Protocol for the Examination of Specimens From Patients With Carcinoma of the Urinary Bladder

Protocol applies primarily to invasive carcinomas and/or associated epithelial lesions, including carcinoma in situ.

Based on AJCC/UICC TNM, 7th edition
Protocol web posting date: June 2012

Procedures
• Bladder Biopsy, Transurethral Resection of Bladder Tumor (TURBT) Specimen
• Cystectomy (Partial, Total)
  - Radical Cystoprostatectomy
  - Pelvic Exenteration

Authors
Mahul B. Amin, MD, FCAP*
Department of Pathology and Laboratory Medicine, Cedars-Sinai Medical Center, Los Angeles, California
Brett Delahunt, MD
Department of Pathology and Molecular Medicine, Wellington School of Medicine and Health Sciences, New Zealand
Bernard H. Bohner, MD
Department of Surgery, Urology Service, Memorial Sloan-Kettering Cancer Center, New York, New York
Jonathan I. Epstein, MD
The Johns Hopkins Hospital, Baltimore, Maryland
David J. Grignon, MD, FCAP
Department of Pathology, Indiana University School of Medicine, Indianapolis, Indiana
Peter A. Humphrey, MD, PhD, FCAP
Department of Pathology and Immunology, Washington University School of Medicine and Barnes-Jewish Hospital, St. Louis, Missouri
Rodolfo Montironi, MD
Institute of Pathological Anatomy and Histopathology, University of Ancona School of Medicine, Ancona, Italy
Gladell P. Paner, MD, FCAP
Department of Pathology and Laboratory Medicine, Loyola University Medical Center, Maywood, Illinois
Andrew A. Renshaw, MD, FCAP
Department of Pathology, Baptist Hospital of Miami, Miami, Florida
Victor E. Reuter, MD, FCAP
Department of Pathology, Memorial Sloan-Kettering Cancer Center, New York, New York
John R. Srigley, MD, FCAP
Department of Laboratory Medicine, Credit Valley Hospital, Mississauga, Ontario, Canada
Ming Zhou, MD, PhD, FCAP†
Department of Pathology, New York University Langone Medical Center, New York, New York
For the Members of the Cancer Committee, College of American Pathologists

* Denotes primary author. † Denotes senior author. All other contributing authors are listed alphabetically.

Previous lead contributor: Donald Earl Henson, MD
© 2012 College of American Pathologists (CAP). All rights reserved.

The College does not permit reproduction of any substantial portion of these protocols without its written authorization. The College hereby authorizes use of these protocols by physicians and other health care providers in reporting on surgical specimens, in teaching, and in carrying out medical research for nonprofit purposes. This authorization does not extend to reproduction or other use of any substantial portion of these protocols for commercial purposes without the written consent of the College.

The CAP also authorizes physicians and other health care practitioners to make modified versions of the Protocols solely for their individual use in reporting on surgical specimens for individual patients, teaching, and carrying out medical research for non-profit purposes.

The CAP further authorizes the following uses by physicians and other health care practitioners, in reporting on surgical specimens for individual patients, in teaching, and in carrying out medical research for non-profit purposes: (1) **Dictation** from the original or modified protocols for the purposes of creating a text-based patient record on paper, or in a word processing document; (2) **Copying** from the original or modified protocols into a text-based patient record on paper, or in a word processing document; (3) The use of a **computerized system** for items (1) and (2), provided that the Protocol data is stored intact as a single text-based document, and is not stored as multiple discrete data fields.

Other than uses (1), (2), and (3) above, the CAP does not authorize any use of the Protocols in electronic medical records systems, pathology informatics systems, cancer registry computer systems, computerized databases, mappings between coding works, or any computerized system without a written license from CAP. Applications for such a license should be addressed to the SNOMED Terminology Solutions division of the CAP.

Any public dissemination of the original or modified Protocols is prohibited without a written license from the CAP.

The College of American Pathologists offers these protocols to assist pathologists in providing clinically useful and relevant information when reporting results of surgical specimen examinations of surgical specimens. The College regards the reporting elements in the “Surgical Pathology Cancer Case Summary” portion of the protocols as essential elements of the pathology report. However, the manner in which these elements are reported is at the discretion of each specific pathologist, taking into account clinician preferences, institutional policies, and individual practice.

