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Challenges in the Pathology of Non–Muscle-Invasive Bladder Cancer: a Dialogue Between the Urologic Surgeon and the Pathologist

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Abstract

Approximately 70% to 80% of urothelial carcinomas are detected at the stage of non–muscle-invasive bladder cancer (NMIBC). Initial management is often successful, but recurrence is common and leads to a long, burdensome, costly disease course. The quality and efficiency of care depends in part on accurate, clearly communicated descriptions of tumor characteristics. This review identifies current best practices, unmet needs, and key issues in the pathology of NMIBC for the practicing urologist. Reasonable and objective recommendations are provided with the goal of improving urologist–pathologist communication, the efficiency of healthcare utilization, and outcomes for patients with NMIBC.

Introduction

Bladder cancer is a common, burdensome, and costly disease. In the United States and Europe, the urinary bladder is the fourth most common site for newly diagnosed cancer in men, and the eleventh and fourteenth most common site for new cancers in women, respectively.^{1,2} Approximately 70% to 80% of urothelial carcinomas (UC) are detected at the stage of non–muscle-invasive bladder cancer (NMIBC), increasing the chances of successful initial management.³ However, NMIBC lesions often recur, especially with high-grade Ta, T1, and carcinoma in situ (CIS) disease. Tumor recurrence occurs in 33% to 39% of patients with Ta or T1 tumors after transurethral resection of the bladder tumor (TURBT) plus intravesical (IVe) bacillus Calmette-Guérin (BCG) immunotherapy.^{4,5} Compared with complete response after induction therapy with BCG, recurrence after a course of BCG is associated with a greater risk of progression to muscle-invasive bladder cancer (MIBC) and death.^{6,7} CIS predisposes patients with BCG-refractory tumors to a greater risk of

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progression and death.⁶ For patients with CIS (median follow-up, 3.6 y), the recurrence rate in complete responders to BCG or chemotherapy was 34% and 50%, respectively.⁸ Risk of recurrence and progression may be best estimated with algorithms that incorporate not only stage and grade, but also multiplicity, diameter, and prior recurrence(s).⁹

Diagnosis and monitoring of bladder cancer involves a comprehensive battery of procedures and treatments, such as cystoscopy (often with biopsy and tumor resection), urine cytology, upper tract imaging, and instillation of immunotherapeutic or chemotherapeutic agents.¹⁰ As a result of protracted disease evolution, patients may undergo multiple diagnostic/surgical procedures and treatments over an extended period of time,¹¹ making bladder cancer the most expensive malignancy in the United States in terms of lifetime per-patient Medicare costs (estimated total:\$154,280–\$284,197,¹¹ adjusted for 2012 medical cost inflation, <http://www.halfhill.com/inflation.html>).

The quality of care for bladder cancer depends in part on accurate descriptions of tumor characteristics. An open communication pathway between urologists and pathologists is essential for accurate diagnosis and appropriate treatment.^{12,13} Multidisciplinary teams have long been recommended for the management of urologic cancers as a way to integrate knowledge from specialists in different fields in a way that results in rapid, effective decision-making.¹⁴ Fostering communication would be expected to lead to more efficient healthcare utilization and better outcomes for patients with NMIBC.

Because medicine, especially oncology, is advancing quickly and becoming increasingly specialized, it is becoming more difficult for physicians to meet the requirements of keeping abreast of current knowledge across a broad range of topics. Discrepancies between surgeons and pathologists on interpretation of pathology reports are common (~30%) and not limited to urology.¹⁵ Several recent articles published in pathology journals have examined best practices for pathologists as they characterize urinary bladder specimens.^{16,17} However, until very recently, there was an absence of current resources on bladder cancer pathology for a urology audience, particularly regarding new best practices for genitourinary pathology. For example, this topic was only recently updated in August 2012 on the American Urological Association (AUA) website, with the previous version dated October 2001. Other updates on bladder cancer pathology, based, in part, on the proceedings from the 2nd International Consultation on Bladder Cancer, were published in late 2012.^{12,13}

This review identifies current best practices, unmet needs, and key issues to be resolved in the pathology of NMIBC for the practicing urologist. The focus is on clinical care of the patient, although directions for future research are briefly delineated, and guidance is given relative to other articles that provide a more in depth discussion on pathology. The goal of this article is to foster more effective collaboration between urologists and pathologists by providing reasonable and objective recommendations for uro-oncology multidisciplinary teams.

