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

Version: 4.2.0.0
Protocol Posting Date: September 2023

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:

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biopsy and transurethral resection of bladder tumor (TURBT)</td>
<td>Includes specimens designated biopsy, and transurethral resection of bladder tumor (TURBT)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carcinomas</td>
<td>Includes invasive carcinomas of the urinary bladder, including urothelial carcinoma, its morphological subtypes, and other carcinoma such as squamous cell carcinoma, adenocarcinoma, Müllerian carcinoma, neuroendocrine carcinoma*</td>
</tr>
</tbody>
</table>

* This protocol is recommended for reporting noninvasive urothelial tumors (papillary and flat), but it is not required for accreditation purposes.

The following should NOT be reported using this protocol:

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Tumor Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystectomy (consider Urinary Bladder Resection protocol)</td>
<td>Urachal Carcinoma</td>
</tr>
<tr>
<td>Lymphoma (consider the Lymphoid Neoplasm protocol)</td>
<td>Sarcoma (consider the Soft Tissue protocol)</td>
</tr>
</tbody>
</table>

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With guidance from the CAP Cancer and CAP Pathology Electronic Reporting Committees.

* Denotes primary author.

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 4.2.0.0

- WHO 5th Edition update to content and Explanatory Notes
- "Muscularis (detrusor muscle)" answer selection clarification
- LVI question update from "Lymphovascular Invasion" to "Lymphatic and/or Vascular Invasion"
Reporting Template

Protocol Posting Date: September 2023
Select a single response unless otherwise indicated.

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

This template is recommended for reporting biopsy and TURBT specimens, but is not required for accreditation purposes.

SPECIMEN (Note A)

Procedure
___ 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
___ Urothelial carcinoma, in situ
___ Urothelial carcinoma, invasive (conventional)
___ Urothelial carcinoma, micropapillary
___ Urothelial carcinoma, nested
___ Urothelial carcinoma, tubular and microcystic
___ Urothelial carcinoma, lymphoepithelioma-like
___ Urothelial carcinoma, plasmacytoid
___ Urothelial carcinoma, sarcomatoid
___ Urothelial carcinoma, giant cell
___ Urothelial carcinoma, poorly differentiated
___ Urothelial carcinoma, lipid-rich
___ Urothelial carcinoma, clear cell (glycogen-rich)
___ Urothelial carcinoma with squamous differentiation
___ Urothelial carcinoma with glandular differentiation
___ Urothelial carcinoma with trophoblastic differentiation
___ Urothelial carcinoma with Müllerian differentiation

Squamous
___ Squamous cell carcinoma
___ Verrucous carcinoma
___ Squamous cell carcinoma in situ (no invasive carcinoma identified)

**Glandular**
___ Adenocarcinoma, NOS
___ Adenocarcinoma, enteric
___ Adenocarcinoma, mucinous
___ Adenocarcinoma, mixed
___ Adenocarcinoma, signet-ring cell
___ Adenocarcinoma in situ (no invasive carcinoma identified)

**Müllerian**
___ Clear cell adenocarcinoma
___ Endometrioid carcinoma

**Neuroendocrine**
___ Small cell neuroendocrine carcinoma
___ Large cell neuroendocrine carcinoma
___ Well-differentiated neuroendocrine tumor
___ Other histologic type not listed (specify): ____________________
___ Carcinoma, type cannot be determined: ____________________

**Specify Percentages of Histologic Subtypes and Divergent Differentiations Present (totaling 100%)** (select all that apply)