The College developed these protocols as an educational tool to assist pathologists in the useful reporting of relevant information. It did not issue the protocols for use in litigation, reimbursement, or other contexts. Nevertheless, the College recognizes that the protocols might be used by hospitals, attorneys, payers, and others. Indeed, effective January 1, 2004, the Commission on Cancer of the American College of Surgeons mandated the use of the required data elements of the protocols as part of its Cancer Program Standards for Approved Cancer Programs. Therefore, it becomes even more important for pathologists to familiarize themselves with these documents. At the same time, the College cautions that use of the protocols other than for their intended educational purpose may involve additional considerations that are beyond the scope of this document.

The inclusion of a product name or service in a CAP publication should not be construed as an endorsement of such product or service, nor is failure to include the name of a product or service to be construed as disapproval.
CAP Urinary Bladder Protocol Revision History

Version Code
The definition of the version code can be found at www.cap.org/cancerprotocols.

Version: UrinaryBladder 3.2.0.0

Summary of Changes
The following changes have been made since the February 2011 release.

Biopsy and TURBT

Note
The word “checklist” was changed to “case summary.”

Histologic Grade (select all that apply)
“Select all that apply” was added, “Adenocarcinoma and squamous cell carcinoma” was changed to “Squamous cell carcinoma or adenocarcinoma,” and “Other carcinoma” was added.

Microscopic Tumor Extension (select all that apply)
Was changed from “Microscopic Extent of Tumor.”
“Urothelial carcinoma in situ” was changed to “Urothelial carcinoma” as follows:
___ Urothelial carcinoma involving prostatic urethra in prostatic chips sampled by TURBT
___ Urothelial carcinoma involving prostatic ducts and acini in prostatic chips sampled by TURBT

Additional Pathologic Findings
“Cystitis cystic glandularis” was changed to “Cystitis cystica et glandularis.”

Cystectomy: Anterior Exenteration

Histologic Grade (select all that apply)
“Select all that apply” was added, “Adenocarcinoma and squamous cell carcinoma” was changed to “Squamous cell carcinoma or adenocarcinoma,” and “Other carcinoma” was added.

Microscopic Tumor Extension
Reporting on this element was changed to the following:

___ Cannot be assessed
___ No evidence of primary tumor
___ Noninvasive papillary carcinoma
___ Carcinoma in situ: “flat tumor”
___ Tumor invades lamina propria
___ Tumor invades muscularis propria
    ___ Tumor invades superficial muscularis propria (inner half)
    ___ Tumor invades deep muscularis propria (outer half)
___ Tumor invades perivesical tissue
    ___ Microscopically
    ___ Macroscopically (extravesical mass)
__ Tumor invades adjacent structures
  ___ Prostatic stroma
  ___ Seminal vesicles
  ___ Uterus
  ___ Vagina
  ___ Adnexae
  ___ Pelvis wall
  ___ Abdominal wall
  ___ Rectum
  ___ Other (specify): ______________________________

Margins
Reporting on margins was changed to include noninvasive high-grade urothelial carcinoma and other significant changes at the margin and a note was added, as follows:

Margins (select all that apply)
___ Cannot be assessed
___ Margin(s) involved by invasive carcinoma
  ___ Ureteral margin
  ___ Distal urethral margin
  ___ Deep soft tissue margin
  ___ Other margin(s) (specify)*: __________________________
___ Margin(s) involved by carcinoma in situ/noninvasive high-grade urothelial carcinoma
  ___ Ureteral margin
  ___ Distal urethral margin
  ___ Other margin(s) (specify)*: __________________________
___ Margins uninvolved by invasive carcinoma/carcinoma in situ/noninvasive high-grade urothelial carcinoma
  + Distance of carcinoma from closest margin: ___ mm
  + Specify margin*: __________________________
  + Other significant changes at margin (specify margin)*: __________________________
  + ___ Low-grade dysplasia
  + ___ Non-invasive low-grade urothelial carcinoma

* For partial cystectomies, if the specimen is received unoriented precluding identification of specific margins, it should be denoted here.

Additional Pathologic Findings
“Cystitis cystic glandularis” was changed to “Cystitis cystica et glandularis.”
Surgical Pathology Cancer Case Summary

Protocol web posting date: June 2012

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

Note: Use of case summary for biopsy specimens is optional

Select a single response unless otherwise indicated.