Unmet Needs and Key Issues for Genitourinary Pathology

Specialization in genitourinary pathology remains relatively rare, and most pathologists work with a large variety of tissue types. This lack of specific expertise in uropathology can lead to inexact reporting. Variance in bladder tumor diagnosis among pathologists is a long-standing concern that has not been completely resolved despite efforts towards standardization and quality control.¹⁸ In 2001, the overall discrepancy rate between first (done by referring pathologists) and second (done by a central laboratory with uropathology specialization) pathology reports for bladder cancer was 18% in one report¹⁹ and 21% in another.²⁰ In another report from 2008, a second TURBT (done by a surgeon with >10 y of experience) within 8 weeks of the first (from a referring clinician) resulted in restaging in 16% of patients with NMIBC when evaluated by an experienced genitourinary pathologist.²¹ Efforts to enhance uropathology training have yielded some improvements in accuracy. After the Cleveland Clinic instituted a program in genitourinary pathology in 2003, discrepancies between first and second pathology findings of CIS versus lower-risk NMIBC decreased significantly; however, overall diagnostic discrepancies decreased only slightly (from 33% to 27%; $P=0.41$).²² The authors concluded that it might be impossible to reduce levels of discrepancy to below 10% to 15% because of the interobserver variation inherent in pathologic interpretation.

Use of standardized terminology is important for diagnosis and subsequent treatment. Although staging of NMIBC tends to be straightforward, grading of NMIBC is more problematic (Table 1), with divergent schemes that are based on previous/current recommendations. As recently as 2011,¹⁸ members of the European Network of Uropathology (ENUP) reported extensive variability in their pathologic handling of TURBT samples,¹⁸ despite systematic attempts at standardization.²³ ENUP member surveys¹⁸ suggested that different World Health Organization (WHO) grading systems are used: 51.7% use WHO 2004,²⁴ 43.6% use WHO 1973,²⁵ and 32.0% use the non-recommended WHO 1999.²⁶ Some ENUP pathologists use both WHO 2004 and 1973,¹⁸ which is recommended by the European Association of Urology (EAU) and the European Society of Pathology (ESP).^{9,27} Because of the issues outlined above, communication between clinicians and pathologists is essential if questions arise regarding the terminology in the pathology report.

Recently, the 2nd International Consultation on Bladder Cancer meeting occurred in Vienna with the goal of unifying pathologic reporting. A comprehensive article on their findings was published in late 2012, and will be a valuable resource to both pathologists as well as urologists who wish to expand their knowledge of bladder cancer pathology.¹³ A complementary article on pathology standards for TURBT and radical cystectomy specimens also provides more information to urologists who wish to expand their knowledge in pathology.¹²

Incomplete or absent clinical information can be a major stumbling block to preparing an accurate, comprehensive pathology report. For example, a recent analysis of Surveillance, Epidemiology and End Results (SEER) diagnostic procedure data suggested that few patients with high-grade NMIBC received all suggested procedures (eg, 8 cystoscopies, 8 cytologies, 2 upper tract imaging studies) per AUA, National Comprehensive Cancer

Network (NCCN), and EAU guidelines for bladder cancer.¹⁰ This suggests that urologists may not follow standardized practices, resulting in variation in the reporting of clinical information to the pathologist. However, incomplete information may sometimes be overcome by careful pathologic examination. For example, negative urine cytologies occurred in 3 of 9 Japanese patients where CIS was later identified by the pathologist based on multiple samples of suspicious urothelium.²⁸ CIS and/or multiplicity of tumors was identified by pathology review of multiple specimens from several areas of the bladder in 22% of cases.²⁸

How Urologists Can Provide Good Specimens for Pathologists

The pathologist's interpretation of the tissue is dependent on the quality of specimens received. Recommendations for good sampling techniques have been published as part of urology guidelines both in the United States and internationally,^{9,27,29,30} as standard protocols by the College of American Pathologists (CAP)³¹ and the ESP,²⁷ and as pathology best practices recommendations.^{16,17} However, technological advances continue to introduce factors that increase the complexity of the pathologist's work and, therefore, are areas in which careful attention by the surgeon can be helpful. For example, laparoscopic and robotic surgery may produce specimens from areas that are not easily sampled with conventional techniques; these samples also may exhibit artifacts particular to the collection technique.^{12,16} Similarly, flexible ureteroscopy has enabled easier sampling of the upper urinary tract than was possible in the past.³² This article focuses on sampling and handling of tissue taken during TURBT that will ultimately provide easily readable pathology material in the diagnosis of urothelial neoplasia (Figure 1 provides images of readily diagnosable CIS).

