



# Protocol for the Examination of Biopsy and Transurethral Resection of Bladder Tumor (TURBT) Specimens From Patients With Carcinoma of the Urinary Bladder

Version: Urinary Bladder Biopsy/TURBT 4.0.1.1

Protocol Posting Date: February 2019

## Accreditation Requirements

The use of this protocol is recommended for clinical care purposes but is not required for accreditation purposes.

## This protocol should be used for the following procedures AND tumor types:

Procedure	Description
Biopsy and transurethral resection of bladder tumor (TURBT)	Includes specimens designated biopsy, and transurethral resection of bladder tumor (TURBT)
Tumor Type	Description
Carcinomas	Includes invasive carcinomas of the urinary tract, including urothelial carcinoma, its morphological variants, and other carcinoma (squamous cell carcinoma, adenocarcinoma, Müllerian carcinoma, neuroendocrine carcinoma, and sarcomatoid carcinoma)

## The following should NOT be reported using this protocol:

Procedure
Resection (consider Urinary Bladder Resection protocol)
Tumor Type
Urachal Carcinoma
Lymphoma (consider the Hodgkin or non-Hodgkin Lymphoma protocols)
Sarcoma (consider the Soft Tissue protocol)

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## Summary of Changes

### Version 4.0.1.1

Biopsy and resection procedures separated into individual protocols  
Minor modifications to the Procedure and Additional Findings sections

## Surgical Pathology Cancer Case Summary

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Protocol posting date: February 2019

### URINARY BLADDER: Biopsy and Transurethral Resection of Bladder Tumor (TURBT)

**Note: This case summary is recommended for reporting biopsy and TURBT specimens but is NOT REQUIRED for accreditation purposes. Core data elements are bolded to help identify routinely reported elements.**

Select a single response unless otherwise indicated.

#### Procedure (Note A)

- Biopsy
- Transurethral resection of bladder (TURBT)
- Other (specify): \_\_\_\_\_
- Not specified

#### Tumor Site (select all that apply)

- Trigone
- Right lateral wall
- Left lateral wall
- Anterior wall
- Posterior wall
- Dome
- Other (specify): \_\_\_\_\_
- Not specified

#### Histologic Type (select all that apply) (Note B)

##### Urothelial

- Papillary urothelial carcinoma, noninvasive
- Papillary urothelial carcinoma, invasive
- Urothelial carcinoma in situ
- Urothelial carcinoma, invasive
- Urothelial carcinoma, nested (including large nested) variant
- Urothelial carcinoma, microcystic variant
- Urothelial carcinoma, micropapillary variant
- Urothelial carcinoma, lymphoepithelioma-like variant
- Urothelial carcinoma, plasmacytoid / signet ring / diffuse variant
- Urothelial carcinoma, sarcomatoid variant
- Urothelial carcinoma, giant cell variant
- Urothelial carcinoma, poorly differentiated variant
- Urothelial carcinoma, lipid-rich variant
- Urothelial carcinoma, clear cell variant
- Urothelial carcinoma with squamous differentiation
  - + Specify percentage of squamous differentiation: \_\_\_\_\_%
- Urothelial carcinoma with glandular differentiation
  - + Specify percentage of glandular differentiation: \_\_\_\_\_%
- Urothelial carcinoma with trophoblastic differentiation
  - + Specify percentage of trophoblastic differentiation: \_\_\_\_\_%
- Urothelial carcinoma with Müllerian differentiation
  - + Specify percentage of Müllerian differentiation: \_\_\_\_\_%

Squamous

- Pure squamous cell carcinoma
- Verrucous carcinoma
- Squamous cell carcinoma in situ (no invasive carcinoma identified)

Glandular

- Adenocarcinoma
- Adenocarcinoma, enteric
- Adenocarcinoma, mucinous
- Adenocarcinoma, mixed
- Adenocarcinoma in situ (no invasive carcinoma identified)

Tumors of Müllerian Type

- Clear cell carcinoma
- Endometrioid carcinoma

Neuroendocrine Tumors

- Small cell neuroendocrine carcinoma  
+ Specify percentage of small cell neuroendocrine component: \_\_\_\_\_%
- Large cell neuroendocrine carcinoma  
+ Specify percentage of large cell neuroendocrine component: \_\_\_\_\_%
- Well-differentiated neuroendocrine carcinoma  
+ Specify percentage of well-differentiated neuroendocrine component: \_\_\_\_\_%
- Other histologic type not listed (specify): \_\_\_\_\_