Procedure (required only for TURBT) (Note A)
- Biopsy
- TURBT
- Other (specify): ____________________________
- Not specified

Histologic Type (Note B)
- Urothelial (transitional cell) carcinoma
- Urothelial (transitional cell) carcinoma with squamous differentiation
- Urothelial (transitional cell) carcinoma with glandular differentiation
- Urothelial (transitional cell) carcinoma with variant histology (specify): ____________________________
- Squamous cell carcinoma, typical
- Squamous cell carcinoma, variant histology (specify): ____________________________
- Adenocarcinoma, typical
- Adenocarcinoma, variant histology (specify): ____________________________
- Small cell carcinoma
- Undifferentiated carcinoma (specify): ____________________________
- Mixed cell type (specify): ____________________________
- Other (specify): ____________________________
- Carcinoma, type cannot be determined

Associated Epithelial Lesions (select all that apply) (Note C)
- None identified
- Urothelial (transitional cell) papilloma (World Health Organization [WHO] 2004/International Society of Urologic Pathology [ISUP])
- Urothelial (transitional cell) papilloma, inverted type
- Papillary urothelial (transitional cell) neoplasm, low malignant potential (WHO 2004/ISUP)
- Cannot be determined

Histologic Grade (select all that apply) (Note C)
- Not applicable
- Cannot be determined
- Urothelial carcinoma
  - Low-grade
  - High-grade
  - Other (specify): ____________________________

+ Data elements preceded by this symbol are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.
__ Squamous cell carcinoma or adenocarcinoma
   __ GX: Cannot be assessed
   __ G1: Well differentiated
   __ G2: Moderately differentiated
   __ G3: Poorly differentiated
   __ Other (specify): ___________________________

__ Other carcinoma
   __ Low-grade
   __ High-grade
   __ Other (specify): ___________________________

+ Tumor Configuration (select all that apply)
  + ___ Papillary
  + ___ Solid/nodule
  + ___ Flat
  + ___ Ulcerated
  + ___ Indeterminate
  + ___ Other (specify): ___________________________

Adequacy of Material for Determining Muscularis Propria Invasion (Note D)
   __ Muscularis propria (detrusor muscle) not identified
   __ Muscularis propria (detrusor muscle) present
   __ Presence of muscularis propria indeterminate

Lymph-Vascular Invasion (Note E)
   __ Not identified
   __ Present
   __ Indeterminate

Microscopic Tumor Extension (select all that apply) (Note F)
   __ Cannot be assessed
   __ Noninvasive papillary carcinoma
   __ Flat carcinoma in situ
   __ Tumor invades subepithelial connective tissue (lamina propria)
   __ Tumor invades muscularis propria (detrusor muscle)
   __ 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

+ Additional Pathologic Findings (select all that apply)
  + ___ Urothelial dysplasia (low-grade intraurothelial neoplasia)
  + ___ Inflammation/regenerative changes
  + ___ Therapy-related changes
  + ___ Cautery artifact
  + ___ Cystitis cystica et glandularis
  + ___ Keratinizing squamous metaplasia
  + ___ Intestinal metaplasia
  + ___ Other (specify): ___________________________

+ Comment(s)

+ Data elements preceded by this symbol are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.
Surgical Pathology Cancer Case Summary

Protocol web posting date: June 2012

URINARY BLADDER: Cystectomy, Partial, Total, or Radical; Anterior Exenteration

Select a single response unless otherwise indicated.

Specimen
___ Bladder
___ Other (specify): ____________________________
___ Not specified

Procedure (Note G)
___ Partial cystectomy
___ Total cystectomy
___ Radical cystectomy
___ Radical cystoprostatectomy
___ Anterior exenteration
___ 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

Tumor Size
Greatest dimension: ___ cm
+ Additional dimensions: ___ x ___ cm
___ Cannot be determined (see Comment)

Histologic Type (Note B)
___ Urothelial (transitional cell) carcinoma
___ Urothelial (transitional cell) carcinoma with squamous differentiation
___ Urothelial (transitional cell) carcinoma with glandular differentiation
___ Urothelial (transitional cell) carcinoma with variant histology (specify): ____________________________
___ Squamous cell carcinoma, typical
___ Squamous cell carcinoma, variant histology (specify): ____________________________
___ Adenocarcinoma, typical
___ Adenocarcinoma, variant histology (specify): ____________________________
___ Small cell carcinoma
___ Undifferentiated carcinoma (specify): ____________________________
___ Mixed cell type (specify): ____________________________
___ Other (specify): ____________________________
___ Carcinoma, type cannot be determined