For specimens taken during TURBT, the depth of sampling should extend into the muscle of the bladder wall. Tumors 1 cm in diameter can be resected en bloc during TURBT,^{9,29} whereas larger tumors should be removed in smaller fragments. The TURBT specimen excised with a diathermy loop may typically be a strip 6 mm in width.¹⁷ One specimen should be submitted to the pathology laboratory per 1 centimeter of tumor diameter as observed prior to resection (up to 10 specimens for each tumor).^{17,27} Areas of the bladder wall other than overt tumors may be sampled to increase the chances of detecting a muscle-invasive or high-grade tumor, even when the less-aggressive tumors are more visually prominent. Such areas include any erythematous, velvety patches (possible CIS), several sites distant from the tumor (to assess degree of urothelial involvement, such as with multifocal tumors), and the prostatic urethra.^{9,17,27} In contrast to a TURBT sample, a typical cold-cup biopsy sample for these areas is smaller, with typical diameter of 2 to 3 mm.^{16,17} Designating the orientation of the biopsy is critical for pathologic interpretation, as missing information on spatial orientation may prevent the pathologist from making an interpretation on the invasion depth.¹² Samples from the tumor base, exophytic portion, and neighboring regions should be submitted to the pathology laboratory in separate containers so that it is clear which segment will be used to determine muscle invasiveness.^{9,17,27,29}

Additional considerations apply to different aspects of specimen collection and handling. Cautery and crush artifacts distort the microscopic appearance of tissue and confound

diagnosis; they should be avoided as much as feasible.^{12,13,29} Excessive handling before fixation can have similar effects.¹⁷ Contact with absorbent materials (eg, dry paper towels) destroys nuclear detail because of desiccation, and should be avoided.³³ Any immediate fixation should follow a protocol that is standardized for fixative type (eg, 10% formalin) and the duration of immersion.¹⁶ Delays in fixation lead to tissue breakdown and loss of specimen quality, but fresh specimens can be briefly held (ice-cooled, but not actually in contact with the ice) if they are to be entered into a tissue bank.¹⁶ Multiple types of sampling issues during TURBT (eg, tangential sectioning, thermal artifact, minimal detrusor muscle in TURBT specimen) can contribute to either overstaging or understaging of disease by the pathologist, so these should be avoided as much as possible.¹²

For accurate pathology reporting, accompanying patient history, disease characteristics, and cystoscopy findings are relevant to the pathologist because they may alter diagnosis.¹² The urologist should provide pertinent patient medical information (Table 2) to the pathologist in a format that is easy to access. If it is uncertain whether a particular piece of information may be useful for the pathologist, it is preferable to include it.

Special requirements apply for “biobanking” of specimens (see section on Future Directions) and several international organizations have issued guidelines for the operation of biorepositories.^{34,35} In the United States, the National Cancer Institute (NCI) Office of Biorepositories and Biospecimen Research publishes best practices recommendations³⁶ and the CAP has established an accreditation program for biorepositories.³⁷ In Europe, extensive biobanking networks are being established by linking existing pathology archives under the supervision of the Biobanking and Biomolecular Resources Research Infrastructure initiative (<http://www.bbmri.eu>) and the PatB Network (<http://www.impactsnetwork.eu/Sections.aspx?section=218>). Although specific protocols must be followed, many of the requirements for biobanking are in concordance with good practice recommendations for uropathology specimens.

How Pathologists Can Provide Good Reports for Urologists

The quality of the pathology results influences the quality of treatment decisions. Standard reporting elements based on defined protocols^{12,13} and synoptic reporting templates, such as those available from the CAP³¹ and as a checklist from the ESP,²⁷ can help produce clear output for the urologist. Use of synoptic templates may reduce incomplete reporting, thus giving a fuller clinical picture. Along with standard templates, a preferred set of terms should be used and, conversely, nonpreferred terminology should be avoided (Table 1). Quality management systems should be instituted in pathology laboratories to ensure consistency and accuracy, and the pathology team should be dedicated to continuous quality improvement. The core components of a quality control system have been described³⁸ and are part of the International Society for Biological and Environmental Repositories³⁵ and NCI best practices.³⁶ As previously mentioned, a specialized training program in uropathology at one institution did significantly reduce discrepancies for CIS diagnosis, although not for other types of NMIBC.²² Additional research is needed to identify strategies that could further reduce discrepancies in pathology reports, yet it is clear that the key is concise, consistent reporting.