Associated Epithelial Lesions (select all that apply) (Note C)

- None identified
- Urothelial papilloma
- Urothelial papilloma, inverted type
- Papillary urothelial neoplasm, low malignant potential (PUNLMP)
- Urothelial dysplasia
- Urothelial proliferation of uncertain malignant potential
- Cannot be determined

**Histologic Grade (Note C)**

For urothelial carcinoma, other variants, or divergent differentiation

- Low-grade
- High-grade
- Other (specify): \_\_\_\_\_

For squamous cell carcinoma or adenocarcinoma

- G1: Well-differentiated
- G2: Moderately differentiated
- G3: Poorly differentiated
- GX: Cannot be assessed
- Other (specify): \_\_\_\_\_
- Not applicable
- Cannot be assessed

Tumor Configuration (select all that apply)

- Papillary
- Solid/nodule
- Flat
- Ulcerated
- Cannot be determined
- Other (specify): \_\_\_\_\_

**Muscularis Propria Presence (Note D)**

- No muscularis propria (detrusor muscle) identified
- Muscularis propria (detrusor muscle) present
- Cannot be determined (explain): \_\_\_\_\_

**Lymphovascular Invasion (Note E)**

- Not identified
- Present
- Cannot be determined

**Tumor Extension (select all that apply) (Note D)**

- Noninvasive papillary carcinoma
- Carcinoma in situ
- Tumor invades lamina propria (subepithelial connective tissue)
- Tumor invades muscularis propria
- Urothelial carcinoma involving prostatic urethra in prostatic chips sampled by TURBT
- Urothelial carcinoma involving prostatic ducts and acini in prostatic chips sampled by TURBT
- Urothelial carcinoma invasive into prostatic stroma in prostatic chips sampled by TURBT
- Cannot be assessed

Additional Pathologic Findings (select all that apply)

- Urothelial dysplasia
- Inflammation/regenerative changes
- Therapy-related changes
- Cautery artifact
- Cystitis cystica et glandularis
- Keratinizing squamous metaplasia
- Intestinal metaplasia
- Other (specify): \_\_\_\_\_

Comment(s)

## Explanatory Notes

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### A. History

A relevant history is important for interpretation of all bladder specimens.<sup>1-4</sup> Cystoscopic visualization findings hold useful information on the nature and extent of bladder lesions in biopsy and TURBT specimens. A history of renal stones, recent urinary tract procedures, infections, or obstruction may influence the interpretation of random biopsies obtained on patients with hematuria. Any neoplasms previously diagnosed should be specified, including the histologic type, primary site, and histologic grade. If prior therapy has been given, it should be described (systemic or intravesical chemotherapy, immunotherapy, radiation, etc).

#### References:

1. Murphy WM. Diseases of the urinary bladder, urethra, ureters and renal pelvis. In: Murphy WM, ed. *Urological Pathology*. 2<sup>nd</sup> ed. Philadelphia, PA: WB Saunders Co; 1997.
2. Ro JY, Staerckel GA, Ayala AG. Cytologic and histologic features of superficial bladder cancer. *Urol Clin North Am*. 1992;19:435-453.
3. Grignon DJ. Neoplasms of the urinary bladder. In: Bostwick DG, Eble JN, eds. *Urologic Surgical Pathology*. St. Louis, MO: Mosby Year Book, Inc; 1997.
4. Hughes JH, Raab SS, Cohen MB. The cytologic diagnosis of low-grade transitional cell carcinoma. *Am J Clin Pathol*. 2000;114(suppl):559-567.