+ Data elements preceded by this symbol are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.
**Associated Epithelial Lesions (select all that apply) (Note C)**

- None identified
- Urothelial (transitional cell) papilloma (World Health Organization [WHO] 2004/ International Society of Urologic Pathology [ISUP])
- Urothelial (transitional cell) papilloma, inverted type
- Papillary urothelial (transitional cell) neoplasm, low malignant potential (WHO 2004/ISUP)
- Cannot be determined

**Histologic Grade (select all that apply) (Note C)**

- Not applicable
- Cannot be determined
- Urothelial carcinoma
  - Low-grade
  - High-grade
  - Other (specify):
- Squamous cell carcinoma or adenocarcinoma
  - GX: Cannot be assessed
  - G1: Well differentiated
  - G2: Moderately differentiated
  - G3: Poorly differentiated
  - Other (specify):
- Other carcinoma
  - Low-grade
  - High-grade
  - Other (specify):

**+ Tumor Configuration (select all that apply)**

+ Papillary
+ Solid/nodule
+ Flat
+ Ulcerated
+ Indeterminate
+ Other (specify):

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

- Cannot be assessed
- No evidence of primary tumor
- Noninvasive papillary carcinoma
- Carcinoma in situ: “flat tumor”
- Tumor invades lamina propria
- Tumor invades muscularis propria
  - Tumor invades superficial muscularis propria (inner half)
  - Tumor invades deep muscularis propria (outer half)
- Tumor invades perivesical tissue
  - Microscopically
  - Macroscopically (extravesical mass)

* Data elements preceded by this symbol are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.
- Tumor invades adjacent structures
  - Prostatic stroma
  - Seminal vesicles
  - Uterus
  - Vagina
  - Adnexae
  - Pelvis wall
  - Abdominal wall
  - Rectum
  - Other (specify): ______________________________

Margins (select all that apply) (Note G)
- Cannot be assessed
- Margin(s) involved by invasive carcinoma
  - Ureteral margin
  - Distal urethral margin
  - Deep soft tissue margin
  - Other margin(s) (specify)*: __________________________
- Margin(s) involved by carcinoma in situ/noninvasive high-grade urothelial carcinoma
  - Ureteral margin
  - Distal urethral margin
  - Other margin(s) (specify)*: __________________________
- Margin(s) uninvolved by invasive carcinoma/carcinoma in situ/noninvasive high-grade urothelial carcinoma
  + Distance of carcinoma from closest margin: ___ mm
  + Specify margin*: __________________________
  + Other significant changes at margin (specify margin)*: __________________________
  + Low-grade dysplasia
  + Non-invasive low-grade urothelial carcinoma

* For partial cystectomies, if the specimen is received unoriented precluding identification of specific margins, it should be denoted here.

Lymph-Vascular Invasion (Note E)
- Not identified
- Present
- Indeterminate

Pathologic Staging (pTNM) (Note F)

TNM Descriptors (required only if applicable) (select all that apply)
- m (multiple primary tumors)
- r (recurrent)
- y (posttreatment)

Primary Tumor (pT)
- pTX: Primary tumor cannot be assessed
- pTX: No evidence of primary tumor
- pTa: Noninvasive papillary carcinoma
- pTis: Carcinoma in situ: “flat tumor”
- pT1: Tumor invades subepithelial connective tissue (lamina propria)
- pT2: Tumor invades muscularis propria (detrusor muscle)
  - pT2a: Tumor invades superficial muscularis propria (inner half)
  + Data elements preceded by this symbol are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.
**pT2b:** Tumor invades deep muscularis propria (outer half)

**pT3:** Tumor invades perivesical tissue

- **pT3a:** Microscopically
- **pT3b:** Macroscopically (extravesicular mass)

**pT4:** Tumor invades any of the following: prostatic stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall

- **pT4a:** Tumor invades prostatic stroma or uterus or vagina
- **pT4b:** Tumor invades pelvic wall or abdominal wall

