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THE EFFECTS OF HISTOLOGICAL GRADE RATIO ON THE PROGRESSION OF HIGH-GRADE NON-MUSCLE INVASIVE BLADDER TUMORS

Yüksek Dereceli Kasa İnvaze Olmayan Mesane Tümörlerinde Histolojik Derecelendirme Oranının Progresyona Etkisi

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The present study was granted approval by Namık Kemal University Faculty of Medicine Non-Interventional Clinical Trials Ethics Committee (approval no. 2018/118/08/09).

Abstract

Aim: Histopathological classification is one of the main prognostic factors for non-muscle invasive bladder tumors (NMIBT). We evaluated the relationship between tumor progression and the ratio of high-grade differentiation plus other routine pathological parameters in NMIBT.

Materials and Methods: Ninety-two patients diagnosed with high grade NIMBT were analyzed between 2010-2018. Demographic information, tumor size, localization, multicentricity, and recurrence/progression situation were evaluated retrospectively. The high/low grade percentage ratio of tumor cells, tumor stage, differentiation, necrosis, lamina-propria invasion, lymphovascular invasion, and carcinoma in-situ presence were also examined by two uro-pathologist. The effect on tumor progression was evaluated with pathological findings.

Results: Seventy-four (80.4%) of the patients were reported as T1 and 18 (19.6%) as Ta. The mean ratio of high-grade findings was 11.9±8.5% and 69.5±28.1% for Ta and T1 patients, respectively(p<0.001). Three levels for classification of high degree ratio were determined as 25%, 50% and 75%. The number of patients with high degree ratio >25%, >50% and >75% was found to be 67(72.8%), 54(58.7%) and 43(46.7%), respectively. The high-grade ratio for >25% was in only 1 Ta patient while it was in 66 of the T1 patients(p<0.001). Forty-three patients (58.1%) in the T1 group were found to have a high-grade ratio >75%(p<0.001). Rate of progression was statistically higher in T1 patients with high-grade ratio greater than >50%(p=0.025).

Conclusion: When evaluating the nuclear grade, defining tumors solely as high-grade leads to stratifying a highly heterogeneous population in a single group. Higher rate of progression is observed in NIMBT patients with high-grade ratio >50%.

Keywords: Bladder, urothelial carcinoma, high-grade, progression, transurethral resection.

Öz

Amaç: Histopatolojik sınıflama kasa invaze olmayan mesane tümörleri (KİOMT) için ana prognostik faktörlerden biridir. Çalışmamızda KİOMT'de yüksek dereceli hücresel farklılaşma oranı ve diğer rutin patolojik parametrelerin progresyona etkisi değerlendirildi.

Materyal ve Metot: Çalışmaya 2010-2018 yılları arasında transüretral mesane rezeksiyonu sonrası yüksek dereceli KİOMT tanısı alan 92 hasta dahil edildi. Hastaların demografik bilgileri, tümör çapı, lokalizasyonu, multisantrisitesi ve nüks/progresyon varlığı-süresi retrospektif olarak değerlendirildi. Ayrıca tümör hücrelerinin yüksek derece/düşük derece yüzdesi, tümör evresi, diferansiyasyon, nekroz, lamina propria invazyonu, lenfovasküler invazyon ve karsinoma in-situ varlığı iki üro-patolog tarafından incelendi. Elde edilen bulguların tümör progresyonu üzerine etkisi araştırıldı.

Bulgular: Hastaların 74'ü(%80,4) T1, 18'i(%19,6) Ta olarak rapor edildi. Ta tanılı hastalarda yüksek derece oranı %11,9±8,5 iken, T1'lerde %69,5±28,1 olarak tespit edildi (p<0.001). Sınıflama yapılabilmesi amacıyla, patoloji spesimenlerindeki yüksek derece oranları; %25, %50 ve %75 olacak şekilde 3 cut-off seviye belirlendi. Tüm çalışma grubunda yüksek derece oranı>%25,>%50 ve>%75 olan hasta sayısının sırasıyla 67(%72,8), 54(%58,7) ve 43(%46,7) olduğu görüldü. Ta olan hastaların sadece 1'inde yüksek derece oranı>%25 olarak gözlenirken, T1 hastalarının 66'sında yüksek derece oranının>%25 olduğu belirlendi (p<0.001). T1 hastalarının 43'ünde (%58,1) ise yüksek derece oranının>%75 olduğu görüldü. T1 yüksek derece oranları>%50 olan hastalarda progresyon, patolojik evresi T1 yüksek derece oranları <%50 olan hastalara göre istatistiksel olarak anlamlı derecede yüksek bulundu (p=0.025).

