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

Version: 4.1.0.0
Protocol Posting Date: June 2021
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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With guidance from the CAP Cancer and CAP Pathology Electronic Reporting Committees.
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Accreditation Requirements
The use of this case summary is recommended for clinical care purposes but is not required for accreditation purposes. The core and conditional data elements are routinely reported. Non-core data elements are indicated with a plus sign (+) to allow for reporting information that may be of clinical value.

Summary of Changes

v 4.1.0.0

- General Reformatting

Reporting Template

Protocol Posting Date: June 2021
Select a single response unless otherwise indicated.

CASE SUMMARY: (URINARY BLADDER: Biopsy and Transurethral Resection of Bladder Tumor (TURBT))
Standard(s): AJCC-UICC 8
This template is recommended for reporting biopsy and TURBT specimens, but is not required for accreditation purposes.

SPECIMEN

Procedure (Note A)
___ Biopsy
___ Transurethral resection of bladder (TURBT)
___ Other (specify): _____
___ Not specified

TUMOR

Tumor Site (select all that apply)
___ Trigone
___ Right lateral wall
___ Left lateral wall
___ Anterior wall
___ Posterior wall
___ Dome
___ Other (specify): _____
___ Not specified

Histologic Type (Note B) (select all that apply)
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 cell / 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
+Percentage of Squamous Differentiation
___ Specify percentage: _____ %
___ Other (specify): _____

___ Cannot be determined
___ Urothelial carcinoma with glandular differentiation
+Percentage of Glandular Differentiation
___ Specify percentage: _____ %
___ Other (specify): _____
___ Cannot be determined
___ Urothelial carcinoma with trophoblastic differentiation
+Percentage of Trophoblastic Differentiation
___ Specify percentage: _____ %
___ Other (specify): _____
___ Cannot be determined
___ Urothelial carcinoma with Müllerian differentiation
+Percentage of Müllerian Differentiation
___ Specify percentage: _____ %
___ Other (specify): _____
___ Cannot be determined

Squamous
___ 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
+Percentage of Small Cell Neuroendocrine Component
___ Specify percentage: _____ %
___ Other (specify): _____
___ Cannot be determined
___ Large cell neuroendocrine carcinoma
+Percentage of Large Cell Neuroendocrine Component
___ Specify percentage: _____ %
___ Other (specify): _____
___ Cannot be determined
___ Well-differentiated neuroendocrine tumor
+Percentage of Well-differentiated Neuroendocrine Component
___ Specify percentage: _____ %
___ Other (specify): _____
___ Cannot be determined
___ Other histologic type not listed (specify): _____
+Histologic Type Comment: _____

Histologic Grade (Note C)
For urothelial carcinoma, other variants, or divergent differentiation
___ Low-grade
___ High-grade
For squamous cell carcinoma or adenocarcinoma
___ G1, well differentiated
___ G2, moderately differentiated
___ G3, poorly differentiated
___ GX, cannot be assessed: _____
Other
___ Other (specify): _____
___ Cannot be assessed: _____
___ Not applicable: _____

Tumor Extent (Note D) (select all that apply)
___ Noninvasive papillary carcinoma
___ Flat carcinoma in situ
___ Invades lamina propria (subepithelial connective tissue)
___ Invades muscularis propria
___ Urothelial carcinoma involves prostatic urethra in prostatic chips sampled by TURBT
___ Urothelial carcinoma involves prostatic ducts and acini in prostatic chips sampled by TURBT
___ Urothelial carcinoma invades into prostatic stroma in prostatic chips sampled by TURBT
___ Cannot be determined: _____

Lymphovascular Invasion (Note E)
___ Not identified
___ Present
___ Cannot be determined: _____

+Tumor Configuration (select all that apply)
___ Papillary
___ Solid / nodule
___ Flat
___ Ulcerated
___ Other (specify): _____
___ Cannot be determined: _____

Muscularis Propria (detrusor muscle)(Note D)
___ Not identified
___ Present
___ Cannot be determined (explain): _____