Improving Communications Between the Urologist and Pathologist

Communication between urologists and pathologists must be bidirectional if it is to be effective. Urologists should consider that pathologists may be able to provide abundant data, but may not always fully appreciate the impact of those data on clinical management. Identification of rare or poorly characterized variants (eg, “micropapillary” and “lipoid”) may be possible, but management of these types may be less well established than for common pathologic types. Pathologists should consider that most urologists have minimal training in pathology and may need to contact the pathologist for clarification.¹² The urologist should contact the pathologist for clarification when (1) the pathology report conflicts with the appearance of the lesions by cystoscopy, (2) tumor staging is incomplete because of a lack of muscle tissue (in which case restaging TURBT may be needed), or (3) the degree of invasion of lamina propria or muscularis propria is not completely clear. Initial lack of concordance or clarity in communication between a urologist and a pathologist can be resolved by active follow-up and collaboration between specialties,¹² as described in the following examples of patients who have undergone TURBT:

Example 1: The urologist receives a pathology report for a patient indicating “dysplasia,” when on visual cystoscopic examination, the clinician suspects CIS

From a pathology standpoint, the term “dysplasia” is used when atypia suggestive of neoplasia are identified, although the criteria to meet CIS is not achieved (Table 1).

Clinical implications: If the urologist suspects CIS based on the presence of flat, erythematous, velvety patches in the urothelium, it may be of value to repeat cystoscopy and biopsy in order to determine whether foci of CIS indeed exist. CIS is found concurrently with 7% to 15% of diagnoses of papillary UC and identified in as many as 90% of cases of UCs upon secondary follow-up procedures.³⁹

Example 2: The urologist receives a report that states the patient has a suspected grade 2 Ta tumor

A grade 2 tumor in the WHO 1973 system corresponds to neoplastic cells that are moderately differentiated, whereas in the WHO 2004 system (where grade 2 has been eliminated), the same cells would be classified as either low-grade or high-grade, based on the pathologist’s assessment.^{9,24,25} In the case of a papillary tumor, the distinction between a low-grade and a high-grade tumor is important because a low-grade tumor can be managed more conservatively (also depends on tumor characteristics such as stage, multiplicity, diameter, and any history of recurrence); for example, a low-grade tumor might be treated with a single post-TURBT dose of IVE chemotherapy, whereas a high-grade tumor would preferably be treated with BCG.^{9,29,30,40}

Clinical implications: This scenario assumes the absence of CIS, which is regarded as high-risk disease,²⁹ or multifocal lesions concurrent with low-grade papillary disease. With high-grade papillary disease, the flattened shoulder region of the tumor also may give the appearance of CIS, making diagnosis less straightforward. In such a case, the urologist

should follow up with the pathologist to confirm whether the pathologist could further classify the lesion as low- or high-grade, as defined by the WHO 2004 classification.

Example 3: The patient has a suspected T1 tumor, but there is no mention of “muscularis propria” in the pathology report

By definition, a T1 tumor has invaded into the lamina propria (subepithelial connective tissue), but muscle invasiveness is unclear in this example.

Clinical implications: the pathologist should be queried as to whether TURBT samples contained sufficient muscularis propria (detrusor muscle) to make a determination of muscle invasion. A second TURBT may be necessary to obtain a definitive diagnosis.

Example 4: Variant histologies in urothelial carcinoma that is presumed NMIBC

Rare histologic types of UC are diagnostically challenging, but are being increasingly recognized in invasive UC. The most common variant histologies are those UCs with squamous and glandular differentiation; less common types include nested, tubular, microcystic, inverted, micropapillary, lymphoepithelioma-like carcinoma, small-cell carcinoma, lymphoma-like, plasmacytoid, sarcomatoid carcinoma, large-cell neuroendocrine carcinoma, giant-cell carcinoma, UC with trophoblastic differentiation, UC with rhabdoid features, UC with clear-cell, lipoid-rich (ie, lipid-cell), osteoclast-rich undifferentiated carcinoma, completely undifferentiated (rarely), squamous cell carcinoma (nonschistosomal; schistosomal; verrucous), and adenocarcinoma variants (clear cell; urachal).^{13,24,41} Their appearance is unusual and may mimic that of other malignant or nonmalignant disease types.^{24,41} Some of these variants are at risk for understaging (eg, micropapillary, nested/ large nested variants of UC, sarcomatoid, microcystic, lymphoepithelioma-like).¹²

Clinical implications: a generalist pathologist may want to obtain a second opinion from a genitourinary pathologist and review the current literature that cites outcomes associated with variant morphology, although many of these studies are limited by small case numbers. Current NCCN guidelines stratify treatment(s) based on the variant histologies that are present.³⁰