Sonuç: KİOMT'lerde nükleer derece değerlendirilirken tümöre sadece yüksek dereceli demek, çok heterojen olan büyük bir grubu tek başlık altında toplamamıza neden olmaktadır. KİOMT'lerde yüksek derece oranları>%50 olan hastalarda progresyon anlamlı derecede artmaktadır.

Anahtar Kelimeler: Mesane, ürotelyal karsinom, yüksek derece, progresyon, transüretral rezeksiyon.

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INTRODUCTION

Urothelial carcinoma (UC) is the most common tumor of the bladder[1]. Approximately 75-80% of UCs are initially non-muscle invasive; however, about one third of these cases become muscle-invasive during the follow-up[2]. In this regard, the main problem lies in predicting which non-muscle invasive bladder tumors (NMIBT) may progress to invasive cancer. Although histopathological features as well as genetic and molecular factors are associated with progression, these fail to fully explain the risk of progression. Tumor size, number of tumors, pathological stage, nuclear grade and presence of carcinoma in situ are the most important prognostic factors to determine the risk of disease recurrence and progression in patients with NMIBT[4]. There is a substantially high risk of progression in patients with T1-stage disease, high nuclear grade, carcinoma in situ, multicentricity and a tumor diameter greater than 3 cm[5]. Clinicians perform transurethral resection (TUR) in patients with NMIBT and choose different intracavitary treatment modalities based on the result of the pathology report. Tumor grade is a prognostic factor as important as tumor stage in non-muscle invasive bladder cancer. The risk of progression and recurrence is higher in high-grade tumors, and more aggressive treatments are preferred in these patients[6]. Despite available treatment methods, some of NMIBT progress to invasive bladder tumors. Therefore, prediction of tumor progression is of great importance[5]. Histopathological grade is one of the main prognostic factors in NMIBT. The 1973 World Health Organization (WHO) classification stratifies bladder tumors into three grades (1, 2 and 3) according to cell differentiation and the clinical course. The subsequent molecular studies have revealed that there are two main pathways in urothelial carcinogenesis, which led to the 2004 WHO/ISUP (WHO/International Society of Urological Pathology) classification that defines bladder cancer as either "low grade" or "high grade" based on histopathology[7,8].

Progression rate of high-grade tumors is significantly higher than that of low-grade tumors. On the other hand, not all bladder tumors are histopathologically homogeneous. It is not uncommon for bladder tumors to have both low- and high-grade properties within the same specimen[7,9,13]. Pathologists do not report this heterogeneity in a standard pathology report. Several pathologists prefer to report the tumor as high-grade, even if only a small percentage is found to exhibit high-grade features[9,11,12,14]. This may result in tumors with different heterogeneity to be categorized in the same class. Evaluating the percentage of low- and high-grade areas may offer prognostic value and may prove to be important in assessing the risk of disease recurrence and progression in NMIBT.

The primary objective of this study is to evaluate the relationship between percentage rate of high-grade differentiation and tumor progression and recurrence in NMIBT. The secondary objective is to compare tumor differentiation, lymphovascular invasion, tumor necrosis and presence of carcinoma in situ versus percentage rate of high-grade differentiation.

MATERIALS AND METHODS

Patients who underwent transurethral bladder tumor resection upon a diagnosis of bladder tumor at the Urology Clinic of Namık Kemal University Faculty of Medicine between 2010-2018, in whom high-grade NMIBT was identified based on pathological evaluation and clinically followed up at our hospital were included in the study. Clinical and follow-up information of the patients were retrieved through a