**Regional Lymph Nodes (pN)**

- **pNX:** Lymph nodes cannot be assessed
- **pN0:** No lymph node metastasis
- **pN1:** Single regional lymph node metastasis in the true pelvis (hypogastric, obturator, external iliac or presacral lymph node)
- **pN2:** Multiple regional lymph node metastasis in the true pelvis (hypogastric, obturator, external iliac or presacral lymph node metastasis)
- **pN3:** Lymph node metastasis to the common iliac lymph nodes

- No nodes submitted or found

**Number of Lymph Nodes Examined**

Specify: __________

- Number cannot be determined (explain): ________________

**Number of Lymph Nodes Involved (any size)**

Specify: __________

- Number cannot be determined (explain): ________________

**Distant Metastasis (pM)**

- Not applicable
- **pM1:** Distant metastasis
  
  + Specify site(s), if known: ____________________________

**Additional Pathologic Findings (select all that apply)**

- **Adenocarcinoma of prostate (use protocol for carcinoma of prostate)**
- **Urothelial (transitional cell) carcinoma involving urethra, prostatic ducts and acini with or without stromal invasion (use protocol for carcinoma of urethra)**
- **Urothelial dysplasia (low-grade intraurothelial neoplasia)**
- **Inflammation/regenerative changes**
- **Therapy-related changes**
- **Cystitis cystica et glandularis**
- **Keratinizing squamous metaplasia**
- **Intestinal metaplasia**
- **Other (specify): ____________________________**

**Comment(s)**
Explanatory Notes

A. History
A relevant history is important for interpretation of all bladder specimens.\textsuperscript{1-4} 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). The method of collection and date also should be specified in urine cytology specimens.

B. Histologic Type
The vast majority (more than 95%) of carcinomas of the urinary bladder, renal pelvis, and ureter are urothelial or transitional cell in origin. A working histologic classification encompassing the wide histologic diversity and histologic range within the different types of carcinomas of the urothelial tract is tabulated 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.\textsuperscript{5-12} The distinction between a urothelial carcinoma with aberrant squamous or glandular differentiation and a primary squamous cell carcinoma or adenocarcinoma is rather arbitrary. Most authorities require a pure histology of squamous cell carcinoma or adenocarcinoma 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 aberrant differentiation.

Classification of Neoplasms of the Urinary Bladder, Including Urothelial (Transitional Cell) Carcinoma and Its Variants*

<table>
<thead>
<tr>
<th>Urothelial (Transitional Cell) Neoplasia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Benign</strong></td>
</tr>
<tr>
<td>Inverted papilloma</td>
</tr>
<tr>
<td>Papillary urothelial neoplasm of low malignant potential (WHO 2004/ISUP); WHO, 1973, grade I)</td>
</tr>
<tr>
<td><strong>Malignant</strong></td>
</tr>
<tr>
<td><strong>Papillary</strong></td>
</tr>
<tr>
<td>Typical, noninvasive</td>
</tr>
<tr>
<td>Typical, with invasion</td>
</tr>
<tr>
<td>Variant</td>
</tr>
<tr>
<td>With squamous or glandular differentiation</td>
</tr>
<tr>
<td><strong>Micropapillary</strong></td>
</tr>
<tr>
<td><strong>Nonpapillary</strong></td>
</tr>
<tr>
<td>Carcinoma in situ</td>
</tr>
<tr>
<td>Invasive carcinoma</td>
</tr>
<tr>
<td><strong>Variants containing or exhibiting</strong></td>
</tr>
<tr>
<td>Deceptively benign features</td>
</tr>
<tr>
<td>Nested pattern (resembling von Brunn's nests)</td>
</tr>
<tr>
<td>Small tubular pattern</td>
</tr>
<tr>
<td>Microcystic pattern</td>
</tr>
<tr>
<td>Inverted pattern</td>
</tr>
<tr>
<td>Squamous differentiation</td>
</tr>
<tr>
<td>Glandular differentiation</td>
</tr>
</tbody>
</table>
Micropapillary histology
Sarcomatoid foci ("sarcomatoid carcinoma")
Urothelial carcinoma with unusual cytoplasmic features
  Clear cell (glycogen rich)
  Plasmacytoid
  Rhabdoid
  Lipoid rich
Urothelial carcinoma with syncytiotrophoblasts
Unusual stromal reactions
  Pseudosarcomatous stroma
  Stromal osseous or cartilaginous metaplasia
  Osteoclast-type giant cells
  With prominent lymphoid infiltrate

