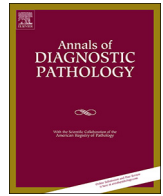




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## Original Contribution

# Assessment of transurethral resection of the bladder specimens with pT1 high-grade urothelial carcinoma for the predictor features of muscularis propria invasion on radical cystectomy specimens

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## 1. Introduction

Urinary bladder cancer is the seventh most frequent cancer worldwide, and its most common type is urothelial carcinoma [1,2]. Treatment modalities change based on whether the tumor is muscle-invasive or not [3]. Radical cystectomy (RC) and bilateral lymphadenectomy are recommended for muscle-invasive disease [3], whereas bladder sparing strategies and guideline-based treatments depending on risk categories are preferred for non-muscle-invasive bladder cancer [4].

High-grade tumors, concomitant carcinoma *in situ* (CIS), multiple and/or large (> 3 cm) tumors, and lymphovascular invasion are some features of high-risk tumors wherein RC should be considered [4]. Beyond these histopathological features, tumor necrosis (TN) is a well-known factor for the poor prognosis in most human cancers [5]. Some studies have shown that TN is an independent factor for adverse clinical outcomes [5] and an independent predictor of both recurrence-free survival and cancer-specific survival in patients with upper urinary tract urothelial carcinoma [6]. Our search limited to studies published in English revealed that in the few studies performed on bladder cancer, TN has been studied only as a histologic feature for assessing the clinical outcome [7,8]. However, TN in the transurethral resection of bladder (TUR-B) specimens has not been analyzed as a predictor of muscularis propria invasion in bladder cancer. The most recent edition of the World Health Organization (WHO) “blue book” for genitourinary tumors notifies that substaging pT1 disease is relevant but there is still no consensus on how to do that [1,4]. Many studies have proposed different methods for measuring the depth of invasion [9–12]. Leivo et al. showed that aggregate linear length of invasive carcinoma (ALLICA) measured by optical micrometer is far superior to other methods and could be applied to 100% of specimens [10].

In our study, we assessed TUR-B specimens of the patients diagnosed as having pT1 high-grade urothelial carcinoma to understand and identify the pathologic features predictive of muscularis propria invasion in RC specimens. We attempted to identify if there was a correlation between histopathological parameters and pT1 substaging in TUR-B specimens with muscularis propria invasion obtained through RC specimens.

## 2. Patients and methods

### 2.1. Ethical approval

According to the ethical standards in Turkey, an ethics committee approval and an informed patient consent were not necessary due to the retrospective design of the study.

### 2.2. Patients

Between January 2008 and December 2017 consequent 218 RC specimens were evaluated in our pathology department. This retrospective study included consequent 66 patients who underwent RC for non-muscle-invasive high-grade urothelial carcinoma diagnosed using TUR-B specimens at our institution between January 2008 and December 2017. One of the major concerns of our study was the presence of TN, thus we excluded the high-grade urothelial carcinoma diagnosed as pTa in TUR-B specimens. During this period, of all the RC specimens evaluated at our institution only 66 were diagnosed as pT1 on TUR-B specimens. They were consequent cases. Indications for RC were recurrent pT1 disease with or without carcinoma *in situ* (CIS) refractory to at least two TUR-B with intravesical immunotherapy. No

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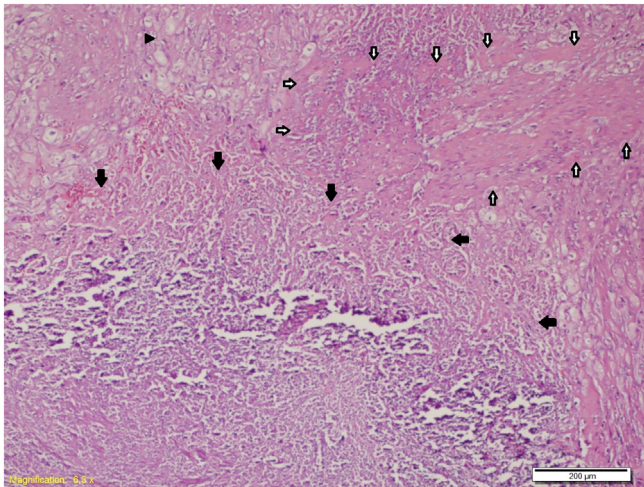


Fig. 1. Presence of tumor necrosis in transurethral resection specimen (arrow: necrosis; arrow head: tumor tissue white arrow: muscle tissue) (HE, × 100).

patient received chemotherapy and/or radiotherapy preoperatively. No patient had distant metastatic disease at the time of RC.