# Applicable for mixed subtypes, divergent differentiations, and other carcinomas
___ Urothelial carcinoma, invasive (conventional): ____________________ %
___ Urothelial carcinoma, micropapillary: ____________________ %
___ Urothelial carcinoma, nested: ____________________ %
___ Urothelial carcinoma, large nested: ____________________ %
___ Urothelial carcinoma, tubular and microcystic: ____________________ %
___ Urothelial carcinoma, lymphoepithelioma-like: ____________________ %
___ Urothelial carcinoma, plasmacytoid: ____________________ %
___ Urothelial carcinoma, sarcomatoid: ____________________ %
___ Urothelial carcinoma, giant cell: ____________________ %
___ Urothelial carcinoma, poorly differentiated: ____________________ %
___ Urothelial carcinoma, lipid-rich: ____________________ %
___ Clear cell (glycogen-rich): ____________________ %
___ Squamous differentiation: ____________________ %
___ Glandular (adenocarcinoma) differentiation: ____________________ %
___ Trophoblastic differentiation: ____________________ %
___ Müllerian differentiation: ____________________ %
___ Small cell neuroendocrine carcinoma: ____________________ %
___ Large cell neuroendocrine carcinoma: ____________________ %
___ Other (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) (specify extent, if possible):
___ Invades muscularis propria
___ Urothelial carcinoma involves prostatic urethra, ducts, or acini without stromal invasion in prostatic chips sampled by TURBT
___ Urothelial carcinoma involves prostatic subepithelial connective tissue in prostatic chips sampled by TURBT
___ Urothelial carcinoma invades into prostatic stroma in prostatic chips sampled by TURBT
___ Cannot be determined: _________________

Lymphatic and / or Vascular 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 in specimen
___ 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
___ Other (specify): _________________
___ Cannot be determined: _________________

+Additional Findings (select all that apply)
___ Inflammation / regenerative changes
___ Therapy-related changes (specify): _________________
___ 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. 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.). A second (repeat) TURBT is now commonly performed after an initial high-grade Ta or T1 tumors and awareness of this procedure is important to correlate the current findings with the prior TURBT findings.

References

B. Histologic Type
The vast majority (more than 95%) of carcinomas of the urinary bladder are urothelial cell in origin. The most recent 2022 World Health Organization (WHO) classification of epithelial tumors of the urothelial tract is provided in this note. Benign epithelial 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.

Several subtypes (formerly variants) and divergent differentiations of invasive urothelial carcinoma are now recognized, and their presence should be documented. Invasive urothelial carcinoma subtypes such as sarcomatoid, micropapillary and plasmacytoid are recognized to be more aggressive and their presence in TURBT has impact to therapy. In cases of mixed urothelial subtypes and/or divergent differentiations, each component should be reported, including admixed neuroendocrine carcinoma if present. The distinction between a urothelial carcinoma with divergent squamous, glandular, or Müllerian differentiation and a pure squamous cell carcinoma, adenocarcinoma or Müllerian carcinoma is important. The 2022 WHO classification, require a pure histology of squamous cell carcinoma, adenocarcinoma or Müllerian to designate a tumor as such, all others with concomitant recognizable papillary, invasive, or flat carcinoma in situ (CIS) urothelial component being considered as urothelial carcinoma with divergent differentiation.

2022 WHO Classification of Epithelial Tumors of the Urothelial Tract

Urothelial tumors
Invasive urothelial carcinoma
   Conventional urothelial carcinoma
Urothelial carcinoma with squamous differentiation
Urothelial carcinoma with glandular differentiation
Urothelial carcinoma with trophoblastic differentiation
Nested urothelial carcinoma
Tubular and microcystic urothelial carcinomas
Micropapillary urothelial carcinoma
Lymphoepithelioma-like urothelial carcinoma
Plasmacytoid urothelial carcinoma
Giant cell urothelial carcinoma
Lipid-rich urothelial carcinoma
Clear cell (glycogen-rich) urothelial carcinoma
Urothelial carcinoma, poorly differentiated

**Noninvasive urothelial lesions**
Urothelial carcinoma in situ
Noninvasive papillary urothelial carcinoma, high grade
Noninvasive papillary urothelial carcinoma, low grade
Papillary urothelial neoplasm of low malignant potential
Urothelial papilloma
Inverted urothelial papilloma