### B. Histologic Type

The vast majority (more than 95%) of carcinomas of the urinary bladder, renal pelvis, and ureter are urothelial cell in origin. The most recent 2016 World Health Organization (WHO) classification of tumors of the urothelial tract, including urethra, urinary bladder, ureter, and renal pelvis, is provided in this note. Benign tumors are included in this classification because, within the same patient, a spectrum of differentiation from benign to malignant tumors may be seen in the bladder, either at the same time or over the clinical course of the disease. Also, clinicians stage most tumors irrespective of histologic grade.<sup>1-9</sup> The distinction between a urothelial carcinoma with divergent squamous, glandular, or Müllerian differentiation and a pure squamous cell carcinoma, adenocarcinoma or Müllerian is rather arbitrary. Most authorities, including the 2016 WHO classification, require a pure histology of squamous cell carcinoma, adenocarcinoma or Müllerian to designate a tumor as such, all others with recognizable papillary, invasive, or flat carcinoma in situ (CIS) urothelial component being considered as urothelial carcinoma with divergent differentiation. A malignant neoplasm with small cell neuroendocrine carcinoma component arising in the urinary tract is designated as small cell carcinoma.

### 2016 WHO Classification of Tumors of the Urothelial Tract

#### Urothelial tumors

##### *Infiltrating urothelial carcinoma*

- Nested, including large nested
- Microcystic
- Micropapillary
- Lymphoepithelioma-like
- Plasmacytoid/signet ring cell/diffuse
- Sarcomatoid
- Giant cell
- Poorly differentiated

##### *Noninvasive urothelial lesions*

- Urothelial carcinoma in situ
- Noninvasive papillary urothelial carcinoma, low grade
- Noninvasive papillary urothelial carcinoma, high grade
- Papillary urothelial neoplasm of low malignant potential
- Urothelial papilloma
- Inverted urothelial papilloma
- Urothelial proliferation of uncertain malignant potential
- Urothelial dysplasia

Squamous cell neoplasms

Pure squamous cell carcinoma  
Verrucous carcinoma  
Squamous cell papilloma

Glandular neoplasms

Adenocarcinoma, NOS  
    Enteric  
    Mucinous  
    Mixed  
Villous adenoma

Urachal carcinomaTumors of Mullerian type

Clear cell carcinoma  
Endometrioid carcinoma

Neuroendocrine tumors

Small cell neuroendocrine carcinoma  
Large cell neuroendocrine carcinoma  
Well-differentiated neuroendocrine tumor  
Paraganglioma

## References:

1. Amin MB, Murphy WM, Reuter VE, et al. Controversies in the pathology of transitional cell carcinoma of the urinary bladder. In: Rosen PP, Fechner RE, eds. *Reviews of Pathology*. Vol. 1. Chicago, IL: ASCP Press; 1996.
2. Reuter VE. The urothelial tract: renal pelvis, ureter, urinary bladder, and urethra. In: Mills SE, Carter D, Greenson JK, Oberman HA, Reuter V, Stoler MH, eds. *Sternberg's Diagnostic Surgical Pathology*. 4<sup>th</sup> ed. Philadelphia, PA: Lippincott Williams and Wilkins; 2004.
3. Amin MB, Young RH. Intraepithelial lesions of the urinary bladder with a discussion of the histogenesis of urothelial neoplasia. *Semin Diagn Pathol*. 1997;14(2):84-97.
4. Eble JN, Young RH. Carcinoma of the urinary bladder: a review of its diverse morphology. *Semin Diagn Pathol*. 1997;14(2):98-108.
5. Mostofi FK, Davis CJ, Sesterhenn IA. Histologic typing of urinary bladder tumors. In: *World Health Organization International Histologic Classification of Tumours*. 2nd ed. Heidelberg, Germany: Springer-Verlag, Berlin; 1999.
6. Eble JN, Sauter G, Epstein JI, Sesterhenn IA. Tumors of the urinary system. In: *World Health Organization Classification of Tumours: Pathology and Genetics of Tumours of the Urinary System and Male Genital Organs*. Lyon, France: IARC Press; 2004.
7. Moch H, Humphrey PA, Ulbright TM, Reuter VE. *WHO Classification of Tumours of the Urinary System and Male Genital Organs*. Geneva, Switzerland: WHO Press; 2016.
8. Murphy WM, Grignon DJ, Perlman EJ. Tumors of the urinary bladder. In: *Tumors of the Kidney, Bladder, and Related Urinary Structures*. AFIP Atlas of Tumor Pathology Series 4. Washington, DC: American Registry of Pathology; 2004.
9. Epstein JI, Amin MB, Reuter VR, Mostofi FK, 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*. 1998;22:1435-1448.