+Tumor Comment: _____

ADDITIONAL FINDINGS

+Associated Epithelial Lesions (Note C) (select all that apply)
___ None identified
___ Urothelial papilloma
___ Urothelial papilloma, inverted type
___ Papillary urothelial neoplasm, low malignant potential (PUNLMP)
___ Urothelial dysplasia
___ Urothelial proliferation of uncertain malignant potential
___ Other (specify): _____
___ Cannot be determined: _____

+Additional 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): _____

COMMENTS

Comment(s): _____

Explanatory Notes

A. History

A relevant history is important for interpretation of all bladder specimens.[1,2,3,4] 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

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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.[1,2,3,4,5,6,7,8,9] 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
Squamous cell carcinoma
Verrucous carcinoma
Squamous cell papilloma

Glandular neoplasms
Adenocarcinoma, NOS
Enteric
Mucinous
Mixed
Villous adenoma

Urachal carcinoma

Tumors 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*. 4th ed. Philadelphia, PA: Lippincott Williams and Wilkins; 2004.
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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.
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C. Histologic Grade

Flat intraepithelial lesions and papillary and invasive lesions are graded separately.[1,2,3,4,5,6,7,8] 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.[9,10] 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.[4,5,6] 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.[4] This system is adopted in the WHO 2004 classification[1] and 2004 Armed Forces Institute of Pathology (AFIP) fascicle,[3] and has been validated by many studies to be prognostically significant. The 2016 WHO system used essentially the same classification with minor modification.[2] Other systems (that were being used previously) may still be used according to institutional preference. Tumor grade according to both the WHO/ISUP (1998)[4] / WHO (2004)[1] system and the older WHO (1973)[6] system may be concurrently used.

2004 WHO / ISUP Consensus Classification for Urothelial Lesions

Normal
- Normal

Hyperplasia
- Flat hyperplasia
- Papillary hyperplasia

Flat Lesions with Atypia
- Reactive (inflammatory) atypia
- Atypia of unknown significance
- Dysplasia (low-grade intraurothelial neoplasia)#
- Carcinoma in situ (high-grade intraurothelial neoplasia)##

Papillary Neoplasms
- Papilloma
- Inverted papilloma
- Papillary neoplasm of low malignant potential
- Papillary carcinoma, low-grade
- Papillary carcinoma, high-grade###

Invasive Neoplasms
- Lamina propria invasion
- Muscularis propria (detrusor muscle) invasion

 # May include cases formerly diagnosed as "mild dysplasia."
Includes cases with "severe dysplasia."
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.
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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).[1,2,3] 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.[4] 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.[5,6] 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.[7,8] 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.[9] 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.[8,10]

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).[11] 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.

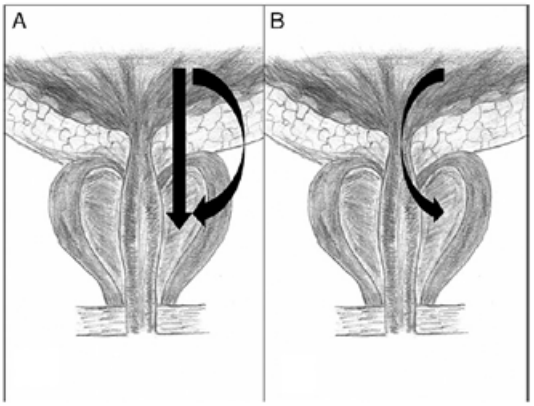

Figure 1. Prostatic invasion from urinary bladder cancer via direct transmural and extravesical route (A) and transurethral invasion (B). From: Patel AR, Cohn JA, El Latif AA, et al. Validation of new AJCC exclusion criteria for subepithelial prostatic stroma invasion from pT4a bladder urothelial carcinoma.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

References

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2. Brierley JD, Gospodarowicz MK, Wittekind C, et al., eds. *TNM Classification of Malignant Tumours*. 8th ed. Oxford, UK: Wiley; 2016.
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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.[1] Presence of lymph-vascular invasion in TURBT specimens is associated with higher nodal metastasis.[2] 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.[3]

References

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