retrospective evaluation of data files in the hospital information system. Patients' characteristics including age, gender, tumor diameter, tumor localization, tumor multicentricity, duration of follow-up, presence and duration of recurrence, and presence and duration of progression were evaluated retrospectively by reviewing medical records. The protocols recommended in the European Association of Urology (EAU) Guidelines were applied in the treatment and follow-up of patients with bladder tumors. During the pathological evaluation, preparations stained with hematoxylin-eosin (H&E) and immunohistochemical dyes were removed from the archive for all patients diagnosed with non-muscle invasive bladder cancer. All of the stained preparations were re-evaluated by two pathologists using an Olympus CX41 light microscope. Patients with mechanically damaged tumor tissues that could interfere with the pathological examination, those with muscle-invasive urothelial carcinoma, all low-grade urothelial carcinomas and tumors with low malignancy potential were excluded from the study. In the preparations that were examined, percentage of high/low grade features in tumor cells, tumor stage, presence of differentiation, presence of necrosis, presence of lymphovascular invasion, presence of carcinoma in situ and depth of lamina propria invasion were evaluated. Low- and high-grade areas observed in all H&E stained preparations of tumors obtained from the patients were labeled. Tumor grading was based on morphological features (increase in nuclear alignment and crowding, impairment and loss of polarity, increased cellularity, nucleus-chromatin pattern variations, nuclear enlargement and pleomorphism, irregularities in cell size and shape, presence of giant cells and anaplasia, high level of mitosis and presence of abundant mitotic figures). In cases where the two pathologists reported discordant findings, Cytokeratin 7 and Cytokeratin 20 staining features and the Ki-67 ratio were utilized. For each case, percentage of high-grade areas was determined based on the total extent of the carcinoma. The percentage rate of the component was estimated with a measurement method similar to the simplified method (tumor-positive chip/total chip size percentage) we currently use for the evaluation of prostate cancer extent in transurethral resection for prostate cancer[12].

Statistical analyses were performed with SPSS version 20.0. Chi-square test was used for the comparison of categorical data. Statistical significance level was accepted as $p < 0.05$. The present study was granted approval by Namık Kemal University Faculty of Medicine Non-Interventional Clinical Trials Ethics Committee (approval no. 2018/118/08/09).

RESULTS

A total of 92 patients pathologically diagnosed with high-grade non-muscle invasive bladder tumor following transurethral resection during 2010-2018 were included in the study. Mean age of the patients was 67.1±11.3 years. The study cohort consisted of 83 men (90.2%) and 9 women (9.8%), with mean age of 67.0±11.1 and 68.8±13.6 years, respectively. In the pathological evaluation, 74 (80.4%) of the patients were reported as T1 and 18 (19.6%) as Ta. Mean age was 61.2±12.1 years in the Ta group and 68.6±10.7 years in those pathologically classified as T1 (P = 0.013). Mean size of the mass was 27.5±11.2 mm in patients with Ta and 35.2±16.1 mm in those with T1 (p=0.023). Tumor characteristics by pathological grade are shown in Table 1.

Table 1. Evaluation of histopathological variables by tumor stage.

		Ta	T1	P-value
Carcinoma in situ	Yes	0	13	0.047
	No	18	61	
Differentiation	Yes	0	13	0.047
	No	18	61	
Necrosis	Yes	1	25	0.012
	No	17	49	
Lymphovascular invasion	Yes	0	14	0.036
	No	18	60	
Mass size >3 cm	Yes	4	49	**0.001**
	No	14	25	
Mean high-grade ratio		11.9±8.5	69.5±28.1	**<0.001**
High-grade ratio >25%	Yes	1	66	**<0.001**
	No	17	8	
High-grade ratio >50%	Yes	0	54	**<0.001**
	No	18	20	
High-grade ratio >75%	Yes	0	43	**<0.001**
	No	18	31	

The mean ratio of high-grade findings in the specimens was 11.9±8.5% and 69.5±28.1% for Ta and T1 patients, respectively (p<0.001). For classification purposes, 3 cut-off levels were specified for the high-grade ratios in pathological specimens, namely 25%, 50% and 75%. Based on these cut-off values, the ratio of high-grade findings was >25% in 67 patients (72.8%) in the entire study cohort, >50% in 54 patients (58.7%) and >75% in 43 patients (46.7%). Evaluation by pathological stage revealed high-grade ratio >25% in only 1 Ta patient while the high-grade ratio was >25% in 66 of the T1 patients (p<0.001). When the cut-off was taken as >50%, none of Ta patients were found to have high-grade ratio greater than 50% while 54 T1 patients (7.29%) had a high-grade ratio >50% (p<0.001). When the cut-off value of 75% was investigated, 43 patients (58.1%) in the T1 group were found to have a high-grade ratio >75% (p<0.001), on the other hand, none of the patients in the Ta group had a high-grade ratio greater than 75%. In conclusion, high-grade ratios were significantly higher in T1 patients compared to Ta patients at every cut-off level investigated herein.