**C. Histologic Grade**

Flat intraepithelial lesions and papillary and invasive lesions are graded separately.<sup>1-8</sup> There has been significant controversy in the classification of these lesions. Flat lesions were graded as mild, moderate, and severe dysplasia and carcinoma in situ; or atypical hyperplasia and carcinoma in situ; or dysplasia and carcinoma in situ.<sup>9,10</sup> Papillary lesions were classified as papillomas (grade 0) and transitional cell carcinomas, grades I, II and

III; or as papillomas, low-grade and high-grade transitional cell carcinomas.<sup>4-6</sup> Due to variable classification systems and the need for a universally acceptable system, the World Health Organization/International Society of Urological Pathology (WHO/ISUP) consensus classification was proposed.<sup>4</sup> This system is adopted in the WHO 2004 classification<sup>1</sup> and 2004 Armed Forces Institute of Pathology (AFIP) fascicle,<sup>3</sup> and has been validated by many studies to be prognostically significant. The 2016 WHO system used essentially the same classification with minor modification.<sup>2</sup> Other systems (that were being used previously) may still be used according to institutional preference. Tumor grade according to both the WHO/ISUP (1998)<sup>4</sup> / WHO (2004)<sup>1</sup> system and the older WHO (1973)<sup>6</sup> system may be concurrently used.

### 2004 WHO / ISUP Consensus Classification for Urothelial Lesions

Normal

Normal<sup>#</sup>

Hyperplasia

Flat hyperplasia

Papillary hyperplasia

Flat Lesions with Atypia

Reactive (inflammatory) atypia

Atypia of unknown significance

Dysplasia (low-grade intraurothelial neoplasia)<sup>#</sup>

Carcinoma in situ (high-grade intraurothelial neoplasia)<sup>###</sup>

Papillary Neoplasms

Papilloma

Inverted papilloma

Papillary neoplasm of low malignant potential

Papillary carcinoma, low-grade

Papillary carcinoma, high-grade<sup>####</sup>

Invasive Neoplasms

Lamina propria invasion

Muscularis propria (detrusor muscle) invasion

<sup>#</sup> May include cases formerly diagnosed as “mild dysplasia.”

<sup>##</sup> Includes cases with “severe dysplasia.”

<sup>###</sup> Option exists to add comment as to the presence of marked anaplasia.

Flat and papillary urothelial hyperplasia has been renamed as “urothelial proliferation of uncertain malignant potential” in the 2016 WHO classification.

Squamous carcinomas and adenocarcinomas may be graded as well-differentiated, moderately differentiated, and poorly differentiated.

### References:

1. Eble JN, Sauter G, Epstein JI, Sesterhenn IA. Tumors of the urinary system. In: *World Health Organization Classification of Tumours: Pathology and Genetics of Tumours of the Urinary System and Male Genital Organs*. Lyon, France: IARC Press; 2004.
2. Moch H, Humphrey PA, Ulbright TM, Reuter VE. *WHO Classification of Tumours of the Urinary System and Male Genital Organs*. Geneva, Switzerland: WHO Press; 2016.
3. Murphy WM, Grignon DJ, Perlman EJ. Tumors of the urinary bladder. In: *Tumors of the Kidney, Bladder, and Related Urinary Structures*. AFIP Atlas of Tumor Pathology Series 4. Washington, DC: American Registry of Pathology; 2004.
4. Epstein JI, Amin MB, Reuter VR, Mostofi FK, 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*. 1998;22:1435-1448.
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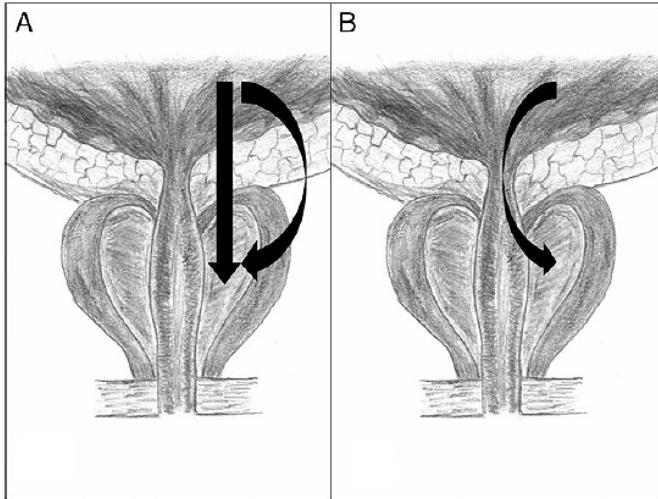
6. Mostofi FK. Histological typing of urinary bladder tumours. In: *WHO Histological Classification of Tumours. No. 10*. Geneva, Switzerland: World Health Organization; 1973.
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8. Friedell GH, Bell JR, Burney SW, Soto EA, Tiltman AJ. Histopathology and classification of urinary bladder carcinoma. *Urol Clin North Am*. 1976;3:265-227.
9. Amin MB, Murphy WM, Reuter VE, et al. Controversies in the pathology of transitional cell carcinoma of the urinary bladder. In: Rosen PP, Fechner RE, eds. *Reviews of Pathology*. Vol. 1. Chicago, IL: ASCP Press; 1996.
10. Amin MB, Young RH. Intraepithelial lesions of the urinary bladder with a discussion of the histogenesis of urothelial neoplasia. *Semin Diagn Pathol*. 1997;14(2):84-97.

