%	0.0%	0.0%	
2		31.0%	20.0%	14.2%	
3		31.0%	80.0%	64.2%	
4		13.7%	0.0%	21.4%	
Lymphovascular invasion	**48**	**27.5%**	**40%**	**21.5%**	**P=0.722**
Lymph node involvement	**48**	**17.3%**	**42.9%**	**40.0%**	**P=0.165**
pN	48				P=0.132
N0		82.7%	57.1%	60.0%	
N1		6.8%	14.2%	20.0%	
N2		10.3%	7.3%	20.0%	
N3		0.0%	21.4%	0.0%	
Stage	**48**				**P=0.431**
I		17.2%	0.0%	0.0%	
II		27.5%	20.0%	14.2%	
III		51.7%	80.0%	78.5%	
IV		3.4%	0.0%	7.1%	
5-year mortality	48	79.3%	80.0%	92.8%	P=0.524
N is the number of non-missing value. TB=Tumor Budding					

Tumor Budding Based on the Alternative Method

The relationship between TB and clinicopathological features is shown in table 3.

Table 3. Clinicopathological features associated with Tumor Budding Based on the Alternative Method

	N	No TB	TB	Test Statistic
		29	**19**	
ptgroups	**48**			**P=0.027**
1		24.1%	0.0%	
2		31.0%	15.7%	
3		31.0%	68.4%	
4		13.7%	15.7%	
Lymphovascular invasion	**48**	**27.6%**	**26.4%**	**P=0.923**
Lymph node involvement	**48**	**17.3%**	**42.2%**	**P=0.058**
pN	48			P=0.093
N0		82.7%	57.8%	
N1		6.8%	15.7%	
N2		10.3%	10.5%	
N3		0.0%	15.7%	
Stage	**48**			**P=0.143**
I		17.2%	0.0%	
II		27.5%	15.7%	
III		51.7%	78.9%	
IV		3.4%	5.2%	
5-year mortality	48	79.3%	89.4%	P=0.356
N is the number of non-missing value. TB=Tumor Budding				

TB was not associated with LVI, stage, and the clinical outcome (p=0.722, p=431, p=0.248). TB was more frequent as pT advanced (p=0.027). It was revealed that TB was marginally associated with LNI (p=0.058). According to the absence or presence of TB, the median survival was 16 months and 10 months, respectively. Statistically, there was no relationship found between TB and overall survival (p=0.130).

DISCUSSION

Bladder cancer is the most common urinary tract cancer and the thirteenth most mortal of malignant neoplasms (1). Urothelial carcinoma is the most frequent cancer type of bladder and is characterized by a propensity of divergent differentiation. Stage, grade, angiolymphatic invasion, and presence of some histological variants such as poorly differentiated and small cell differentiation are important prognostic parameters (2).

There have been limited studies on TB in bladder cancer and there is no consensus to evaluate TB (10-15). TB cut-off values in bladder urothelial carcinoma change according to the studies. In Brieu et al. each tumor bud, in Kucuk et al. 5 tumor buds, in Seker et al. and Raventós Busquets et al. 6 tumor buds, in Fukumoto et al. 10 tumor buds and in Lorenzo Soriano et al. 14 tumor buds cut-offs were used (10-15). In this study, ITBCC recommendations and most used AM were followed (3,8-10). TB was significantly associated with pT as Seker et al. and Brieu et al. (11-12). While TB was found to be associated with LVI in the study of Seker et al., Raventós Busquets et al., and Fukumato et al., it was unrelated in our study and Kucuk's study (10, 12-14). While TB was statistically significant with LNI in Lorenzo Soriano et al., in this study as Seker et al., was found to be marginally significant (12,15).

The evaluation of TB in many organ cancers is based on ITBCC and different cut-off values used by different authors (3-9). In our study, we evaluated TB in urothelial carcinomas according to ITBCC and the cut-off value most commonly used in alternative methods (3,8-10).

CONCLUSION

While according to ITBCC recomendations, TB was insignificant with prognostic parameters, in AM TB was found to be associated with pT and marginally significant with lymph node involvement suggesting that TB may also be associated with a worse prognosis in urothelial carcinomas. Therefore, we found the cut-off value in AM more useful than ITBCC recomendations.

In our study, although overall survival decreased in the presence of TB, no relationship was found between TB and overall survival. This may be due to the relatively small number of cases in our study. Therefore, studies with larger case series are needed on this subject.

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Conflict of Interest: *The authors declare that they have no competing interest.*

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