Example 5: A TURBT and concurrent sampling of the prostatic urethra is performed but no mention of prostatic urethral involvement is made

This is a risk factor for progression, especially with stromal or ductal involvement, and may prompt immediate radical cystoprostatectomy.^{9,30,40} In the current example, the pathology report does not include details regarding whether or not the prostatic urethra is involved. Sampling of both the prostate and bladder within the same submitted specimen may be challenging. Although histological landmarks may guide the pathologist in determining whether a chip is of prostatic or bladder origin, superficial samples may not be readily classified. If the urologist is truly interested in distinguishing extent of involvement, separate specimens from each location should be submitted.

Clinical implications: If only the mucosal layer of the prostatic urethra is involved, transurethral resection of the prostate (TURP) followed by BCG may suffice.^{9,30} However, if

there is intraductal spread and/or stromal invasion, radical cystoprostatectomy should be considered as an alternative.^{9,30,40}

Improving Efficiency of Urologist–Pathologist Interactions

Laboratory turnaround time can affect treatment decisions because waiting to begin a medical or surgical treatment may have a negative effect on the clinical course of bladder cancer. Therefore, the urologist may have to weigh whether it is preferable to make a rapid treatment decision with limited information or to delay treatment to ascertain the clinical situation more fully. Rapid delivery of good-quality pathology results can avoid the need to make this difficult judgment. However, pathologists are limited in their testing by the quantity and quality of specimens available to them, whereas urologists are limited in their sampling by the conditions they experience during surgery. Finally, both urologists and pathologists should understand that members of the other specialty experience significant time and cost pressures.

Electronic records have the potential for faster and less error-prone transfer of information. However, some urologists and pathologists may find electronic systems less convenient than paper, especially considering the time needed to set them up and train staff. Multiple groups have endeavored to define a common structured data format for oncologic pathology reporting^{42,43} and templates from CAP are now widely used. Several studies have shown that using voice recognition technology shortened turnaround time while reducing transcription errors.^{44,45} Use of voice recognition systems is smoothest when reporting templates are incorporated. Ultimately, the worth of electronic medical record systems for pathology will be seen if they improve turnaround time, accuracy, and treatment decisions.

Future Directions

Pathology requirements, especially for clinical trials, are likely to become more complex and well-defined in the future. Identification of biomarkers for diagnostic and prognostic purposes has been an area of interest and is likely to expand. Biobanking, which is already active at numerous academic institutions and many other facilities in the United States and internationally, has implications for future clinical trials and soon may become more common outside of academic centers. For example, there is interest in biobanking of specimens from patients from the general population (ie, those not involved in a clinical trial) to provide the broadest possible sampling and to avoid excluding some categories of patients from research. Cultivating a relationship between the urologist and a pathology laboratory that does biobanking will facilitate participation in research initiatives.

Conclusions

Effective diagnosis and treatment of NMIBC requires active collaboration between urologists and pathologists due to the complex nature of the disease. It is incumbent upon urologists to make their best efforts to provide good-quality, well-documented specimens for pathologists. Pathologists in turn should strive for timely release of informative, unambiguous results. Consistent adherence by both groups to a common terminology for

pathologic findings is critical for a clear understanding of the clinical situation. To this end, the trend toward greater use of standardized electronic data transfer may improve efficiency, reduce errors, and minimize costs.

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Figure 1.
(A) Low magnification and (B) high magnification view of urothelial carcinoma in situ (CIS) of the bladder. Images provided by author (JS Miller).