Squamous Cell Carcinoma
  Typical
  Variant
    Verrucous carcinoma
    Basaloid squamous cell carcinoma
    Sarcomatoid carcinoma

Adenocarcinoma
  Anatomic variants
    Bladder mucosa
    Urachal
    With extrophy
    From endometriosis
  Histologic variants
    Typical intestinal type
    Mucinous (including colloid)
    Signet-ring cell
    Clear cell
    Hepatoid
    Mixture of above patterns – adenocarcinoma not otherwise specified (NOS)

Tumors of Mixed Cell Types
Undifferentiated Carcinoma###
  Small cell carcinoma
  Large cell neuroendocrine carcinoma
  Lymphoepithelioma-like carcinoma
  Osteoclast-rich carcinoma
  Giant cell carcinoma
  Not otherwise specified

Metastatic Carcinoma

# Modified from Amin et al.5

## Papillary tumors may be invasive or noninvasive, and when invasive may be microinvasive (invasive to a depth of 2 mm or less) or frankly invasive (like nonpapillary tumors).

### Refers to tumors that are undifferentiated by light microscopy.

C. Histologic Grade
Flat intraepithelial lesions and papillary and invasive lesions are graded separately.10-16 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.\textsuperscript{5,7} 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.\textsuperscript{12-14} 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.\textsuperscript{12} This system is adopted in the WHO 2004 “blue book”\textsuperscript{10} and 2004 AFIP fascicle.\textsuperscript{11} Other systems (that were being used previously) may still be used according to institutional preference. Until the WHO/ISUP system is clinically and prognostically validated, tumor grade according to both the WHO/ISUP (1998)\textsuperscript{12} / WHO (2004)\textsuperscript{10} system and the older WHO (1973)\textsuperscript{14} system, e.g., papillary urothelial neoplasm of low malignant potential (WHO/ISUP, 1998)/transitional cell carcinoma, grade I (WHO, 1973), may be concurrently used.

The WHO (1999) classification of bladder tumors\textsuperscript{9} differs only slightly from the WHO/ISUP (1998)\textsuperscript{12} and WHO (2004)\textsuperscript{10} system\textsuperscript{12} in that carcinomas are graded on a I to III scale in the former and low-grade and high-grade in the latter. Most cases designated as grade II and III by the WHO (1999) system correspond to high-grade carcinomas in the WHO/ISUP (1998) and WHO (2004) Consensus Classification.

**World Health Organization (WHO) 2004/ International Society of Urologic Pathology (ISUP) Consensus Classification for Urothelial (Transitional Cell) Lesions**

<table>
<thead>
<tr>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal#</td>
</tr>
<tr>
<td>Hyperplasia</td>
</tr>
<tr>
<td>Flat hyperplasia</td>
</tr>
<tr>
<td>Papillary hyperplasia</td>
</tr>
<tr>
<td>Flat Lesions with Atypia</td>
</tr>
<tr>
<td>Reactive (inflammatory) atypia</td>
</tr>
<tr>
<td>Atypia of unknown significance</td>
</tr>
<tr>
<td>Dysplasia (low-grade intraurothelial neoplasia)#</td>
</tr>
<tr>
<td>Carcinoma in situ (high-grade intraurothelial neoplasia)##</td>
</tr>
<tr>
<td>Papillary Neoplasms</td>
</tr>
<tr>
<td>Papilloma</td>
</tr>
<tr>
<td>Inverted papilloma</td>
</tr>
<tr>
<td>Papillary neoplasm of low malignant potential</td>
</tr>
<tr>
<td>Papillary carcinoma, low-grade</td>
</tr>
<tr>
<td>Papillary carcinoma, high-grade###</td>
</tr>
<tr>
<td>Invasive Neoplasms</td>
</tr>
<tr>
<td>Lamina propria invasion</td>
</tr>
<tr>
<td>Muscularis propria (detrusor muscle) invasion</td>
</tr>
</tbody>
</table>

* 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.