#### D. Extent of Invasion

A critical role of the surgical pathologist is to diagnose the depth and extent of invasion into the subepithelial connective tissue/lamina propria/submucosa (pT1), muscularis propria (pT2), or beyond (pT3 or pT4).<sup>1-3</sup> In papillary tumors, invasion occurs most often at the base of the tumor and very infrequently in the stalk. In the urinary bladder, a tumor infiltrating the lamina propria (pT1) is sometimes overdiagnosed as vascular invasion; hence, caution should be exercised when diagnosing this feature, which in some cases may be supported by performing immunohistochemical studies for endothelial markers.<sup>4</sup> Depth of invasion is a critical prognostic determinant in invasive urothelial carcinoma. In T1 disease, several substaging methods have been proposed but have been difficult to adopt due in part to the inherent lack of orientation of the specimen.<sup>5,6</sup> Pathologists are, however, encouraged to provide some assessment as to the extent of lamina propria invasion (ie, maximum dimension of invasive focus, or depth in millimeters, or by level – above, at, or below muscularis mucosae). Designation of a tumor as merely muscle invasive is inappropriate, but the type of muscle invasion, ie, muscularis mucosae (pT1 tumors) versus muscularis propria (pT2 tumors) invasion, needs to be clearly stated.<sup>7,8</sup> Descriptive terminology, such as “urothelial carcinoma with muscle invasion, indeterminate for type of muscle invasion,” may be used when it is not possible to be certain whether the type of muscle invaded by the tumor is hypertrophic muscularis mucosae or muscularis propria. A comment on thermocoagulation effect may be made, especially if its presence impedes diagnostic evaluation.<sup>9</sup> In TURBT specimens invasive into muscularis propria, no attempt should be made to substage the depth of muscularis propria invasion. Since fat may be present in the lamina propria and muscularis propria, the presence of tumor in adipose tissue is not necessarily diagnostic of extravesical spread; this determination is reserved for cystectomy specimens.<sup>8,10</sup>

Involvement of the prostate gland may occur in several different patterns. Tumors (flat carcinoma in situ, papillary or invasive carcinoma) can first spread along the prostatic urethral mucosa and prostate glands and subsequently invade prostatic stroma (transurethral mucosal route) (Figure 1, B). Tumors may also invade through the bladder wall and the base of the prostate directly into the prostate gland (Figure 1, A, straight arrow).<sup>11</sup> Tumors can also invade into extravesical fat and then extend back into the prostate gland (Figure 1, B, curved arrow). The latter two routes are considered direct transmural invasion. The American Joint Committee on Cancer (AJCC) 8th edition staging manual defines direct extension of urinary bladder cancer into the prostate gland as T4 disease and excludes transurethral mucosal prostatic stroma invasion from the pT4a staging status. However, there is limited data on the best methodology to stage urothelial carcinoma that concurrently involves the urinary bladder and the prostatic urethra. In patients who have a large urinary bladder carcinoma that has invaded through the full thickness of the bladder wall and thereby secondarily involves the prostatic stroma, a T4 stage should be assigned per urinary bladder staging. In other circumstances in which involvement by urothelial carcinoma is seen in both sites, separate urinary bladder and prostatic urethral staging should be assigned. Transmucosal route into prostatic stroma from a bladder cancer without transmural prostatic stromal invasion is now categorized as pT2 per urethral cancer staging, and the concomitant bladder proper cancer is given a separate stage category according to the bladder cancer staging.