Table 1**Staging of Bladder Cancer Tumors and Grading of NMIBC**

2010 AJCC Stage^{*46}	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Ta	Noninvasive papillary carcinoma
Tis	Carcinoma in situ “flat tumor”
T1	Tumor invading subepithelial connective tissue (lamina propria)
T2	Tumor invading muscularis propria bladder wall (ie, detrusor muscle)
T2a	Invasion of inner half (superficial)
T2b	Invasion of outer half (deep)
T3	Tumor invades perivesical tissue
T3a	Microscopically
T3b	Macroscopically (extravesical mass)
T4	Tumor invades any of the following: prostatic stroma, seminal vesicles, uterus, vagina, pelvic wall, and abdominal wall
T4a	Tumor invades prostatic stroma, uterus, or vagina
T4b	Tumor invades pelvic or abdominal wall
Modified 2004 WHO^{†‡} Grading of NMIBC^{9,13,24}	
<i>Preferred grade description(s)</i>	<i>Nonpreferred grade descriptions</i>
Papillary lesions	
• Urothelial papilloma (a benign lesion)	• Low-grade intraurothelial neoplasia, atypical hyperplasia, intraepithelial neoplasia grades I to II, intraurothelial neoplasia I to II, dysplasia grades I to II, low-grade dysplasia, mild-moderate dysplasia
• Papillary urothelial neoplasm of low malignant potential	• Superficial bladder cancer (including invasive or noninvasive disease)
• Low-grade papillary urothelial carcinoma	• Grade 1, 2, 3
• High-grade papillary urothelial carcinoma ± invasion	
Flat lesions	
• Urothelial CIS ± invasion	• High-grade dysplasia, high-grade urothelial dysplasia, high-grade intraurothelial neoplasia, severe dysplasia, grade III CIS, grade III intraurothelial neoplasia
• Hyperplasia (flat lesion lacking atypia, but with thickened mucosa or papillary)	• Superficial bladder cancer
• Reactive atypia (flat lesion with atypia), atypia of unknown significance	

AJCC=American Joint Committee on Cancer; CIS=carcinoma in situ; NMIBC=non-muscle-invasive bladder cancer; UC=urothelial carcinoma; WHO=World Health Organization.

^{*} AJCC⁴⁶ criteria for bladder cancer is adapted from chapter 45, page 502 (staging definitions).

[†] Encompasses the 2004 WHO grading system.²⁴

[‡] For additional information on bladder cancer reporting and guidelines for pathology reports, please see the 2nd International Consultation on Bladder Cancer recommendations.¹³

Table 2**Recommended Components of Reports Between Urologists and Pathologists**

Components of the Urology Report to Accompany Specimens Obtained From Bladder Biopsy or TURBT^{12,16,27,36}	
<i>Category</i>	<i>Characteristics</i>
Patient	Name, medical record number, sex, age, race and ethnicity, height and weight, smoking history, alcohol use, comorbidities, medications
Disease history	Types and duration of symptoms, time of first diagnosis, secondary occurrences of NMIBC, diagnostic/procedural method(s) (eg, TURBT, biopsy, cystoscopy), previous surgical or pharmacologic treatment(s)
Specimen(s)	Sampling date, sampling method, fresh or fixed, locations sampled (possibly include bladder map), appearance, tumor size(s), suspected tumor type(s), * any special requests for stains or tests; labels on containers with patient name, identifier, and location sampled
Components of the Pathology Report on Specimens Obtained From Bladder Biopsy or TURBT^{12,17}	
<i>Macroscopic findings</i>	
Biopsy samples	<ul style="list-style-type: none"> • Approximate number and dimensions of tissue fragments (submit all) • Presence or absence of papillary growth
TURBT samples	<ul style="list-style-type: none"> • Approximate number, dimensions, and total weight of tissue fragments <ul style="list-style-type: none"> ◦ 10 block cassettes for initial evaluation or entire specimen if <10 cassettes ◦ May submit entire specimen if lamina propria is invaded, to assess invasion of muscularis propria • The percentage of specimen that was submitted for processing
<i>Microscopic findings</i>	
General	<ul style="list-style-type: none"> • Presence or absence of muscularis propria (detrusor muscle) • Artifacts that may interfere with evaluation • Presence or absence of superficial lesions (eg, in situ lesions)
Tumor-specific	<ul style="list-style-type: none"> • Anatomic location • Overall architecture (eg, papillary or flat) • Histologic stage (TNM criteria), grade, and diagnosis (ie, invasive or noninvasive urothelial carcinoma or variant histology with description) • If invasive <ul style="list-style-type: none"> ◦ Lymphovascular invasion (present, absent, or indeterminate) ◦ Extent/depth of tumor invasion (pathological stage), including an indication of whether the muscularis propria is involved (present, absent, or indeterminate) and staging for in situ or invasive disease ◦ Pathological subtype
Background mucosa	<ul style="list-style-type: none"> • Presence or absence of dysplasia, CIS, and any other abnormalities (eg, intestinal metaplasia, keratinizing squamous metaplasia, inflammation) in the adjacent mucosa

CIS=carcinoma in situ; NMIBC=non-muscle-invasive bladder cancer; TURBT=transurethral resection of the bladder tumor.

* For example, from a cystoscopy, include size, number, location, and appearance of lesions, especially in cases where red patches occur, which is suggestive of CIS. Also include whether special or additional procedures were performed that might help inform the pathologist.