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

**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).\textsuperscript{17-19} 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. Although attempts at substaging bladder pT1 tumors have been made, the WHO/ISUP committee recommended that it is currently not necessary for the practice to be universally adopted. Pathologists are, however, encouraged to provide some assessment as to the extent of lamina propria invasion (ie, focal versus extensive, 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. 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 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.

Involvement of the prostate gland may occur in several different patterns. The prostatic urethra may be involved (flat carcinoma in situ, papillary or invasive carcinoma), or the prostate gland may be involved. Involvement of the prostate gland may be evident as involvement of prostatic ducts and acini without stromal invasion (carcinoma in situ involving prostate glands) or as urothelial carcinoma involving prostatic stroma (either from prostatic urethral carcinoma, carcinoma extending directly through the bladder wall, or carcinoma involving prostatic ducts and acini additionally with stromal invasion).

E. Lymph-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 the “micropapillary variant” of urothelial carcinoma.

F. TNM and Stage Groupings
The TNM Staging System for carcinomas of the urinary bladder of the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) is recommended. A cystoprostatectomy specimen may contain 3 separate primaries: carcinoma of the urinary bladder, carcinoma of the prostate and carcinoma of the urethra. Depending on the pathology in a given case, the number of protocols to be used in a cystoprostatectomy specimen will vary.

By AJCC/UICC convention, the designation “T” refers to a primary tumor that has not been previously treated. The symbol “p” refers to the pathologic classification of the TNM, as opposed to the clinical classification, and is based on gross and microscopic examination. pT entails a resection of the primary tumor or biopsy adequate to evaluate the highest pT category, pN entails removal of nodes adequate to validate lymph node metastasis, and pM implies microscopic examination of distant lesions. Clinical classification (cTNM) is usually carried out by the referring physician before treatment during initial evaluation of the patient or when pathologic classification is not possible.
Pathologic staging is usually performed after surgical resection of the primary tumor. Pathologic staging depends on pathologic documentation of the anatomic extent of disease, whether or not the primary tumor has been completely removed. If a biopsied tumor is not resected for any reason (eg, when technically unfeasible) and if the highest T and N categories or the M1 category of the tumor can be confirmed microscopically, the criteria for pathologic classification and staging have been satisfied without total removal of the primary cancer.

**Primary Tumor (T)** (Figure 1)

The suffix “m” should be added to the appropriate T category to indicate multiple tumors. The suffix “is” may be added to any T to indicate the presence of associated carcinoma in situ.


<table>
<thead>
<tr>
<th>TNM Stage Groupings</th>
<th>Stage 0a</th>
<th>Stage 0is</th>
<th>Stage I</th>
<th>Stage II</th>
<th>Stage III</th>
<th>Stage IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ta</td>
<td>N0</td>
<td>M0#</td>
<td>T1</td>
<td>T2a</td>
<td>T3a</td>
<td>T4b</td>
</tr>
<tr>
<td>Tis</td>
<td>N0</td>
<td>M0</td>
<td>N0</td>
<td>N0</td>
<td>N0</td>
<td>N0</td>
</tr>
<tr>
<td>T1</td>
<td>N0</td>
<td>M0</td>
<td>N0</td>
<td>N0</td>
<td>N0</td>
<td>N0</td>
</tr>
<tr>
<td>T2a</td>
<td>N0</td>
<td>M0</td>
<td>T2b</td>
<td>T3a</td>
<td>T4a</td>
<td>T4b</td>
</tr>
<tr>
<td>T2b</td>
<td>N0</td>
<td>M0</td>
<td>N0</td>
<td>N0</td>
<td>N0</td>
<td>N0</td>
</tr>
<tr>
<td>T3a</td>
<td>N0</td>
<td>M0</td>
<td>T3b</td>
<td>T4a</td>
<td>N1,2,3</td>
<td>N0</td>
</tr>
<tr>
<td>T3b</td>
<td>N0</td>
<td>M0</td>
<td>N0</td>
<td>N0</td>
<td>M0</td>
<td>N0</td>
</tr>
<tr>
<td>T4a</td>
<td>N0</td>
<td>M0</td>
<td>N0</td>
<td>N0</td>
<td>N1,2,3</td>
<td>M0</td>
</tr>
<tr>
<td>T4b</td>
<td>N0</td>
<td>M0</td>
<td>N0</td>
<td>N0</td>
<td>N0</td>
<td>M1</td>
</tr>
</tbody>
</table>

# M0 is defined as no distant metastasis.
TNM Descriptors
For identification of special cases of TNM or pTNM classifications, the “m” suffix and “y” and “r” prefixes are used. Although they do not affect the stage grouping, they indicate cases needing separate analysis.