**Figure 1.** Prostatic invasion from urinary bladder cancer via direct transmural and extravesical route (A) and transurethral invasion (B). From: Patel AR, Cohn JA, El Latif AA, et al. Validation of new AJCC exclusion criteria for subepithelial prostatic stroma invasion from pT4a bladder urothelial carcinoma. *J Urol.* 2013;189:53-58. Reproduced with permission.

#### References:

1. Amin MB, Edge SB, Greene FL, et al, eds. *AJCC Cancer Staging Manual*. 8th Ed. New York: Springer; 2017.
2. Brierley JD, Gospodarowicz MK, Wittekind C, et al, eds. *TNM Classification of Malignant Tumours*. 8th ed. Oxford, UK: Wiley; 2016.
3. Jimenez RE, Keane TE, Hardy HT, Amin MB. pT1 urothelial carcinoma of the bladder: criteria for diagnosis, pitfalls, and clinical implications. *Adv Anat Pathol.* 2000;7(1):13-25.
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7. Ro JY, Ayala AG, El-Naggar A. Muscularis mucosa of urinary bladder: importance for staging and treatment. *Am J Surg Pathol.* 1983;136:265-271.
8. Paner GP, Ro JY, Wojcik EM, Venkataraman G, Data MW, Amin MB. Further characterization of the muscle layers and lamina propria of the urinary bladder by systematic histologic mapping: implications for pathologic staging of invasive urothelial carcinoma. *Am J Surg Pathol.* 2007;31:1420-1429.
9. Murphy WM. ASCP survey on pathology examination of the urinary bladder. *Am J Clin Pathol.* 1994;102:715-723.
10. Philip AT, Amin MB, Tamboli P, Lee TJ, Hill CE, Ro JY. Intravesical adipose tissue: a quantitative study of its presence and location with implications for therapy and prognosis. *Am J Surg Pathol.* 2000;24:1286-1290.
11. Patel AR, Cohn JA, El Latif AA, et al. Validation of new AJCC exclusion criteria for subepithelial prostatic stroma invasion from pT4a bladder urothelial carcinoma. *J Urol.* 2013; 189:53-58.

#### E. Lymphovascular Invasion

Urothelial carcinoma may invade blood vessels or lymphatic channels. Lymphovascular invasion has been shown to be an independent predictor of recurrence and decreased overall survival.<sup>1</sup> Presence of lymph-vascular invasion in TURBT specimens is associated with higher nodal metastasis.<sup>2</sup> In suspicious cases, blood vessels can be highlighted by immunohistochemical staining for factor VIII-related antigen, CD31 or CD34. Staining will not resolve the problem of differentiating lymphatic versus artifactual space entrapment by tumor cells, and as mentioned, this is frequently seen in urothelial tumors invading the lamina propria. Retraction artifact is also prominent in the “micropapillary variant” of urothelial carcinoma.<sup>3</sup>

References:

1. Lotan Y, Gupta A, Shariat SF, et al. Lymphovascular invasion is independently associated with overall survival, cause-specific survival, and local and distant recurrence in patients with negative lymph nodes at radical cystectomy. *J Clin Oncol*. 2005;23:6533-6539.
2. Kunju LP, You L, Zhang Y, Daignault S, Montie JE, Lee CT. Lymphovascular invasion of urothelial cancer in matched transurethral bladder tumor resection and radical cystectomy specimens. *J Urol*. 2008;18:1928-1932.
3. Amin MB, Young RH. Intraepithelial lesions of the urinary bladder with a discussion of the histogenesis of urothelial neoplasia. *Semin Diagn Pathol*. 1997;14(2):84-97.