2.3. Pathologic evaluation

TUR-B specimens were processed according to standard pathologic procedures. In all cases, hematoxylin and eosin (H&E)-stained sections of TUR-B specimens were meticulously re-evaluated independently by two genitourinary pathologists who were blinded to the outcomes of cases. Each case with grading discrepancies was subsequently placed under joint review and was assigned a score agreed upon by both pathologists. Each case was assigned according to the 2004 two-tier WHO/International Society of Urologic Pathology classification [1]. TN was defined as the presence of microscopic coagulative necrosis lacking inflammation or fibrosis [5] (Fig. 1). TN was considered as present when microscopic coagulative necrosis occupying at least one high power field was recognizable to pathologists on the evaluation of all available tumor blocks of TUR-B specimens [5]. Thermoablative necrosis caused by cautery and necrosis due to intravesicle Bacille Calmette-Guérin treatment were not classified as TN [7]. Undifferentiated morphology and adenoid, micropapillary, sarcomatoid, squamous, and small-cell differentiation were all assessed as variant histology. TNM staging was done according to the 2010 American Joint Committee on Cancer (AJCC) guidelines [13]. We evaluated pT1 tumors according to “aggregate linear length of invasive carcinoma (ALLICA)” measurement, which uses an optical micrometer to measure the largest dimension of the foci of all tumors identified as invasive based on TUR specimens and adds them together (Fig. 2). Tumors with ALLICA measurements < 2.4 mm and ≥ 2.4 mm were substaged as pT1a and pT1b, respectively. In a study Leivo et al. compared benefits

and limitations of seven different methods previously described for substaging pT1 disease to predict probable progression to a greater stage disease; and found that ALLICA method was far superior to other methods [10]. The presence of concomitant CIS was assessed in all sections. Lymphovascular invasion (LVI) was defined as the presence of tumor cells within an endothelium-lined space without the underlying muscular walls. Tumor diameter was defined as the largest measurable diameter assessed during gross and/or microscopic examination of RC specimens. Tumors were divided based on the diameter being ≥ 3 cm or < 3 cm [7]. Tumors with a diameter ≥ 3 cm were defined as large tumors. Invasion of large and compact bundles of muscles was considered as muscularis propria invasion on histopathological evaluation of RC specimens [1]. Information about tumor multifocality and repeat TUR-B procedures was collected from the recorded clinical data.

2.4. Statistical analysis

We used the statistical softwares NCSS 2007 and PASS 2008 (Utah, USA) for statistical analysis. The primary end-point of our study was the identification of muscularis propria invasion in RC specimens. The secondary end-point was to reveal the pathological features of TUR-B specimens that were related to TN. To compare qualitative/quantitative parameters, the Student’s *t*-test, Fisher’s exact test,  $\chi^2$ -test with Yates’ continuity correction, and Fisher–Freeman–Halton test were performed; *p* < 0.05 was considered statistically significant. Multivariate logistic regression models were used to assess the relationships between pathological factors and the outcome of interest.

3. Results

In this study, we included 66 patients with non-muscle-invasive high-grade urothelial carcinoma who underwent RC. Table 1 shows the descriptive characteristics of patients. Median age was 65 years (range: 46–82 years). Of these patients, 61 (93%) were men and only 5 (7%) were women (male-to-female ratio: 12.2:1). Overall, tumors in 25 patients were staged as pT1a (38%) and 41 (62%) as pT1b according to ALLICA method. Lymphovascular invasion was detected in 3 (5%) TUR-B specimens. Thirty-three (50%) of these tumors were ≥ 3 cm and 12

Table 1  
Descriptive clinicopathologic characteristics of 66 patients.

	n	%
Age(yr) min-max, mean ± sd	46–82	65,41 ± 9,07
Gender		
Male	61	92
Female	5	8
CIS		
Present	16	24
Absent	50	76
LVI		
Present	3	5
Absent	63	95
Presence of muscle invasion on RC specimen		
Present	36	55
Absent	30	45
Tumor size		
≥ 3 cm	33	50
< 3 cm	33	50
Multifocality		
Present	12	18
Absent	54	82
Repeated TUR-B		
Yes	42	64
No	24	36
Muscularis propria		
Present	30	46
Absent	36	54
TN		
Present	23	35
Absent	43	65
Variant histology		
Present	12	18
Absent	54	82
pSubstaging		
pT1a pT1b	25	38
	41	62

CIS: carcinoma *in situ*, LVI: lymphovascular invasion, RC: radical cystectomy, TUR-B: transurethral resection of bladder, TN: tumor necrosis.

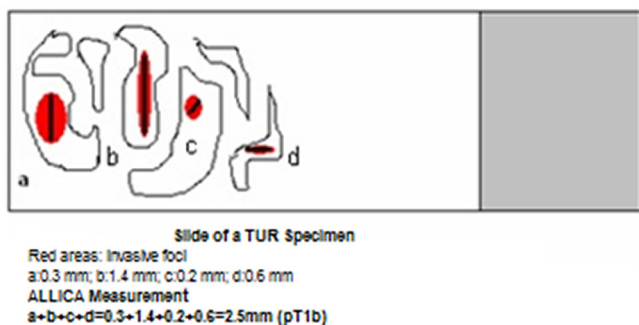


Fig. 2. ALLICA method to measure invasive cancer in TUR-B specimens.

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