The “m” suffix indicates the presence of multiple primary tumors in a single site and is recorded in parentheses: pT(m)NM.

The “y” prefix indicates those cases in which classification is performed during or following initial multimodality therapy (ie, neoadjuvant chemotherapy, radiation therapy, or both chemotherapy and radiation therapy). The cTNM or pTNM category is identified by a “y” prefix. The ycTNM or ypTNM categorizes the extent of tumor actually present at the time of that examination. The “y” categorization is not an estimate of tumor prior to multimodality therapy (ie, before initiation of neoadjuvant therapy).

The “r” prefix indicates a recurrent tumor when staged after a documented disease-free interval, and is identified by the “r” prefix: rTNM.

Additional Descriptors
Residual Tumor (R)
Tumor remaining in a patient after therapy with curative intent (eg, surgical resection for cure) is categorized by a system known as R classification, shown below.

RX Presence of residual tumor cannot be assessed
R0 No residual tumor
R1 Microscopic residual tumor
R2 Macroscopic residual tumor

For the surgeon, the R classification may be useful to indicate the known or assumed status of the completeness of a surgical excision. For the pathologist, the R classification is relevant to the status of the margins of a surgical resection specimen. That is, tumor involving the resection margin on pathologic examination may be assumed to correspond to residual tumor in the patient and may be classified as macroscopic or microscopic according to the findings at the specimen margin(s).

G. Sections for Microscopic Evaluation
Bladder
Sections of bladder for microscopic evaluation are as follows. In TURBT specimens, submit 1 section per centimeter of tumor diameter (up to 10 cassettes). If the tumor is noninvasive by the initial sampling, additional submission of tissue (including possibly submitting all tissue) is necessary to diagnose or rule out the presence of invasion. If tumor is invasive into lamina propria in the initial sampling, additional sections (including possibly submitting the entire specimen) may be necessary to diagnose or rule out the possibility of muscularis propria invasion. In cystectomy specimens, several representative sections of the tumor, including the macroscopically deepest penetration, should be sampled. Submit several sections of the mucosa remote from the carcinoma, especially if abnormal, including the lateral wall(s), dome, and trigone. Submit 1 section of ureteral margin, unless submitted separately as frozen section specimens, and 1 section of urethral margin. If a long segment of the ureter(s) is present, then additional sections from the mid-portion may be necessary, as urothelial cancer often is multifocal.
Prostate and Prostatic Urethra
Prostatic urethral involvement should be carefully investigated in cystectomy specimens. Sections should include the prostatic urethra, including at the margin and with the surrounding prostatic parenchyma. Representative sections of the peripheral zone, central zone, and seminal vesicles should be included. Close gross examination may help target sampling of selective abnormal-appearing areas.

Lymph Nodes
Submit 1 section from each grossly positive lymph node. All other lymph nodes should be entirely submitted, as presence of nodal disease may be used as an indication for adjuvant therapy. Lymph nodes may be grossly or microscopically detected in the perivesical fat.

Other Tissues
Submit 1 or more sections of uterus (as indicated) and 1 or more sections of vagina, seminal vesicles, and other organs (as indicated). If the tumor grossly appears to invade the prostate, uterus, or vagina, sections should be targeted, such that the relationship of the infiltrating tumor in the bladder wall and the adjacent viscus is clearly demonstrable.

H. Margins
Resection margins, including those mentioned in Note G, should be carefully specified. Statements about deep soft tissue margins should specify whether peritoneal surfaces are involved by tumor. In cases of urachal adenocarcinoma in which partial cystectomy with excision of the urachal tract and umbilicus is performed, the margins of the urachal tract, ie, the soft tissue surrounding the urachus and the skin around the umbilical margin, should be specified. In renal pelvis, ureter, and nephroureterectomy specimens, the margins may include radial hilar soft tissue margin; bladder cuff; and ureteral, renal parenchymal, and Gerota’s fascia margins, depending on the type of surgical specimen.

References
Background Documentation