**Squamous cell neoplasms**
Squamous cell carcinoma
Verrucous carcinoma
Squamous papilloma

**Glandular neoplasms**
Adenocarcinoma, NOS
   Enteric
   Mucinous
   Mixed
   Signet-ring cell
   Adenocarcinoma in situ
Villous adenoma

**Urachal and diverticular neoplasms**
Urachal carcinoma
Diverticular carcinoma

**Tumors of Mullerian type**
Clear cell adenocarcinoma
Endometrioid carcinoma

**Neuroendocrine neoplasms**
Small cell neuroendocrine carcinoma
Large cell neuroendocrine carcinoma
Mixed neuroendocrine neoplasm
Well-differentiated neuroendocrine tumor
Paraganglioma
References

C. Histologic Grade
Flat intraepithelial lesions and papillary and invasive lesions are graded separately. In the 1973 WHO classification, papillary lesions were classified as papillomas and transitional cell carcinomas, grades 1, 2 and 3. Due to the need for a universally acceptable system, the World Health Organization/International Society of Urological Pathology (WHO/ISUP) consensus classification was proposed in 1998. This system is adopted in the 2004 WHO classification and has been validated by many studies to be prognostically significant. The 2016 WHO and 2022 WHO systems used essentially the same classification with minor modifications. Other systems may still be used according to institutional preference. Tumor grade according to both the 2004 WHO system and the 1973 WHO system may be concurrently used. The 2022 WHO system includes descriptive reporting of papillary urothelial carcinoma with mixed grades (low-grade with <5% high-grade component).

2004 WHO/1998 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 provide descriptive diagnosis on low grade papillary urothelial carcinoma with focal high-grade component.

The vast majority of invasive urothelial carcinoma are high-grade with uncommon cases of invasive low-grade tumors are reported, that usually have limited involvement of the lamina propria. Invasive urothelial carcinoma subtypes are graded as high-grade tumors, although these tumors should not be considered as a homogenous group in terms of behavior. Pure squamous carcinomas and adenocarcinomas are graded based on tumor differentiation as well-differentiated, moderately differentiated, and poorly differentiated.

References
8. Epstein JI, Amin MB, Reuter VR, Mostofi FK, the Bladder Consensus Conference Committee. The World Health Organization/ International Society of Urological Pathology Consensus classification


**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 (T1), muscularis propria (T2), or beyond (T3 or T4), with the latter two categories amenable only in cystectomy specimens.12,3 In papillary tumors, invasion occurs most often at the base of the tumor and very infrequently in the stalk. A tumor infiltrating the lamina propria (T1) 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. Depth of invasion is a critical prognostic determinant in invasive urothelial carcinoma. In T1 disease, determining the extent of lamina propria is shown to have prognostic value. Several T1 subcategorization methods (e.g., micrometric and histoanatomic) have been proposed but have been difficult to adopt due in part to the inherent lack of orientation of the specimen and inconsistencies of the histoanatomic landmarks. Pathologists are, however, encouraged to provide some assessment as to the extent of lamina propria invasion (i.e., 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, i.e., muscularis mucosae (T1 tumors) versus muscularis propria (T2 tumors) invasion, needs to be clearly stated. 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. In TURBT specimens invasive into muscularis propria, no attempt should be made to subcategorize 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.

Involvement of the prostate gland may occur in several different patterns. Tumors (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). Tumors may also invade through the bladder wall and the base of the prostate directly into the prostate gland. Tumors can also invade into extravesical fat and then extend back into the prostate gland. The latter two routes are considered direct transmural invasion. The 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 T4a 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 T2 per urethral cancer staging, and the concomitant bladder proper cancer is given a separate stage category according to the bladder cancer staging. Thus, TUR showing involvement of prostatic tissue should not be automatically labeled as T4 disease.

References

E. Lymphatic and/or Vascular 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. Presence of lymph-vascular invasion in TURBT specimens is associated with higher nodal metastasis. 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 micropapillary urothelial carcinoma.
References