Since high-grade ratios were low in patients with a pathological stage of Ta, high-grade ratios were compared with carcinoma in situ, cell differentiation, necrosis and presence of lymphovascular invasion in the specimens only in patients pathologically classified as T1. The comparison of high-grade ratios versus carcinoma in situ, cell differentiation, necrosis and presence of lymphovascular invasion in the specimens is shown in Table 2. Presence of carcinoma in situ in patients pathologically classified as T1 was markedly higher in those with high-grade ratio greater than 75%. There was no statistically significant association between cell differentiation and high-grade ratios. Higher rates of tumor necrosis and lymphovascular invasion were observed in patients with high-grade ratio >50% compared to those without. Furthermore, the difference was statistically more significant in patients with high-grade ratio >75%.

Mean duration of follow-up of the patients was 32.6 months (min: 3 months - max: 82 months). Recurrent mass was detected in 39 patients (42.3%) in the entire study cohort. Recurrence was observed in 5 patients (27.7%) with a pathological stage of Ta and in 34 patients (45.9%) classified as T1. There was no correlation between high-grade ratios and recurrence rates in patients pathologically classified as T1. Stage progression was identified in 18 patients (19.5%) in the entire cohort. While 17 patients with stage progression progressed from T1 to T2, 1 patient progressed from Ta to T1. Rate of progression was higher, with a statistically significant difference, in patients with a pathological stage

of T1 and a high-grade ratio greater than 50% compared to those with a pathological stage of T1 and a high-grade ratio lower than 50%. Frequency of recurrence and progression in patients with a pathological stage of T1 by high-grade ratios in corresponding pathology specimens are shown in Table 3.

Table 2: The comparison of high-grade ratios versus carcinoma in situ, cell differentiation, necrosis and presence of lymphovascular invasion

		<25%	>25%	<50%	>50%	<75%	>75%
Carcinoma in situ	**Yes**	0	13	1	12	1	12
	No	8	53	19	42	30	31
p-value		0.167		0.084		**0.006**	
Differentiation	**Yes**	0	13	1	12	4	9
	No	8	53	19	42	27	34
p-value		0.167		0.084		0.371	
Necrosis	**Yes**	1	24	2	23	5	20
	No	7	42	18	31	26	23
p-value		0.178		**0.008**		**0.006**	
Lymphovascular invasion	**Yes**	0	14	0	14	1	13
	No	8	52	20	40	30	30
p-value		0.148		**0.011**		**0.003**	

Table 3: Frequency of recurrence and progression in patients with a pathological stage of T1 by high-grade ratios.

		<25%	>25%	<50%	>50%	<75%	>75%
T1 Recurrence	**Yes**	3	31	8	26	14	20
	No	5	35	12	28	17	23
P-value		0.612		0.532		0.908	
T1 Progression	**Yes**	0	17	1	16	3	14
	No	8	49	19	38	28	29
P-value		0.102		**0.025**		**0.021**	

DISCUSSION

Non-muscle invasive bladder tumors are the most common urothelial tumors in the Western population. The clinical behavior of this entity appears to be quite heterogeneous. These tumors are associated with recurrence rates of up to 75% with stage progression in the range of 8-30%[15,16]. The progression of NMIBT to muscle invasive bladder cancer (MIBC) is the nightmare of both patients and clinicians. Estimation of potential disease progression is of great importance in terms of patient survival. The stage of the disease is the most important parameter in determining the prognosis and the pathological grade of the tumor represents another important prognostic factor. Low-grade tumors tend to grow superficially, while high-grade tumors tend to have more infiltrative characteristics[17]. However, not all high-grade tumors may show the same invasion features. This may be related to the different percentage of histological grades in these tumor cells. There is only a limited number of studies in the literature that mention the heterogeneity of tumor grades[1,12,18,19]. Reis et al. [12] described tumors with a high grade component of 5% or less as mixed UC in their study, and compared the data of these patients versus data of those with pure low- and pure high-grade UC. They reported that the prognosis of patients with the mixed type was more similar to that of patients with low-grade carcinoma rather than those with high-grade; however, if left untreated, there was more progression in these patients compared to those with low-grade tumors. Gofrit et al[18]. described tumors with a NMIBT high grade component of 10% or less as mixed UC, and compared the data of these patients versus data of those with pure low- and pure high-grade UC. They found similar five-year recurrence-free survival rates in these three groups. They also showed significantly lower rates of five-year progression-free survival in patients with pure high-grade UC (73.9%, p <0.0001); however, the rates appeared to be similar in those with high-grade and mixed-grade tumors (99% and 96.9%,

respectively, p = 0.167). Consistently, they reported significantly poorer disease-specific survival in patients with pure high-grade tumors (p<0.0001) whereas the rates were similar in those with high-grade and mixed-grade lesions (p=0.679). They showed significantly lower rates of five-year progression-free survival in patients with pure high-grade disease (73.9%, p <0.0001); however, the rates appeared to be similar in those with high-grade and mixed-grade tumors (99% and 96.9%, respectively, p = 0.167). Schubert et al. [19] described tumors with a high grade component of 50% or less as mixed UC in their study, and compared the data of these patients versus data of those with high-grade UC. They reported the prognosis in 88.2% of patients with the mixed type and 48.5% in those with high-grade disease, stating better response to treatment with interferon and BCG in mixed UC. Mai et al.[1] described tumors with high-grade component of 10-80% as mixed UC and stratified these tumors into two groups. Group A consisted of patients with previous history of low-grade UC and Group B consisted of de novo patients. They reported that the risk of recurrence and progression was higher in the de novo patient group, however they did not comment on high-grade ratios. Our patient group consisted of de novo patients, and similar to the aforementioned study, increased progression was observed with increasing high-grade ratios.

Unlike other studies in the literature, the low-grade tumor group was excluded in our study. Only the high-grade tumor group was included, and these were stratified into 25, 50 and 75 percentiles according to the high-grade ratio. Evaluation by pathological stage revealed high-grade ratio >25% in only 1 Ta patient while the high-grade ratio was >25% in 66 of the T1 patients (p<0.001). When the cut-off was taken as >50%, none of the Ta patients were found to have high-grade ratio greater than 50% while 54 T1 patients (7.29%) had a high-grade ratio >50% (p<0.001). When the cut-off value of 75% was investigated, 43 patients (58.1%) in the T1 group were found to have a high-grade ratio >75% (p<0.001). On the other hand, none of the patients in the Ta group had a high-grade ratio greater than 75%. In conclusion, high-grade ratios were significantly higher in T1 patients compared to Ta patients at every cut-off level investigated herein. Accordingly, one may conclude that high-grade ratio >50% increase the likelihood of lamina propria invasion in NMIBT.

Since high-grade ratios were low in patients with a pathological stage of Ta, high-grade ratios were compared with carcinoma in situ, cell differentiation, necrosis and presence of lymphovascular invasion in the specimens only in patients pathologically classified as T1. Presence of carcinoma in situ in patients pathologically classified as T1 was markedly higher in those with high-grade ratio greater than 75%. Higher rates of tumor necrosis and lymphovascular invasion were observed in patients with high-grade ratio >50% compared to those without. Furthermore, the difference was statistically more significant in patients with high-grade ratio >75%. There was no statistically significant association between cell differentiation and high-grade ratio.

Mean duration of follow-up of the patients was 32.6 months (min: 3 months - max: 82 months). Recurrent mass was detected in 39 patients (42.3%) in the entire study cohort. Recurrence was observed in 5 patients (27.7%) with a pathological stage of Ta and in 34 patients (45.9%) classified as T1. There was no correlation between high-grade ratios and recurrence rates in patients pathologically classified as T1. Stage progression was identified in 18 patients (19.5%) in the entire cohort. While 17 patients with stage progression progressed from T1 to T2, 1 patient progressed from Ta to T1. Rate of

progression was higher, with a statistically significant difference, in patients with a pathological stage of T1 and a high-grade ratio greater than 50% compared to those with a pathological stage of T1 and a high-grade ratio lower than 50%.

CONCLUSION

Nuclear grade ratio is the second most important prognostic factor after tumor stage in NMIBT. When evaluating the nuclear grade, defining tumors solely as high-grade leads to stratifying a highly heterogeneous and large group of patients in a single group. There is a significantly increased likelihood of lamina propria invasion in patients with high-grade ratio >75% accompanied by carcinoma in situ. A significantly higher rate of progression is observed in T1 patients with NMIBT whose tumors exhibit high-grade ratio >50%.

Taken together, we believe that it is important to specify the high-grade ratio as percentage in pathology reports of high-grade urothelial tumors and that more intensive treatment is warranted for bladder tumors exceeding the 50% cut-off value as the risk of progression may be higher in these patients.

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